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TITLE OF THESIS..... Some Halogenated 2-Phenylpyrroles.....

UNIVERSITY..... Carleton.....

DEGREE FOR WHICH THESIS WAS PRESENTED..... Ph.D.....

YEAR THIS DEGREE GRANTED..... 1973.....

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THE SYNTHESSES OF SOME
HALOGENATED 2-PHENYLPYRROLES

by

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A thesis submitted to the Faculty of
Graduate Studies in partial fulfilment
of the requirements for the degree of
Doctor of Philosophy

Carleton University
Ottawa, Ontario.

October, 1973

David Garnet Durham

1974

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M.Sc., in partial fulfilment of the requirements
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.....
Chairman, Department of Chemistry

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Supervisor

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To my wife Linda and Timothy.

Abstract

A small number of halogenated benzoyl and phenyl pyrroles occur in nature as metabolites from bacterial or marine sources. The occurrence and biological activities of these metabolites are reviewed. In particular the marine bacterium Pseudomonas bromoutilis produces a substituted 2-phenylpyrrole, 2-(2'-hydroxy-3',5'-dibromophenyl)-3,4,5-tribromopyrrole, which has also been called pentabromopseudilin and exhibits potent antibiotic activity against some Gram-positive bacteria.

As part of a wider examination of the structure/activity relationships of halogenated 2-benzoyl and phenylpyrroles as antimicrobial agents, a study was undertaken to investigate new routes to 2-phenylpyrroles, unsubstituted by a stabilising electron withdrawing group and in particular to synthesise bromine and chlorine containing analogues of pentabromopseudilin. The literature pertaining to syntheses of 2-phenylpyrroles is reviewed.

Starting from 4-bromo- and 4-chloroanisole Friedel-Craft acylation with cyclopropyl carbonyl chloride, or γ -chlorobenzoyl chloride followed by treatment with base, gave aryl cyclopropyl ketones. These ketones when subjected to Leuckart reaction conditions gave 2-aryl-1-formylpyrrolidines as the

major rearranged products. Hydrolysis with acid gave 2-arylpyrrolidines. The conversion of pyrrolidines to pyrroles was effected via intermediate pyrrolines and 3-bromopyrrolines. Non specific halogenation of the pyrrole rings with bromine or sulphuryl chloride gave O-methyl-tetrabromo and tetrachloropseudilins.

An alternative synthetic route started from halogenated o-anisic acids, whose acid chlorides were condensed with glycine to give N-benzoylglycines. Treatment of N-benzoylglycines with acetic anhydride or dicyclohexyl-carbodiimide gave unstable substituted 2-phenyl- Δ^2 -oxazolin-5-ones, which reacted as azomethine ylids in 1,3 dipolar addition with acetylenic diesters, to give 2-phenylpyrrole-3,4 diesters. Hydrolysis, and subsequent decarboxylation gave analogues of O-methylpseudilin with 3,5-dihalogen substitution in the phenyl ring. The bromination and chlorination of 2-phenylpyrrole diesters were investigated, together with the hydrolysis and decarboxylation of these products, in an effort to obtain other analogues of O-methylpseudilin having halogen substitution in both the phenyl and more selectively in the pyrrole ring.

The two synthetic routes investigated were complementary, the first gave mono and tetrahalogenated O-methylpseudilins, while the latter route led to

di and pentahalogenated products. A synthesis of 2-(3',5'-dibromo-2'-methoxyphenyl) pyrrole was achieved by the second route and represents a new formal synthesis of the antibiotic, pentabromopseudilin.

The 2-(2'-methoxyphenyl)pyrroles synthesized were found to be sensitive to light and air. It was demonstrated that the pyrrole ring of O-methyl-tetrabromopseudilin underwent 2,5-oxygen addition in a ring opening reaction to give an aryl keto-amide after autoxidation. A similar oxidation of the pyrrole ring occurred during halogenation, in the presence of reagent in excess of that required to substitute all vacant ring positions.

Pentachloropseudilin, the chloroanalogue of the natural product, was synthesised and submitted for micro-biological evaluation.

ACKNOWLEDGEMENTS

The Author wishes to acknowledge with gratitude the encouragement and advice offered to him by his joint supervisors; Dr. A. H. Rees (Trent University) who first introduced him to this problem together with the fascination and frustrations of pyrrole chemistry, and Professor J. W. ApSimon for his interest and hospitality afforded during the time spent at Carleton University.

Dr. J. S. Kaltenbronn of Parke, Davis and Co., Ann Arbor, is thanked for spectra and an authentic sample of 2-(2',5'-dibromo-2'-methoxyphenyl)pyrrole and Professor A. G. Harrison (University of Toronto) for recording the High Resolution Mass Spectrum of Pentachloropseudilin. The Sankyo Co. Ltd. (Tokyo) is thanked for microbiological results.

The Author wishes to thank Mr. J. Cashmore for his help in recording the n.m.r. and mass spectra, and the technical staff in the Chemistry Departments of both Universities for assistance with apparatus and materials.

The Author would also like to thank both Carleton and Trent Universities for financial support in the form of Teaching assistantships.

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INTRODUCTION

The Naturally Occurring Halogen Substituted Pyrroles.

The investigation of pigments, formed as secondary metabolites by widely diverse species of organisms has led to the isolation and structural elucidation of a select group of compounds, which have the common structural feature of being halogen substituted pyrroles. Compounds which are either bromine or chlorine substituted pyrroles have been isolated and characterised. All known examples of the naturally occurring chloropyrroles are bacterial metabolites obtained from species of Pseudomonas, while the bromine containing compounds have been isolated from species of sponge and a bacterium from marine sources.

Oroidin and Dibromophakellin.

Studies on the metabolites of Porifera have led to the isolation of several bromopyrroles from the sponge Agelas oroides.¹ Extraction of fresh material with methanol, followed by ether afforded four closely related dibromopyrroles, whose structures were established as the nitrile (1), the amide (2) and the acid (3) together with its methyl ester (4). The ester however was considered to be an artefact of the extraction procedure, since it was not obtained under

different extraction conditions. From an n-butanol soluble fraction a dibromopyrrole, oroidin was isolated and a structure proposed. Subsequent re-examination and the de novo synthesis of a derivative led other workers to re-assign the structure as (5).¹³¹ Oroidin appears to be closely related biogenetically to dibromophakellin (6), a bromopyrrole containing alkaloid isolated from the sponge Phakellia flabellata by Sharma and Burkholder.²

(1)

(2)

(3) R=H

(4) R=CH₃

(5)

(6)

Pyrrolnitrin, Oxypyrrolnitrin and Isopyrrolnitrin.

Pyrrolnitrin was first isolated by Arima and co-workers, from among the metabolites of a culture of bacterial cells of Pseudomonas pyrocinia.³ Chemical degradation of this metabolite by the same authors established this compound as a chlorine containing 3-phenylpyrrole, with the total structure 3-chloro-4-(2'-nitro-3'-chlorophenyl)pyrrole (7).⁴ This structure has been confirmed by the total synthesis of pyrrolnitrin by Nakano et al.,⁵ and Gosteli.⁶

Further investigation of the culture broths of pyrrolnitrin producing Pseudomonads has led to the isolation and identification of two minor related metabolites, both of which were also shown to be chlorine containing 3-phenylpyrroles. The structure of isopyrrolnitrin, which was isomeric with pyrrolnitrin, was shown to be 2,3-dichloro-4-(2'-nitrophenyl)pyrrole (8), while that of oxypyrrolnitrin was established as being 3-chloro-4-(2'-nitro-3'-chloro-6'-hydroxyphenyl)pyrrole (9), by Hashimoto and Hattori.^{7,8}

Certain strains of the bacterium Pseudomonas pyrrolnitrica have been isolated, which when grown on a suitable medium having NH_4Br as a bromine source produce bromo-analogues of pyrrolnitrin,⁹ among which have been

identified 3-bromo-4-(2'-nitro-3'-bromophenyl)pyrrole (10)
and 2,3-dibromo-4-(2'-nitro-3'-bromophenyl)pyrrole (11).

(7) X=Cl

(10) X=Br

(8)

(9)

(11)

Pyoluteorin.

Pyoluteorin is a bright yellow pigment produced by certain strains of Pseudomonas aeruginosa grown on a medium containing calcium chloride.¹⁰ The structure of pyoluteorin was established as that of a 2-benzoylpyrrole by degradative studies,^{11,12} while n.m.r. studies showed the chlorine substitution to correspond to that of a 4,5,-disubstituted pyrrole with the total structure 4,5-dichloro-2-(2',6'-dihydroxybenzoyl)pyrrole (12).¹³ The structure has been confirmed by the synthesis of pyoluteorin by a number of different routes.¹⁴⁻¹⁷

Pentabromopseudilin.

A bromine rich phenylpyrrole containing over 70% by weight of bromine was isolated from a marine bacterium, classified by Burkholder¹⁸ as Pseudomonas bromoutilis. Lovell¹⁹ on the basis of X-ray crystallographic studies, showed the structure to be that of a pentabromo-2-(2'-hydroxyphenyl)pyrrole (13). The name "pseudilin" has been proposed for the parent compound 2-(2'-hydroxyphenyl)pyrrole, so that the natural product would be named 3,3',4,5,5'-pentabromopseudilin.²⁰ The assigned structure was confirmed by synthesis, the product being identical with a sample of the naturally occurring metabolite.²¹

(12)

(13)

The Structure/Activity of Halogeno-pyrrole Antibiotics.

The various halogeno-pyrroles produced as metabolites of Pseudomonas species of bacteria have been shown to exhibit antibiotic activity against a number of micro-organisms.

Pyoluteorin was reported to have a strong inhibitory action in vitro on the growth of a number of bacteria and protozoa including Mycobacterium tuberculosis, Trichomonas and Tetrahymena, but little action against fungi or yeasts.¹⁰ Contrary to this report, pyoluteorin was later shown to be active against fungi, and especially suitable in dilute concentrations for the treatment of fungal infestations in plants.²² These fungistatic properties have been demonstrated by the inhibition of growth in cultures of Aspergillus niger and the prevention of spore germination of Phytophthora infestans under otherwise optimal growth conditions. The ratio of effective fungicidal activity to phytotoxicity was found to compare favourably with other commercially available fungicidal compounds. The structure/activity relationship of a number of pyoluteorin analogues has been reported.²³ The activities of a range of analogues show that the minimum requirements are the 2-(2'-hydroxybenzoyl)pyrrole unit with electron withdrawing groups at positions 5 (and 4). Both

deoxyphyoluteorins²⁴ and nitro-analogues of phyoluteorin²⁵ are generally more active than the naturally occurring compound.

Pyrrolnitrin was shown by Nishida et al²⁶ to be mainly active against dermatophytic fungi especially against members of the genus Trichophyton, and has been employed for the treatment of superficial dermatophytic infections. The antimicrobial spectrum of pyrrolnitrin shows that bacteria are generally less susceptible or naturally resistant.⁴ The structure/activity of a number of pyrrolnitrin analogues has been investigated.²⁷ The presence of an ester group substituted at any position of the pyrrole ring results in pyrrolnitrins with reduced antifungal activity. Substitution of either the 1, or both the 2 and 5-positions of the pyrrole ring by alkyl groups also leads to reduced activity. Some analogues however, mono-substituted only by an alkyl group at either the 2 or 5-position, showed almost the same level of activity as pyrrolnitrin itself. The nitro-group itself does not appear to be a requirement for antifungal activity. Denitro-pyrrolnitrin analogues showed broader and stronger antimicrobial activity than those of the parent nitrophenyl compound. Removal of chlorine substitution at the 3-position of the pyrrole

ring results in decreased antifungal activity.¹

The biological properties of pentabromopseudilin are of special interest in relation to its great activity against Grampositive bacteria. Strains of Staphylococcus aureus, Diplococcus pneumoniae and Streptococcus pyogenes are inhibited in vitro at concentrations as low as 0.0063 µg/ml. The antibiotic is also active against Mycobacterium tuberculosis in a synthetic medium but was inactive against Gram-negative bacteria and Candida albicans.¹⁸

Castro et al²⁸ have investigated the antimicrobial properties of a number of pyrrole derivatives including 2-phenylpyrrole, which itself shows significant activity. 2-(3'-Chlorophenyl)-4-methylpyrrole is claimed to show antibiotic activity,²⁹ as well as the 2-phenylpyrrole isomer of pyrrolnitrin, 2-(3'-chloro-2'-nitrophenyl)-3-chloropyrrole.³⁰ 1-Phenylpyrroles substituted by chlorine or bromine atoms in either the 2 and/or 5-positions of the pyrrole ring show bacteriostatic activity in inhibiting the growth of Bacillus subtilis.³¹

In view of the natural occurrence and interesting antimicrobial properties of halogenated benzoyl and phenylpyrroles, a study was initiated to investigate new synthetic routes to 2-phenylpyrroles, which would lead in particular to bromine and chlorine analogues of pentabromopseudilin.

The Syntheses of 2-Phenylpyrroles.

The chemical literature contains details of a number of routes which have been used in the syntheses of 2-phenylpyrroles.

a) The most general pyrrole synthesis is that of Knorr, in which an α -aminoketone is condensed with a ketone containing a reactive methylene group in the presence of acetic acid.³² Umio et al³³ treated ethyl 3-chlorobenzoyl acetate (14), with 3-amino-2-propanone hydrochloride (15) in an acetic acid/sodium acetate buffer solution to obtain ethyl 2-(3'-chlorophenyl)-4-methylpyrrole-3-carboxylate (16). Hydrolysis and subsequent decarboxylation gave the 2-phenylpyrrole (17). These authors also obtained the same product (17) by the condensation of 1-(3'-chlorophenyl)-1,3-butanedione (18) with diethyl aminomalonate (19) via a mixture of enamines (20) and (21). The reactivity of the carbonyl groups of 1-aryl-1,3-butanediones is dependent on the electronic and steric effects of substituents in the phenyl ring. The mixture of enamines on treatment with sodium ethoxide underwent base catalysed cyclisation to give the isomeric 2- and 3-phenylpyrroles (22) and (23). The former after hydrolysis and subsequent decarboxylation gave the pyrrole (17).

b) 1-Phenylpyrrole may be converted to 2-phenylpyrrole by thermal rearrangement at a temperature of 700°C.^{35,36}

It has also been demonstrated that N-substituted 2'-pyridyl and 3'-pyridylpyrroles undergo rearrangement at similar temperatures to give mixtures of the corresponding 2- and 3-substituted pyrroles.^{37,38}

1-Methyl-2-(2'-pyridyl)pyrrole undergoes a similar pyrogenetic rearrangement to 2-methyl-5-(2'-pyridyl)-pyrrole.³⁹ Patterson and co-workers have investigated the rearrangement of a number of 1-substituted alkyl, aryl and benzyl pyrroles at temperatures between 500-600°C. and found that they give mixtures of 2- and 3-substituted pyrroles. The products obtained in the thermal isomerisations of 2,5-dimethyl-1-phenyl and 2,5-diphenyl-1-methylpyrroles could best be accounted for by the formation of an intermediate 2H-pyrrole.⁴⁰ Rearrangement of 1-(1'-phenylethyl)pyrrole was found to take place with retention of configuration during the transfer of the migrating group.⁴¹ Wibaut and Dhont showed that 1-(2'- or 3' - or 4'-chlorophenyl)pyrrole (24) and 1-(3'-bromophenyl)pyrrole each rearranged to its corresponding 2-substituted pyrrole isomer at 700°C.⁴²

c) Condensation of 1,2-dichloroether (25) with ethyl benzoylacetate in the presence of ammonia gives a mixture of ethyl 2-phenyl furan and pyrrole-3-carboxylates.

The latter on hydrolysis and decarboxylation gave

2-phenylpyrrole.⁴³ Wibaut and Dhont prepared 2-(4'-chlorophenyl)pyrrole (28) from ethyl 4-chlorobenzoylacetate (26) via the 3-ester substituted pyrrole (27) by a similar method.⁴²

d) 2-Phenylpyrrole derivatives have been prepared from substituted pyrimidines by ring contraction with zinc in 50% aqueous acetic acid.⁴⁴ Pyrroles have only been produced in the reaction when the pyrimidine is substituted in the 2-position by a phenyl or 4'-chlorophenyl group. 2-(4'-Chlorophenyl)-4,6-dichloropyrimidine (29) undergoes dehalogenation and subsequent ring contraction to give 2-(4'-chlorophenyl)pyrrole (28).⁴⁵

e) Adkins and Lundsted have investigated the dehydrogenation of a number of hydroaromatic compounds.⁴⁶ 2-Phenylpyrrolidine in benzene may be dehydrogenated over a nickel on nickel chromite catalyst at 300°C. to give 2-phenylpyrrole in good yield.

f) Ketones with an α -methyl or methylene group react with 1-nitro-2-dimethylaminoethylene in the presence of potassium ethoxide and ethanol to give 1-acyl-3-nitro-propylene salts.⁴⁷ Substituted acetophenones (30) react with the nitro-amines (31) to give nitro-ketones (32), which undergo reductive cyclisation on treatment with sodium dithionate to yield the pyrroles (33).^{48,49}

Hanessian and Kaltenbronn employed this procedure, starting from 3,5-dibromo-2-methoxyacetophenone (34) to obtain the 2-phenylpyrrole (35), an intermediate in their route to the synthesis of pentabromopseudilin.²¹

g) Acetophenone oxime undergoes an addition reaction with dimethyl acetylenedicarboxylate in boiling methanol in the

presence of sodium methoxide to give a mixture of the cis and trans O-vinyloximes (36). Heating this mixture of isomers at 170°C. results in rearrangement to the iminoketone, which cyclizes and dehydrates to yield dimethyl 2-phenylpyrrole-4,5-dicarboxylate (37).⁵⁰

h) N-Acyl- α -amino acids (38) on treatment with acetic anhydride yield azlactones (Δ^2 -oxazolin-5-ones) (39), which may be considered as anhydrides of the acylamino acids. When azlactones are heated with acetylene derivatives they are capable of undergoing 1,3-dipolar cycloaddition, with the elimination of carbon dioxide to form pyrroles.⁵¹ Huisgen and co-workers have investigated the behaviour of some 2,4-disubstituted alkyl-phenyl- Δ^2 -oxazolin-5-ones with dimethyl acetylenedicarboxylate. The products formed suggest that cycloadditions are preceded by a tautomerization of the parent azlactone (39) to a mesoionic oxazetium-5-oxide (40) which, as a cyclic azomethine ylide, combines with the dipolarophile to give the pyrrole diester (41).⁵²

Dimethyl 2-methyl-5-phenylpyrrole-3,4-dicarboxylate (44), obtained as the product from 4-methyl-2-phenyl- Δ^2 -oxazolin-5-one (42) and dimethyl acetylenedicarboxylate (43), was converted to 2-methyl-5-phenylpyrrole (44) by alkaline hydrolysis and pyrolysis.⁵² A number of workers have demonstrated that 2,4-diphenyl- Δ^2 -oxazolin-5-ones^{51,53} and benzoyl-phenyl- Δ^2 -oxazolin-5-ones^{54,55} undergo similar cycloaddition reactions to yield the corresponding pyrroles. While oxazolin-5-ones with identical substituents at the 2 and 4 positions react with acetylene monoesters to give symmetrical pyrrole products, those with differing substituents react to give mixtures of two products. The oxazolin-5-one (42) and acetylene monoester (46) give a mixture of methyl 2-methyl-5-phenylpyrrole 3- and 4-carboxylates (47) and (48),^{51,53} in a ratio of 1:5.

N-acyl-N-alkyl or -N-aryl- α -amino acids on treatment with acetic anhydride give cyclic derivatives, which can be formulated only as zwitterionic structures (50). These mesoionic oxazolin-5-ones undergo cycloadditions with alkynes to produce N-substituted pyrroles (51).^{56,57} The N-substituted oxazolin-5-ones (50) with differing substituents at the 2 and 4 positions, in contrast to those with no N-substituent, give only one product (52) on the addition of non-symmetrical alkynes. The direction of cycloaddition is determined mainly by the nature of the oxazolium-5-oxide rather than the substituents in the 2 and 4 positions.

R R ' '

X=Ph or H

$$Y = H \text{ or } COOC_2H_5$$

1,3-Dipolar cycloaddition of alkynes, with the elimination of carbonyl sulphide occurs with N-substituted thiazolin-5-ones to yield N-substituted pyrroles.⁵⁸ Oxazolin-5-ones also undergo dipolar addition with alkenes to yield pyrrolines. Azlactones of type (39) give Δ^1 -pyrroline derivatives (53)⁵⁹, while the N-substituted mesionic oxazolin-5-ones (50) yield Δ^2 -pyrrolines (54).⁶⁰ These Δ^1 and Δ^2 -pyrrolines are converted to pyrroles by dehydrogenation over palladium/charcoal catalysts.

It has been demonstrated that trans-2-phenyl-3-benzoyl-aziridines (55) add to acetylene dicarboxylate esters in a thermal process involving the carbon-carbon scission of the aziridine ring and dehydrogenation to yield 2-benzoyl-5-phenylpyrrole diesters (56).^{54,55}

N-Substituted aziridines undergo thermal ring opening by a conrotatory process to give azomethine ylids, which on addition of acetylene dicarboxylate esters give 2,5-cis-disubstituted Δ^3 -pyrrolines (58).¹³² 2,3-Diarylazirenes (57) however, are reported not to undergo thermal cycloaddition with dipolarophiles,⁶¹ but undergo photochemical cycloadditions with electron deficient olefins⁶² or acetylenic diesters⁶³ to yield Δ^1 -pyrrolines (59) and 2,5-diarylpyrroles (41) respectively.

A number of routes which are available for the syntheses of 2-phenylpyrroles in which the pyrrole ring is stabilised by the presence of an electron withdrawing group, as well as routes to "simple" unsubstituted 2-phenylpyrroles have been reviewed. The latter are often more difficult to prepare due to their instability. Since some of the routes already outlined are not readily applicable to the syntheses of halogen containing pyrroles, a study was undertaken to investigate new routes to 2-phenylpyrroles, unsubstituted by a stabilising electron withdrawing group. Of particular interest was the development of routes to 2-(2'-hydroxyphenyl)pyrrole and the subsequent preparation of bromine and chlorine containing analogues.

of 3,3',4,5,5'-pentabromopseudilin, which is a naturally occurring 2-phenylpyrrole.

DISCUSSION

1-Phenylpyrroles as Precursors of 2-Phenylpyrroles.

The structure of pseudilin was taken as the focus for the syntheses of halogen containing 2-phenylpyrroles, which might exhibit biological activity as potential antibiotics. Attempts to explore several synthetic routes to 2-phenylpyrroles met with varying degrees of success.

The synthesis of 2-phenylpyrrole by thermal rearrangement from 1-phenylpyrrole has already been outlined (p.12). Although the phenyl migration usually takes place at high temperatures it was hoped that migration might take place at lower temperatures during the decarboxylation of 1-phenylpyrrole-2-carboxylic acid salts. The only product observed however from the decarboxylation reaction carried out at 200°C. was 1-phenylpyrrole.⁶⁴ Heating together mucic acid (60) and aniline results in cyclisation and decarboxylation to give 1-phenylpyrrole.⁶⁵ Since Wibaut⁴² synthesised by this means, from appropriately substituted bromo- and chloroanilines, a number of 1-(halophenyl)-pyrroles including 1-(2'-halophenyl)pyrroles (61), which underwent phenyl migration to give 2-(2'-halophenyl)pyrroles, attempts were made to synthesise 1-(2'-methoxyphenyl)pyrroles (62) in a similar fashion. p-Nitroaniline does not yield a 1-phenylpyrrole product under similar conditions⁶⁶ and other workers have

reported that substituted anilines containing electron withdrawing groups do not undergo ring closure to form substituted pyrroles.⁶⁷ The heating together of mucic acid and o-anisidine resulted in pyrolysis of the mucic acid with recovery of the unchanged o-anisidine and the absence of any pyrrole formation. Further investigation of the syntheses of 2-phenylpyrroles via 1-phenylpyrroles was not pursued. The method of Clauson-Kaas⁶⁸ of treating diethers of 2,5-dihydroxytetrahydrofuran (63) with substituted anilines has been shown to yield 1-phenylpyrroles (64) previously inaccessible by the mucic acid route.⁶⁹⁻⁷² This might offer a route to 1-(2'-methoxyphenyl)pyrrole, but was not further examined.

The Syntheses of 2-Phenylpyrroles by Dehydrogenation of Pyrrolidines.

i) Friedel-Craft ketone syntheses from haloanisoles.

The second route to 2-phenylpyrroles which was examined involved the syntheses of 2-phenylpyrrolidines, and dehydrogenation of this system to give pyrroles. Breuer and Stein⁷³ have shown that aryl cyclopropyl ketones on heating with formamide give 1-formyl-2-arylprrrolidines. The initial synthetic step required the production of suitable intermediate aryl cyclopropyl ketones which would ultimately lead to the desired pyrrole system.

The use of Friedel-Craft reactions in aromatic ketone syntheses has been extensively reviewed.⁷⁴ Close investigated the reaction of γ -chlorobutyryl chloride (65) with benzene, using aluminum chloride as the catalyst and found that only the acyl halide predominantly enters into the reaction to give an aryl chloroketone (66) as the major product.⁷⁵ Treatment with base of this compound without extensive purification resulted in 1,3 elimination of HCl with cyclisation to phenyl cyclopropyl ketone (67) in good yield. Halo substituted aromatic ethers are acylated either in the para position where possible or otherwise ortho to the ether grouping. Acylation of 4-chloroanisole by chloroacetyl chloride with aluminum

chloride in carbon disulphide is reported to yield 5,α-dichloro-2-methoxyacetophenone.⁷⁶ 4-Bromo-, 4-chloro-, and 2,4-dibromoanisoles were chosen as readily available starting materials, which would yield precursors suitable for the syntheses of pseudilin analogues.

Attempts to acylate 4-bromoanisole with γ-chlorobutyryl chloride using AlCl_3 in CS_2 were unsuccessful. The use of nitrobenzene, in which the AlCl_3 -acid halide complex was soluble, led to 5-bromo-2-methoxyphenyl-γ-chloropropyl ketone (68) in high yield and only a small amount of the phenolic ketone (69), provided the temperature was carefully controlled. The use of excess aluminum chloride and temperatures in excess of 20°C . resulted in increasing cleavage of the aromatic ether to yield 5-bromo-2-hydroxyphenyl-γ-chloropropyl ketone (69) as the major product. Nitrobenzene was removed by steam distillation, but further attempted purification of the product by either chromatography on silica gel or distillation under reduced pressure resulted in extensive decomposition. As a result it was found to be more advantageous to treat the crude aryl propyl ketone with base without further purification to give 5-bromo-2-methoxyphenyl cyclopropyl ketone (70) and several minor byproducts, which were then more readily separable by chromatography. 5-Bromo-2-hydroxyphenyl-γ-chloropropyl ketone (69) similarly underwent base catalysed cyclisation

to yield the phenolic cyclopropyl ketone (71).

4-Chloroanisole under similar conditions underwent acylation with γ -chlorobutyryl chloride to give 5-chloro-2-methoxyphenyl γ -chloropropyl ketone (72). Treatment with excess base however gave only low yields of the phenyl cyclopropyl ketone (73) and the phenolic cyclopropyl ketone (74).

The major product, which on chromatography exhibited more polar behaviour than these ketones gave on elemental analysis the expected empirical formula $C_{11}H_{11}Cl_2O_2$, but the mass spectrum showed parent ion peaks (M^+ 210:212) of the ketone (73). This together with the chlorine isotopic abundance pattern suggested that this product was a dimer. The base peak at m/e 169:171 indicated an ion peak derived from a 5-chloro-2-methoxybenzoyl group within the molecule. The presence of hydroxyl and ketone groups were revealed by bands in the infrared spectrum at 3600 and 1645 cm^{-1} respectively. The n.m.r. spectrum (spectrum 1) showed a series of proton signals with complex splitting patterns, which could best be accommodated by either the structural formulae (75) or (76).

(75)

(76)

Triplet signals centered at τ 5.56 and τ 6.95 showed equivalent coupling constants, integrated for two protons

apiece and are assigned to the protons of the hydroxyethyl side chain. The triplet signal at τ 4.55 integrated for a single proton. The chemical shift would appear to be consistent with an assignment to the allylic cyclopentene ring proton adjacent to a benzoyl group, although the vinylic proton of structure (76) might be expected to show a similar shift. The quartet at τ 7.98 integrated for two protons and was coupled to the low field proton at τ 4.55 and the triplet at τ 6.54, which also represented two protons. The pair of allylic ring protons of structure (75) would be expected to resonate at lower field than the methylene ring protons and might be expected to also show splitting into a triplet and quartet respectively, while the allylic ring protons of structure (76) resonating as a quartet would be at lower field than the methylene triplet. This former situation appears to correspond to the observed spectrum. The assignment of the signals to the various protons by expected chemical shift and coupling constants suggests that structure (75) was more in accordance with the observed data.

A spectroscopically similar product (78) derived as a byproduct from the action of base on the bromoketone (68), was assigned as the bromo analogue of (75). It is suggested that these compounds arise by an initial

intermolecular elimination of HCl to give (77) followed by an intramolecular aldol condensation with dehydration to the cyclopentenones.

To eliminate these unwanted products the Friedel-Craft reaction was attempted using cyclopropyl carbonyl chloride (81) as the acylating agent. Kishner⁷⁷ has shown that cyclopropyl carbonyl chloride could be used to acylate benzene to give the cyclopropyl phenyl ketone (67). The desired acylation was found to take place with both 4-bromo- and 4-chloroanisoles. Since 5-chloro-2-methoxyphenyl cyclopropyl ketone (73) was appreciably volatile, material was lost during the removal of nitrobenzene by steam distillation. It was found that dichloroethane, which was more easily removed could be substituted as a suitable solvent and led to higher yields.

The chemical literature appears to be almost devoid of references to the acylation of 2,4-dihaloanisoles.

Schoot and Klaassens⁷⁸ acylated 2,4-dichloroanisole with chloroacetyl chloride, using AlCl_3 in CS_2 and obtained the demethylated product, 3,5-dichloro-2-hydroxy- α -chloroacetophenone under the conditions used. However Kalinowsky and Kalinowsky⁷⁹ were unable to prepare the same compound by Fries rearrangement from 2,4-dichlorophenyl chloroacetate. Friedel-Craft butyrylation of 2,4-dibromophenol at a temperature of 120°C gave 3,5-dibromo-2-hydroxy-butyrophenone, which was identical with a sample prepared by Fries arrangement of 2,4-dibromophenyl butyrate.⁸⁰ Attempts to acylate 2,4-dibromoanisole with either γ -chlorobutyryl chloride or cyclopropyl carbonyl chloride using AlCl_3 as catalyst and nitrobenzene, dichloroethane or CS_2 as solvent under a number of differing conditions were unsuccessful. The dibromoanisole was either recovered unchanged or had undergone demethylation to 2,4-dibromophenol. The failure of acylation to take place under the conditions used may be ascribed to the joint deactivating effect of the 2- and 4-bromo substituents on the 6-position of the aromatic ring.

ii) The synthesis of pyrrolidines by the Leuckart reaction on cyclopropyl ketones.

The reaction of a ketone or aromatic aldehyde with formamide or ammonium formate, known as the Leuckart reaction, involves condensation to form an imine followed

by reduction to an amine. Cyclopropyl ketimines are known to rearrange to pyrrolines⁸¹ and the reaction has been applied to the syntheses of myosmine and apo-ferrosamine.⁸² Breuer and Stein⁷³ reported that the reaction of an aryl cyclopropyl ketone (67) with formamide yields in addition to the expected N-formyl- α -cyclopropyl benzylamine (82), a rearranged product, which was identified as 1-formyl-2-phenylpyrrolidine (83). This suggested that a ketimine may be initially formed and rearranges to a pyrroline, which further undergoes reduction to a pyrrolidine.

5-Bromo-(70) and 5-chloro-2-methoxyphenyl cyclopropyl ketone (73) also underwent the reaction with formamide in the presence of catalytic amounts of $MgCl_2$ at 180°C to give the corresponding 1-formyl-2-arylpyrrolidines (84) and (85) as the major products, whose structures were established spectroscopically. Molecular ion peaks appeared in the mass spectra corresponding to the expected molecular weights for either the benzylamine or pyrrolidine; however the absence of N-H stretching bands at 3300-3500 cm^{-1} in the infrared spectra indicated that these products were not benzylamines. No resonances were observed in the n.m.r. spectra at chemical shifts consistent with the presence of cyclopropyl ring protons, but proton signals were rather those expected for pyrrolidine ring systems. In keeping with the observations of Breuer and Stein⁷³ the formyl hydrogens appeared as two singlets of unequal intensity.

The n.m.r. spectrum of dimethyl formamide shows two methyl group signals due to hindered rotation about the N-CO bond, which exhibits partial double bond character.¹³³ For a similar reason the acetyl methyl groups of some 1-acetyl-2-benzylpyrrolidines have also been observed to appear as temperature dependent doublets.¹³⁴

The appearance of the formyl hydrogens of 1-formyl-2-phenylpyrrolidines as two singlets of unequal intensity may be similarly rationalised on the basis of hindered rotation about the N-CO bond.

The 2-aryl-1-formylpyrrolidines were readily hydrolysed with dilute acid to give 2-arylpyrrolidines (86)-(88).

(67) $X=Y=H$

(70) $X=OCH_3$ $Y=Br$

(73) $X=OCH_3$ $Y=Cl$

(82) $X=Y=H$

(83) $X=Y=H$

(84) $X=OCH_3$ $Y=Br$

(85) $X=OCH_3$ $Y=Cl$

(86) $X=Y=H$

(87) $X=OCH_3$ $Y=Br$

(88) $X=OCH_3$ $Y=Cl$

iii) Dehydrogenation of pyrrolidines.

Adkins and Lunsted⁴⁶ have demonstrated that 2-phenylpyrrolidines may be catalytically dehydrogenated under suitable conditions to 2-phenylpyrrole. Dehydrogenation of a compound containing easily reduced functions may lead both to dehydrogenation and concurrent hydrogenation. The presence of a halogen substituent in the aromatic ring was unfavourable to this as the method of choice for dehydrogenation. An initial exploratory dehydrogenation of (70) using palladium on charcoal did not give any detectable pyrrole derivative. When a sample of (70) was heated with sulphur at 160°C. hydrogen sulphide was evolved. Preparative t.l.c. of the resultant mixture led to the isolation of a product, which showed signals at τ 3.1, 3.4 and 3.85 in the n.m.r. spectrum corresponding to the resonances expected of pyrrole ring protons. This line of investigation was not developed further as it was found more advantageous to dehydrogenate in a stepwise fashion by the conversion of pyrrolidines to pyrroles via readily isolable pyrroline intermediates.

2-Phenylpyrrolines (90) - (92) were prepared from their respective pyrrolidines (86) - (88) by the method of Fuhlhage and VanderWerf.⁸⁹ Treatment of pyrrolidinium salts with sodium hypochlorite solution gave chloramines (89), which were not characterised, but were immediately treated with ethanolic KOH, with a resulting elimination of

HCl to give 2-phenylpyrrolines.

The preparation of 2-phenylpyrroline (90) by a number of other routes is reported in the literature.^{81,83,84} Some confusion has been apparent with respect to the nomenclature. Although originally designed Δ^2 -phenylpyrroline, this structure has now been shown to be untenable. Maginnity and Cloke⁸⁵ demonstrated that 2-phenylpyrroline possessed an azomethine structure since it did not behave as a secondary amine in releasing active hydrogen as determined by the Zerevitinov method. The ultraviolet spectra of Schiff's bases, with the partial structure Ph-CH=N- exhibit λ_{max} 247 m μ . (ϵ = 17000), while a characteristic band at about 6.15 μ appears in their infrared spectra.⁸⁷ Burckhalter and Short⁸⁸ reported a band at 6.2 μ in the infrared spectrum of 2-phenylpyrroline. This together with the absence of N-H stretch

at 3.02 μ established it as having the Δ^1 -structure. Attempts by the same authors to prepare the possible Δ^5 -isomer by the treatment of γ -phenyl- γ -aminobutyraldehyde diethyl acetal with acid were unsuccessful.

Comparison of the ultraviolet spectra of the 2-phenylpyrrolidines (86) - (88) with the 2-phenylpyrrolines (90) - (92) revealed a bathochromic shift due to the extended conjugation of the pyrroline double bond with the phenyl ring. Infrared absorption above 1600 cm^{-1} and the absence of any N-H stretching bands at 3300-3500 cm^{-1} were also indicative that these compounds were Δ^1 -pyrrolines. The n.m.r. spectra were consistent with this assignment, showing three multiple peaks (τ 6.1, 7.1 and 8.1) for the pairs of pyrroline ring protons, but no single proton resonance with a great enough chemical shift for the vinylic proton, which might be expected in a Δ^2 or Δ^5 -isomer.

Knott was unable to dehydrogenate 2-phenylpyrroline to 2-phenylpyrrole with selenium.⁸⁴ Attempts to effect the dehydrogenation with either DDQ or chloranil were unsuccessful. Monitoring the reactions by t.l.c. it was observed that with both of these reagents the starting material rapidly disappeared, but no product having the expected mobility of 2-phenylpyrrole was formed. The product obtained using chloranil was a mauve dye, the structure of which was not established.

iv) Bromination of 2-phenylpyrrolidines with N-bromosuccinimide.

In an attempt to introduce unsaturation into the pyrrolidine ring by bromination and subsequent dehydrobromination 1-formyl-2-phenylpyrrolidine (83) was treated with N-bromosuccinimide in carbon tetrachloride in the presence of a catalytic amount of hydrogen peroxide. After refluxing overnight, t.l.c. showed that the starting material was no longer present. Neither of the two major products formed however, had undergone the desired benzylic bromination. The absence of any absorption in the carbonyl region of their infrared spectra indicated that both of these products had undergone cleavage of the formyl group. The more polar compound exhibited λ_{max} 243 m μ . and its n.m.r. spectrum showed three multiplet signals, which integrated for two protons apiece, at similar chemical shifts to those of 2-phenylpyrroline (90). A picrate derivative of the compound showed the same melting point as that of the picrate from 2-phenylpyrroline, while a mixed melting point was undepressed, confirming its structure. The faster running compound on t.l.c. showed λ_{max} 252 m μ ., while its n.m.r. and infrared spectra were identical with those of 3-bromo-2-phenylpyrroline (93).

The treatment of 1-formyl-2-phenylpyrrolidine with N-bromosuccinimide in CCl₄ in the absence of peroxide

gave a mauve dye, which turned red in basic solution. The structure of this "indicator" was not established. The use of aqueous dioxane as solvent for the reaction resulted in the isolation of 2-phenylpyrroline (90) as the only product in circa 28% yield.

When 2-phenylpyrrolidine (86) was brominated with N-bromosuccinimide in methylene chloride, the products obtained were identical spectroscopically with those products (90) and (93) previously isolated from the reaction with 1-formyl-2-phenylpyrrolidine. The formation of these products indicated that the pyrrolidines were first being converted to 2-phenylpyrroline which then underwent further bromination to the brominated pyrroline (93).

Treatment of the 2-phenylpyrrolines (90)-(92) with N-bromosuccinimide in CCl_4 gave the bromopyrrolines (93)-(95) in almost quantitative yields. Elemental analyses of these compounds, which were unstable and difficult to purify were satisfactory. They gave picrate derivatives however, which gave unsatisfactory microanalysis results in keeping with the proposed molecular formulae. Parent ion peaks in their mass spectra were consistent with the expected molecular weights. The infrared spectra as expected did not show any absorption in the region $3300\text{--}3500\text{ cm}^{-1}$ associated with N-H stretch. A bathochromic shift was observed in the wavelength of absorption in the ultraviolet region of these bromo-2-phenylpyrrolines as compared with their pyrroline precursors. The position of bromine substitution in the pyrrolines was assigned on the basis of the n.m.r. spectra.

The n.m.r. spectra of 2-phenylpyrrolines (90)-(92) (Spectrum 2) showed resonances for pyrroline ring protons at circa τ 7.1, 8.1 and 6.1, which were assigned to those attached to C_3 , C_4 and C_5 respectively. The spectra of the bromopyrrolines (93)-(95) showed signals at circa τ 4.4-4.8 (t, 1), 7.5 (m, 2) and 5.6-6.0 (m, 2). Since bromination would be expected to take place in an allylic position (C_3 or C_5) to the C=N double bond, the signal at highest field (τ 7.5) is assigned to the C_4 protons. This assignment shows that only a small downfield chemical shift

(circa 0.4 ppm) due to the bromine attached to an adjacent carbon atom, has occurred from the value assigned for the C₄ protons in the 2-phenylpyrrolines. The low-field triplet signal at τ 4.4-4.8 was obviously that from the proton attached to a carbon bearing the bromine atom. The chemical shift (2.7 ppm) of this resonance value from that of the C₃ proton (τ 7.1) in the pyrrolines (90)-(92) was consistent with that expected by the substitution of bromine into the five membered ring at the 3-position.* The signal for the C₅ protons (τ 5.6-6.0) again showed only a small downfield chemical shift (circa 0.3 ppm) from that of the parent 2-phenylpyrrolines. The position of substitution is thereby established as being at the 3-position in the pyrroline ring rather than at the alternative 5-position. Compounds (93)-(95) are therefore 3-bromo-2-phenyl-pyrrolines.

The bromination of 2-methoxypyrrolines with N-bromosuccinimide to give the 3-bromo-derivatives has recently been reported.¹³⁵

*Cyclopentane protons resonate at τ 8.49. The methine proton in an acyclic chain $\begin{smallmatrix} R \\ | \\ R \end{smallmatrix} \text{CH-Br}$, resonates at τ 5.97.⁹¹ Additional chemical shift due to ring strain in a five membered ring is -0.25.⁹² The expected position of resonance of the methine proton in bromocyclopentane would be τ 5.72 and the chemical shift due to bromine substitution in a five membered ring therefore 2.77 ppm.

v) Dehydrobromination of 3-bromo-2-phenylpyrrolines.

Secondary alkyl halides, where a β hydrogen is present, may on treatment with a base undergo competing nucleophilic substitution and elimination reactions to give mixtures of products. Elimination is favoured over substitution by increasing the temperature, whether the mechanism of the reaction is E_1/S_N1 or E_2/S_N2 .⁹⁰

When 3-bromo-2-phenylpyrroline (93) was heated at 100°C. with methanolic NaOH, dehydrobromination occurred with the formation of 2-phenylpyrrole (96), identified by its melting point,³⁵ n.m.r. spectrum⁴⁵ and mass spectrum (M^+ 143). The same reaction at room temperature, when elimination became less favoured over substitution gave a mixture of 2-phenylpyrrole and 3-methoxy-2-phenylpyrroline (97), whose structure was established spectroscopically.

The molecular ion peak (M^+ 175) in the mass spectrum of (97) suggested a molecular formula of $C_{11}H_{13}NO$. This was further supported by the elemental analysis of a picrate derivative for $C_{17}H_{16}N_4O_8$. The ultraviolet spectrum exhibited λ_{max} 242 m μ ., while no absorption corresponding to the presence of an amine group was observed in the infrared spectrum. The n.m.r. spectrum showed a peak at τ 6.76 (s, 3) due to the methoxy group. Other signals at τ 5.15 (m, 1), 6.05 (m, 2) and 8.0 (m, 2) were assigned to the pyrroline ring protons attached to C_3 , C_5 and C_4 respectively on the basis of their chemical

shift in an analogous fashion to the method used for the bromopyrrolines. The downfield chemical shift for the C₃ methine proton from the resonance values for the C₃ protons of pyrrolines (90)-(92) was 2.0 ppm., while the chemical shifts for the C₄ and C₅ protons were in comparison very small as expected. The shift in the C₃ proton value approximates to the shielding contribution quoted for shifts caused by a methoxy group on a methine proton in an acyclic chain (2.36 ppm).⁹¹ This establishes compound (97) as 3-methoxy-2-phenylpyrroline arising from a nucleophilic displacement of bromide by a methoxide ion.

3-Bromo-2-(5'-bromo- or 5'-chloro-2'-methoxyphenyl)-pyrrolines (94) and (95) when treated with methanolic NaOH at 100°C. underwent the expected elimination to give the pyrroles (98) and (99). These products although stable at temperatures below 0°C, rapidly decomposed at normal room temperature.

(93) X=Y=H

(96) X=Y=H

(97) X=Y=H

(94) X=OCH₃, Y=Br

(98) X=OCH₃, Y=Br

(95) X=OCH₃, Y=Cl

(99) X=OCH₃, Y=Cl

The Syntheses of 2-Phenylpyrroles by 1,3 Dipolar
Cycloaddition.

A possible alternative route to 2-phenylpyrroles involved the syntheses of unstable 2-phenyl- Δ^2 -oxazolin-5-ones as intermediates. These it was believed, would react as azomethine ylids, in 1,3 dipolar additions with acetylenic diesters to give 2-phenylpyrrole-3,4-diester. o-Anisic acid, 5-bromo, 5-chloro-, 3,5-dibromo- and 3,5-dichlorosalicylic acids were selected as suitable readily available starting materials, which would lead to a variety of halogenated O-methylpseudilin analogues.

1) The preparation of substituted hippuric acids.

The initial step in this synthetic route required protection of the phenolic group of the halogenated salicylic acids by methylation. 5-Chloro-, 3,5-dibromo- and 3,5-dichlorosalicylic acids were methylated using dimethyl sulphate and aqueous sodium hydroxide, but yields of the corresponding methyl 2-methoxybenzoates (101)-(103) were only fair.⁹⁴ The use of the modified procedure of Bickoff *et al*⁹⁵ in which methylation is carried out with dimethyl sulphate and potassium carbonate in acetone, led to greatly improved yields of the required esters (100), (102) and (103). Alkaline hydrolysis of the methyl esters gave the halogenated 2-methoxybenzoic acids (104)-(107).

The benzoic acids (104)-(108) were converted to their acid chlorides by the action of thionyl chloride. Condensation of these benzoyl chlorides with sodium glycinate by the Schotten-Baumann procedure⁹³ gave substituted hippuric acids (110)-(114). The reaction of benzoyl chloride with the sodium salt of alanine gave N-benzoylalanine (115). The hippuric acids were purified from unreacted benzoic acids by fractional recrystallisation. All the hippuric acids prepared showed characteristic absorption in their infrared spectra, N-H stretch 3400-3450, acid carbonyl 1720-1740, amide carbonyl 1620-1630 cm^{-1} . The melting points of known compounds were consistent with the literature values, while the new compounds prepared gave satisfactory elemental analyses. Methoxybenzoylglycine (110) was found to recrystallise from aqueous solvents as a monohydrate. All the mass spectra showed molecular ion peaks consistent with the expected masses.

- (109) $R=R'=X=Y=H$
 (110) $R=OCH_3$ $R'=X=Y=H$
 (111) $R=OCH_3$ $X=Y=Br$ $R'=H$
 (112) $R=OCH_3$ $X=Y=Cl$ $R'=H$
 (113) $R=OCH_3$ $X=R'=H$ $Y=Br$
 (114) $R=OCH_3$ $X=R'=H$ $Y=Cl$
 (115) $R=X=Y=H$ $R'=CH_3$

(ii) The syntheses of 2-phenyl- Δ^2 -oxazolin-5-ones.

The Erlenmeyer azlactone synthesis in which an aromatic aldehyde is condensed with hippuric acid in the presence of acetic anhydride, has been known for many years.⁹⁶ It has been suggested that this reaction involves the prior conversion of hippuric acid to 2-phenyl- Δ^2 -oxazolin-5-one, but that this intermediate is unstable and isolable only with difficulty.⁹⁷ Mohr prepared 4-methyl-2-phenyl- Δ^2 -oxazolin-5-one from N-benzoylalanine by the use of acetic anhydride as the cyclising agent.⁹⁸ Several groups of workers have demonstrated that 2-phenyl- Δ^2 -oxazolin-5-one itself, although readily hydrolysed on exposure to moist air, may be isolated after preparation in the presence of perchloric acid results in the formation of more stable perchlorate salts.¹⁰⁰

Greco et al¹⁰¹ sought to prepare 1-methyl-2-phenyl-oxazolin-5-one from N-benzoylsarcosine using dicyclohexylcarbodiimide, but obtained a dimeric product arising as a result of acylation at the 4-position of the ring. During the present investigation it was found that the use of dicyclohexylcarbodiimide and hippuric acid or N-benzoyl alanine result in increased yields of the 2-phenyloxazolin-5-ones (116) and (117)¹⁴⁸ over the previous methods of preparation with acetic anhydride.^{98,99} The mechanism of this reaction probably involves the initial formation of an acylated intermediate, which

undergoes an internal cyclisation of the tautomeric imidol species via a six-centered transition state. Development of a tetrahedral intermediate during carbonyl substitution would assist in the formation of the planar cyclic transition state and subsequent C-O bond cleavage would generate the Δ^2 -oxazolin-5-one and dicyclohexylurea.

Samples of (116) were prepared by both methods and shown to be identical from their infrared spectra. Other previously unreported substituted 2-phenyl- Δ^2 -oxazolin-5-ones (118) and (119) were synthesised by this method and identified by their infrared and mass spectra, but not fully characterised due to their unstable nature. All of the oxazolin-5-ones prepared showed a characteristic carbonyl band at $1810-1820\text{ cm}^{-1}$ in their infrared spectra.

(116) $R=R'=X=Y=H$

(117) $R=X=Y=H$ $R'=CH_3$

(118) $R=OCH_3$ $X=Y=Br$ $R'=H$

(119) $R=OCH_3$ $X=Y=Cl$ $R'=H$

iii) 1,3 Dipolar cycloadditions of acetylenic diesters with 2-phenyl- Δ^2 -oxazolin-5-ones.

The behaviour of aromatic or aliphatic 2,4-disubstituted oxazolin-5-ones (39) in 1,3 dipolar cycloaddition reactions with acetylenic esters to give 2,5-disubstituted pyrroles (41) has been extensively studied by Huisgen and co-workers. Some attention has also been given to the analogous reaction with 2,3-disubstituted mesionic oxazolin-5-ones (50) which gives N-substituted pyrroles (51). The literature pertaining to

these reactions has been reviewed in the introduction.(p.16). In contrast there appears to be no documentation of the action of acetylenic diesters on oxazolin-5-ones substituted only at the 2-position (116). Were these to undergo a similar dipolar addition to the more highly substituted oxazolin-5-ones, this would offer an attractive route from 2-phenyl- Δ^2 -oxazolin-5-ones to 2-phenylpyrrole-3,4-diester, cleavage of whose ester groups would give 2-phenylpyrroles.

From his studies Huisgen⁵¹ has shown that alkyl-oxazolin-5-ones, which are unstable and difficult to purify may be generated and used in situ without prior isolation to give pyrroles. The reaction of diethyl acetylene dicarboxylate with several 2-phenyl- Δ^2 -oxazolin-5-ones generated and used in situ was investigated, as well as the comparable reactions with isolated oxazolin-5-ones.

Pyrrole-3',4'-diesters <u>2'-Substituent</u>	Yield	
	<u>From Oxazolin</u> <u>5-one</u>	<u>In situ prep.</u>
Phenyl (120)	33	41
3,5-Dibromo-2-methoxyphenyl (123)	19	14
3,5-Dichloro-2-methoxyphenyl (124)	-	34
5-Bromo-2-methoxyphenyl (125)	-	33
5-Chloro-2-methoxyphenyl (126)	-	53
2-Methoxyphenyl (121)	-	56
Phenyl-4'-methyl (122)	82	-

The yields of pyrroles obtained indicate that neither of the methods of preparation is obviously superior. In comparison with the results of Huisgen⁵¹ the yields of pyrroles from 2-phenyl- Δ^2 -oxazolin-5-ones were lower than those from the 2,4-disubstituted oxazolin-5-ones. The yields of 4-methyl-2-phenylpyrrole esters, dimethyl (71%)⁵¹ and diethyl (122) (82%), suggest that this difference is not attributable to differences in the dipolarophiles employed. Disubstitution of the 4-position of the oxazolin-5-one would preclude the formation of an azomethine ylid. Consistent with this expectation the oxazolin-5-one from α -benzoylamido-isobutyric acid (170) was found to be "stable" to dimethyl acetylenedicarboxylate.⁵² In contrast the absence of any substitution at the 4-position might be expected to result in an azomethine ylid (40) from a 2-substituted oxazolin-5-one, ($R'=H$), having decreased stability over one derived from a 2,4-disubstituted "parent", resulting in a more transient species less available to undergo cycloaddition. The major byproduct formed from the reactions were the corresponding benzoic acids arising as a result of hydrolytic cleavage of the oxazolin-5-ones.

iv) Bromination of 2-phenylpyrrole-3,4-diester.

The halogenation of pyrrole systems in the presence of sufficient reagent leads to substitution of all the vacant ring positions. Dhont and Wibaut¹⁰² treated 1-phenylpyrroles, substituted in either the phenyl or pyrrole rings by a nitro group, with bromine in acetic acid and isolated the respective tetra or tribromo derivatives formed as a result of complete substitution in the pyrrole ring. The bromination of 1-benzylpyrrole with 1 mole. of bromine in CCl_4 gave a mixture of products with varying degrees of bromine substitution.¹⁰³ Hodge and Rickards¹⁰⁴ have investigated the halogenation of methyl pyrrole-2-carboxylate with bromine and a number of chlorinating agents. Using bromine in acetic acid (1 mole.) they obtained a mixture of 4-, 5-monobromo and 4,5-dibromopyrrole esters. With 2 moles of reagent the major product was the 4,5-dibromopyrrole ester, while the use of 3 moles gave exclusively the tribromopyrrole substituted at all vacant ring positions. The swamping catalytic effect of AlCl_3 has been used to control selective bromination in the 4-position of 2-formylpyrroles¹⁰⁵. The use of N-halosuccinimides in buffered dioxan is reported to halogenate 1-phenylpyrrole only at the α -positions.³¹ Methyl pyrrole-3-carboxylate gives the 5-monobromo product with dioxan dibromide, while treatment with bromine in CCl_4 gives the tribromopyrrole.¹⁰⁶

The pyrrole derivatives prepared by 1,3 dipolar cycloaddition in this investigation were unsubstituted only at the 5-position. Treatment of 2-phenylpyrrole-3,4-diester (120) with bromine in CHCl_3 gave the corresponding 5-bromoderivative (127), with no substitution occurring in the phenyl ring. In contrast treatment of the methoxyphenylpyrrole-3,4-diester (121) with 1 mole of bromine in CHCl_3 gave, what was shown by n.m.r. to be a mixture of products. These behaved as a single spot on thin layer silica gel in a number of solvent systems and could not be resolved by fractional crystallisation. The use of a quantity of bromine in excess of a 2 mole. ratio gave a dibromo compound (128). Substitution had occurred at the 5-position of the pyrrole ring as expected and the n.m.r. spectrum showed that under the activating influence of the methoxy group bromination had also occurred in the phenyl ring at the para position to this group. Bromination of the pyrrole-3,4-diester (125) resulted only in substitution at the 5-position of the pyrrole ring without further substitution in the phenyl ring, to give the dibromo compound (128), identical spectroscopically and by mixed melting point with the product obtained from dibromination of 2-methoxyphenylpyrrole-3,4-diester (121). Similarly the dibromopyrrole (123) underwent bromination in the vacant position of the pyrrole ring to give a tribromopyrrole-3,4-diester (129).

- (120) $R=X=Y=Z=H$
- (121) $R=OCH_3 \quad X=Y=Z=H$
- (122) $R=X=Y=H \quad Z=CH_3$
- (123) $R=OCH_3 \quad X=Y=Br \quad Z=H$
- (124) $R=OCH_3 \quad X=Y=Cl \quad Z=H$
- (125) $R=OCH_3 \quad Y=Br \quad X=Z=H$
- (126) $R=OCH_3 \quad Y=Cl \quad X=Z=H$
- (127) $R=X=Y=H \quad Z=Br$
- (128) $R=OCH_3 \quad X=H \quad Y=Z=Br$
- (129) $R=OCH_3 \quad X=Y=Z=Br$
- (130) $R=X=Y=H \quad Z=Cl$
- (131) $R=OCH_3 \quad X=Y=H \quad Z=Cl$
- (132) $R=OCH_3 \quad X=H \quad Y=Z=Cl$
- (133) $R=OCH_3 \quad X=Y=Z=Cl$

v) Chlorination of 2-phenylpyrrole-3,4-diesters.

The chlorination of pyrrole with sulphuryl chloride gives in the presence of sufficient reagent a pentachloropyrrolenine (134), which is hydrolysable to dichloromaleimide (135).¹⁰⁷ The chlorination of methyl 1-phenylpyrrole-2-carboxylate with chlorine in acetic acid gave a mixture of mono-, di and trichlorinated products, while the use of excess chlorine over that required to substitute all positions of the pyrrole ring led to "overchlorination" and the isolation of a trichlorinated pyrroline ester (136).¹⁰⁸ Hodge and Rickards¹⁰⁴ showed that while chlorine in acetic acid or sulphuryl chloride in 1 molar ratios gave mixtures of chlorinated products

with methyl pyrrole-2-carboxylate, t-butyl hypochlorite gave the 5-chloro compound as the major product. The use of 2 molar ratios of chlorine in acetic acid and t-butyl hypochlorite gave predominantly the 4,5- and 3,5-dichloro esters respectively, while sulphuryl chloride again gave a non-specific chlorination leading to a mixture of products. Recent work has shown that 1-phenylpyrroles readily "overchlorinate" to give dichloromaleimides or more highly chlorinated pyrrolidones.¹⁰⁹

A number of the 2-phenylpyrrole-diester previously prepared were chlorinated using sulphuryl chloride. Yields of the desired chlorinated products were usually lower than those obtained in the analogous brominations due to the reduced specificity of the chlorinating agent resulting in "overchlorination" of the pyrrole ring to give mixtures of byproducts.

(134)

(135)

(136)

The treatment of 2-phenylpyrrole-3,4-diester (120) with sulphuryl chloride in CHCl_3 gave as the major product the 5-chloro substituted pyrrole (130). In contrast to the bromination of the 2'-methoxyphenylpyrrole-diester (121), the chlorination with 1 mole of reagent, although resulting in a mixture of products gave the 5-chloropyrrole (131), which was readily separable by thin layer chromatography. Attempts to chlorinate the 5'-position of the phenyl ring by the use of a 2 mole ratio of either chlorine in acetic acid or sulphuryl chloride did not result in the isolation of any of the desired product (132). Attack of the second mole of chlorinating agent took place preferentially at the pyrrole ring rather than the phenyl ring to give as the major product a compound which on the spectral evidence was assigned the structure (137).

The n.m.r. spectrum of (137) showed the presence of 4 aromatic protons resonating as a multiplet (τ 2.2-3.3), as well as multiplets for the ethyl groups of the esters at τ 5.65 (4 protons) and τ 8.7 (6 protons). The protons of the methoxy group resonated as a singlet at τ 6.2. A signal corresponding to the presence of a proton attached to nitrogen was not observed. The infrared spectrum, while showing three carbonyl absorption bands at 1750, 1730 and 1670 cm^{-1} , also exhibited a band at 1600 cm^{-1} consistent with the presence of a C=N bond.

The region above 3000 cm^{-1} was conspicuously void of any absorption. Mass spectrometry gave molecular ion peaks at m/e 401:403:405 in isotopic abundance ratios in agreement with the presence of two chlorine atoms and a molecular formula $C_{17}H_{17}NO_6Cl_2$. This molecular formula and spectral data may best be accommodated by the proposed structure (137).

(137)

The chloropyrrole-diesters (124) and (126) underwent substitution at the 5-position of the pyrrole ring on treatment with 1 mole of sulphuryl chloride to give the dichloro- and trichloropyrrole-diester (132) and (133).

vi) Spectral correlations of Diethyl 2-phenyl-pyrrole-3,4-dicarboxylate and its analogues.

Examination of the spectral data for the 2-phenyl-pyrrole-3,4-diester (120)-(133) indicates that differing substitution of the parent nucleus results in characteristic absorption bands in both the infrared and ultraviolet spectra. The infrared spectra of all diesters determined in carbon tetrachloride show absorption bands at 3475 cm^{-1} (N-H) and $1710\text{--}1720\text{ cm}^{-1}$ (C=O). The lowering of the latter absorption frequency from that more normally associated with ester carbonyl groups is ascribed to the contribution of hybrid species conjugated with the pyrrole ring nucleus.

In contrast the spectra recorded in nujol show lowering of both the N-H and carbonyl absorption bands, with the latter in some cases appearing as two bands. This may be due to a number of contributing factors, hydrogen bonding, different conjugated hybrid species or steric interaction between ester groups which would be strongest for groups on adjacent positions of the ring and hence lead to differentiation of the ester groups resulting in

distinct absorption bands. Eisner and Erskine have cautioned the use of solid state spectra in the identification of pyrroles, since they report that similarly structured compounds did not give consistent results.¹⁴⁴ The infrared and ultraviolet spectral data appears in Appendix Table 1 (p 184).

Diethyl 2-phenylpyrrole-3,4-dicarboxylate (120) and its 5-methyl analogue (122) show only single carbonyl absorption bands at 1685 cm^{-1} , while the dimethyl ester (148) shows bands at both 1720 and 1680 cm^{-1} . Substitution of a halogen function in the 5-position of the pyrrole ring, (127) and (130), also results in the appearance of two bands at ~ 1725 and 1680 cm^{-1} . Ethyl esters with a methoxy-group substituted at the 2'-position of the phenyl ring (121), including those also bearing a 5'-halogen substituent, (125) and (126), show a single band at 1710 cm^{-1} , while the dimethyl 2-(2'-methoxyphenyl)-pyrrole diesters (149) exhibits carbonyl absorption bands at both 1725 and 1685 cm^{-1} . All of the other diesters examined, whether 5,5'-dihalogen, 3',5'-dihalogen or 3',5',5-trihalogen substituted showed two bands in the ranges $1710\text{--}1720$ and $1675\text{--}1690\text{ cm}^{-1}$.

The ultraviolet spectra of ethyl 2-phenylpyrrole-5-carboxylate⁵ and dimethyl 2-phenylpyrrole-4,5-dicarboxylate⁵⁰ are reported in the literature and are shown in Appendix table 2 (p 185) together with methyl 2-phenylpyrrole-4-carboxylate (147) and the dimethyl 2-phenylpyrrole-3,4-

diesters (148) and (149). While 2-phenylpyrrole itself has $\lambda_{\max}$ 287 m μ (4.04),¹⁴⁵ the substitution of an ester group into the 5-position of the pyrrole ring results in a bathochromic shift of 20 m μ with an increase in the extinction coefficient value. In contrast substitution at the 4-position by an ester group (147) results in a chromophore showing reduced conjugation having $\lambda_{\max}$ 278 (4.20). While 3-substituted pyrroles absorb at wavelengths 15-20 m μ shorter than the 2-derivatives, the absorption of the 4-ester below 2-phenylpyrrole itself appears to be somewhat anomalous. The spectrum of the 4,5-diester contains bands at $\lambda_{\max}$ 276 (4.37) and 306 (4.41) m μ , closely approximating the existence of separate non-interacting chromophores, as well as an additional band at $\lambda_{\max}$ 296 m μ (4.4). The presence of the second ester group of the 3,4-diester, however does not appear to result in any change in the chromophore over that of the 4-ester, [$\lambda_{\max}$ 278 (4.11)], apart from a decrease in the value of the extinction coefficient, which may be due to displacement of the second ester group from coplanarity. Substitution of the 5-position of 2-phenylpyrrole-3,4-diester by a methyl group (122), consistent with the observation in other pyrrole systems, results in a bathochromic shift of 6 m μ and enhancement of the extinction coefficient. The presence of a halogen substituent, however at the 5-position does not result

in any significant change either in the position of the maximum or the extinction coefficient. 2'-Methoxy substitution in the phenyl ring (121), while leading to a slight shift to shorter wavelength $\lambda_{\max}$ 274 m μ (4.09), also results in a second absorption maximum at 293 m μ (4.02). This second band shows a bathochromic shift of 11 m μ when a halogen substituent is also present in the 5-position of the phenyl ring, (125) and (126). Again further halogen substitution at the 5-position of the pyrrole ring, (128) and (132), results in only small reductions in the value of the extinction coefficient. The presence of 3',5'-dihalogen substitution in the phenyl ring in addition to the 2'-methoxy group results in a single absorption maximum at $\lambda_{\max}$ 283 m μ (~4.0).

While no direct correlation of these results is possible with definitive structure, a combination of the infrared and ultraviolet spectra serves as a partial indication of the substitution pattern present. (Table 1 p.184)

The n.m.r. spectra of diethyl 2-phenylpyrrole-3,4-dicarboxylates and its analogues clearly show the non-equivalence of the two ester groups. Equivalent ester groups would be expected to show similar chemical shifts resulting in superimposable triplet and quartet signals for the methyl and methylene protons respectively, for example diethyl pyrrole-3,4-dicarboxylate.¹³⁶ Differences in the chemical shifts of the methyl and methylene protons

from each ester group result in composite spectral patterns. The coupling constant ($J=6.8$ cps) between the methyl and methylene protons for each group is the same, however when $\delta_{3,4}$ methyl* is less than J ($\delta_{3,4}$ methyl < 6.8 cps) the resulting signal appears as six-lines due to two non-superimposed triplets. (Spectrum 3). When $\delta_{3,4}$ methyl $\approx J$ the methyl signals appear as four slightly broadened lines, a result of two partially superimposed triplets displaced by a chemical shift equal to the coupling constant. (Spectrum 4). In the case of the methylene protons the value $\delta_{3,4}$ methylene[†] always lies between $J > \delta_{3,4}$ methylene > 0 , so that in the resulting spectral patterns when $\delta_{3,4}$ methylene $= 0$ the signal consists of two superimposed quartets, while when $\delta_{3,4}$ methylene $< J$, the resultant signal appears as eight lines. (Spectrum 5). No examples of $\delta_{3,4} = J$, which would result in a pattern of five lines, by partial overlap of two quartets, were observed. The n.m.r. results are tabulated in the Appendix Table 3, (p 186) however no simple correlation between the chemical shift of the methyl and methylene protons of the ester groups with the nature and pattern of the substituents has been possible.

* $\delta_{3,4}$ methyl is defined as the difference in chemical shift between the methyl groups of the ester substituents at positions 3 and 4 of the pyrrole ring.

† $\delta_{3,4}$ methylene defined, similarly as above, represents the difference in chemical shift between the methylene protons of each ester group.

Spectrum 5

500 400 300 200 100 0 Hz
900 800 700 600 500 400 300 200 100 0 Hz

Spectrum 6

The mass spectrometry of pyrrole-3,4-diesters has been discussed by Groves et al¹³⁶. Due to the non-symmetry of the 2-phenylpyrrole-3,4-diesters they exhibit some distinctive features in their fragmentation pathways. The mass spectral fragmentation of the parent compound closely resembles that reported by Groves and is shown in scheme 1.

Scheme I. Possible Fragmentation Pathways in the mass spectrum of Diethyl 2-phenylpyrrole-3,4-dicarboxylate, and 5-halogenated analogues.

An initial loss of an ethoxy group leads to a peak at $(M-45)^+$, which further expels a molecule of ethylene from the second ester group to form ions at $(M-73)^+$. The resultant ion then eliminates a molecule of water to give further fragments at $(M-91)^+$ followed by loss of CO to give $(M-119)^+$ ions. This pathway is clearly established by the accompanying metastable peaks for the transitions. The presence of a halogen substituent at the 5-position of the pyrrole ring, (127) and (130) does not markedly influence this breakdown and the elimination of the halogen substituent is not observed as an important step in the pathway. In contrast substitution of this position by a methyl group (122), which is able to donate a proton by transfer to the adjacent ester group, a process known to occur in other pyrrole systems¹⁴⁶, results in the elimination of a molecule of ethanol from the 4-ester group to give an ion $(M-46)^+$. This is then followed by elimination of the alkyl portion of the second ester group either as C_2H_5 or C_2H_4 to give ions $(M-74)^+$ or $(M-75)^+$. Further major fragmentation routes are outlined in scheme 11.

The presence of a methoxy group at the 2'-position of the phenyl ring allows for the elimination of methanol from the ion $(M-73)^+$ to give $(M-105)^+$ ion as an alternative to the loss of H_2O . This is then followed by the loss

of HCN to give an ion $(M-132)^+$. These pathways appear to be common to all 2'-methoxyphenyl diesters, whether or not further substituted by halogens in the 5' or 3',5'-positions of the phenyl ring. Again the loss of halogen does not seem to be an important initial fragmentation route. (scheme III). The presence of several halogen atoms as well as leading to distinctive isotopic abundance patterns for the ion peaks, results in a large number of ion fragments.

Scheme II. Main fragments in mass spectrum of Diethyl 5-methyl 2-phenylpyrrole-3,4-dicarboxylate.

Scheme III. Fragmentation Pathways observed in the Mass Spectra of Diethyl 2-(2'-methoxyphenyl)pyrrole-3,4 dicarboxylates.

The result of substitution by several halogen atoms make the assignment of low mass ion peaks unreliable. While doubly charged ions which arise from odd mass species occur between whole mass units and are readily recognised, similar ions arising from species with an even mass number will appear at half the mass of their parent, i.e. M^{2+} appears at $\frac{1}{2} M/e$ for M^+ , and may not be readily distinguished from other fragments by low resolution mass spectrometry. As a consequence the assignment of further fragmentations are unreliable, but the initial pathways serve to give distinctive patterns for these classes of compounds. The results are tabulated in the Appendix Tables 4 and 5 (pp 187-189).

vii) The hydrolysis of 2-phenylpyrrole-3,4-diester.

The hydrolysis of pyrrole esters to the corresponding carboxylic acids may be readily carried out under either basic or acidic conditions. In compounds where two ester substituents are present in the pyrrole ring, adjustment of the hydrolysis conditions may be used to effect selective hydrolysis of α -substituted ester groups over those in the β -position, or vice versa.¹¹⁰

In this study hydrolyses of ester groups occupying 3,4- or β -positions in the pyrrole ring were required. Huisgen and coworkers⁵² hydrolysed dimethyl 2-methyl-5-phenylpyrrole-3,4-dicarboxylate by refluxing with 30% ethanolic KOH solution to a "diacid", prior to decarboxylation to 2-methyl-5-phenylpyrrole. Anderson¹³⁶ et al have shown that under controlled basic conditions using one equivalent of alkali, dimethyl pyrrole-3,4-dicarboxylate may be hydrolysed to the half-ester, methyl pyrrole-3-carboxylate-4-carboxylic acid.

The saponification of diethyl 2-phenylpyrrole-3,4-dicarboxylate (120), by refluxing with an excess of 6% ethanolic KOH for 4 hours gave a mixture of two acids (138) and (139), which were separable by column chromatography on silica gel. The faster running component on thin layer silica gel showed the expected infrared absorption at 3375 cm^{-1} (pyrrole N-H), 2600 cm^{-1} (acidic OH)

and 1645 cm^{-1} (acid carbonyl). A molecular ion peak at m/e 187 in the mass spectrum suggested that this compound was a mono-carboxylic acid and this was confirmed by elemental analysis. A small bathochromic shift (279 to 287 m μ) was observed in the ultraviolet spectrum on the addition of alkali, but there was no noticeable increase in the value of the extinction coefficient. Of the two possible isomeric structures, the acid was established as 2-phenylpyrrole-4-carboxylic acid (138) by methylation with diazomethane to the methyl ester (147) and subsequent assignment of the substitution on the basis of n.m.r. spectral data. The spectrum of this methyl ester (in d_6 -DMSO) showed two pyrrole protons resonating as quartets at τ 2.49 and 3.1, with coupling constants $J_{AB}=1.4$, $J_{AX}=2.8$ and $J_{BX}=3.0$ cps, which on addition of D_2O collapsed to two doublets, $J_{AB}=1.4$ (Spectrum 9). In other pyrrole systems the coupling constants for $J_{1,3}$, $J_{1,4}$ and $J_{1,5}$ usually have values of between 2.5-3.0 cps., while $J_{3,5}=1.4-1.7$ cps. and $J_{4,5}=2.5-3.0$ cps. 45,92,106. As a result of these values in which $J_{1,3}=J_{1,4}=J_{1,5}=J_{4,5}$, the signals from the C-4 and C-5 protons of pyrroles having substitution at the 2 and 3 positions may appear as triplets. (Spectrum 7). In contrast, in pyrroles with substitution at the 2 and 4 positions, in which the magnitude of $J_{3,5}$ is only

approximately half that of $J_{1,3}$ or $J_{1,5}$, the resultant splitting patterns of the C_3 and C_5 proton signals appear as quartets. (Spectrum 8). On this basis the coupling constants and splitting patterns are consistent with the proton assignment to the 3 and 5 positions, thus establishing the parent acid as the 4-isomer (138).

- (138) $R=R'=X=Y=Z=H$ $R''=COOH$
 (139) $R=X=Y=Z=H$ $R'=R''=COOH$
 (140) $R=X=Y=Z=H$ $R'=COOH$ $R''=COOC_2H_5$
 (141) $R=X=Y=H$ $Z=Br$ $R',R''=COOH, COOC_2H_5$
 (142) $R=X=Y=H$ $Z=Cl$ $R',R''=COOH, COOC_2H_5$
 (143) $R=OCH_3$ $X=Y=Z=H$ $R'=R''=COOH$
 (144) $R=OCH_3$ $X=Y=Br$ $Z=H$ $R'=R''=COOH$
 (145) $R=OCH_3$ $Y=Z=Br$ $X=H$ $R',R''=COOH, COOC_2H_5$
 (146) $R=OCH_3$ $X=Y=Cl$ $Z=H$ $R'=R''=COOH$
 (147) $R=R'=X=Y=Z=H$ $R''=COOCH_3$
 (148) $R=X=Y=Z=H$ $R'=R''=COOCH_3$
 (149) $R=OCH_3$ $X=Y=Z=H$ $R'=R''=COOCH_3$
 (150) $R=OCH_3$ $X=Y=Z=H$ $R'=COOCH_3$ $R''=COOH$
 (151) $R=OCH_3$ $R''=X=Y=Z=H$ $R'=COOCH_3$
 (161) $R=R'=X=Y=Z=H$ $R''=COOC_2H_5$

Spectrum 7

Spectrum 8

D₂O exchange

Spectrum 9: N.m.r. Spectrum of Methyl 2-Phenylpyrrole-4-carboxylate aromatic and pyrrole protons.

Kondo and Suzuki⁴³ have previously prepared the isomeric 2-phenylpyrrole-3-carboxylic acid, whose reported melting point (192-193°C.) differed from that of the compound (138) now prepared (dec. 170°C).

The more polar diacid (139) in addition to the expected infrared spectral features, also exhibited by acid (138), showed a second carbonyl absorption band at 1695 cm^{-1} . Its ultraviolet spectrum showed only a small bathochromic shift (283 to 286 m μ .) on the addition of alkali, but a marked increase in the value of the extinction coefficient was observed. The mass spectrum, when recorded at sufficiently low temperatures showed a small molecular ion peak at m/e 231, with the base peak at m/e 187. Failure to operate at low enough temperature led to a spectrum with no peaks above m/e 187, giving the erroneous impression that this compound was also a mono-carboxylic acid. No satisfactory elemental analysis was obtained, but the structure was established as the dicarboxylic acid (139) by methylation with diazomethane to the dimethyl ester (148). This diester was fully characterised both spectroscopically and by elemental analysis. The presence of a single pyrrole proton resonating in the n.m.r. spectrum as a singlet at τ 2.84 confirmed the 3,4-diester substitution and hence the structure of the original 2-phenylpyrrole-3,4-dicarboxylic acid (139).

It was found that this diacid underwent a slow spontaneous decarboxylation to the mono-acid (138) on standing even at room temperature.

The hydrolysis of diethyl 2-phenylpyrrole-3,4-dicarboxylate (120) with concentrated sulphuric acid at 60°C, conditions known to hydrolyse β -carboxylic acids¹¹¹, gave a mixture of acidic products, which were separable by thin layer chromatography. The faster running component was shown by comparison of its infrared spectrum to be identical with the mono-acid (138) previously prepared. The more polar component (140) showed infrared absorption bands at 3300 and 2650 cm^{-1} as well as double carbonyl absorption at 1710 and 1620 cm^{-1} . The ultra-violet spectrum did not show a bathochromic shift in alkali and had only a small increase in the extinction coefficient value. The mass spectrum showed a molecular ion peak at m/e 259, which was consistent with the structure of the half-ester (140). The position of the ester and acid group were not rigorously established, but the presence of the pyrrole-4-carboxylic acid among the reaction products suggests that the half-ester with 3-acid-4-ester substitution might undergo decarboxylation prior to hydrolysis of the second ester group to give the observed mono-acid. The presence of the ethyl pyrrole-4-carboxylate (161), which might be expected to appear in the neutral extracts to substantiate this mechanism

under these conditions, was not confirmed.

Treatment of pyrrole esters by concentrated sulphuric acid at a temperature of 100°C . is known to result in decarbalkoxylation as well as hydrolysis.¹³⁷ Concentrated phosphoric acid at 80°C . has been proposed as a preferable alternative reagent, since the incidence of polymerisation as a side reaction is reduced under these conditions.¹³⁸ From a reaction mixture of concentrated phosphoric acid and the pyrrole-diester (120) we isolated 2-phenylpyrrole (96) and ethyl 2-phenylpyrrole-4-carboxylate (161), as well as the products previously observed by treatment with sulphuric acid. This again suggests that either the 3-ester group was undergoing hydrolysis and subsequent decarboxylation before attack on the ester group at the 4-position, or that preferential decarbalkoxylation was occurring at the 3-position.

The structure of the ethyl ester (161) was again assigned on the basis of its n.m.r. spectrum. The observed coupling constants between pyrrole protons and pyrrolic N-H were identical with those previously observed for the methyl ester (147), consequently the compound was assigned in an analogous fashion as being ethyl phenyl pyrrole-4-carboxylate.

The 5-bromo- and 5-chloropyrrole-3,4-diester (127) and (130) when refluxed with NaOH in aqueous ethanol gave the half esters (141) and (142). These products showed characteristic infrared absorption at circa 3200, 2650, 1680 and 1620 cm^{-1} . The ultraviolet spectra in alkali showed a marked shift (280 to 316 m μ .) from the absorption maxima observed in acidic media, with the appearance of an additional peak at 250 m μ . The mass spectra showed molecular ion peaks at m/e 337:339 and 293:295, with the expected isotopic abundance patterns associated with a mono-bromo and mono-chloro compound respectively. This together with elemental analyses supported the assignment of these compounds as half esters. Diethyl 2-(5'-bromo-2'-methoxyphenyl)-5-bromopyrrole-dicarboxylate (128) underwent a similar alkaline hydrolysis to give a half ester (145), with similar infrared and ultraviolet spectral characteristics to compounds (141) and (142). Mass spectrometry and elemental analysis were again consistent with the assigned structure. The positions of the acid and ester groups in these compounds were not conclusively established, nor whether these might not be mixtures of the two possible isomers. Hodge and Rickards¹⁰⁴ have shown that the acidity of the pyrrole imino proton in methyl-4,5-dichloropyrrole-2-carboxylate is markedly increased over that of the

unhalogenated pyrrole, with the result that base-catalysed hydrolysis of the chloro-ester is slower than that of the unsubstituted ester. It is suggested that the presence of a 5-halo substituent in the half esters (141), (142) and (145), renders the pyrrole imino protons sufficiently acidic to hinder further hydrolysis to diacids.

2-Phenylpyrrole-diesters (121), (123) and (124), substituted in the 2'-position of the phenyl ring by a methoxy group gave on alkaline hydrolysis the diacids (143) (144) and (146) respectively. The infrared spectra were again characteristic within this group of compounds, showing absorption bands at circa 3350, 2550 cm^{-1} and two acid carbonyl bands at 1680 and 1640 cm^{-1} . The ultra-violet spectra showed absorption maxima at 280 m μ ., which shifted to 301 m μ . in alkali, with a substantial increase in the value of the extinction coefficients. The highest peak in the mass spectrum of the 2-methoxyphenyl-diacid (143) occurred at m/e 217 indicating a mono-carboxylic acid. Partial methylation with diazomethane however gave a mixture of the dimethyl ester (149) and the methyl half ester (150). These two compounds were fully characterised both spectroscopically and by elemental analyses and hence (143) is established as a diacid.

The mass spectra of the dihalo-2'-methoxyphenyl-pyrrole acids (144) and (146) showed molecular ion peaks at 417:419:421 and 329:331:333, consistent with the

molecular weights for the diacids. None of the three diacids however gave a satisfactory elemental analysis.

vii) The decarboxylation of 2-phenylpyrrole carboxylic acids.

The decarboxylation of pyrrole carboxylic acids has been effected by a number of means. The most commonly employed method has been to heat the acid, suspended in a suitable high boiling solvent, e.g. glycerol¹¹² or glymes, at a sufficiently high temperature for decarboxylation to occur. An increase in the number of electron withdrawing groups substituted in the pyrrole ring leads to an increase in the temperature required for decarboxylation. Hence the pyrrole acid (154) undergoes decarboxylation at a lower temperature than the acid (155) in which a methyl group has been replaced by an ester group.¹¹³ Comparison of a pair of isomeric α and β substituted pyrrole carboxylic acids (155) and (156) showed that the α -carboxylic acid decarboxylated at a lower temperature than its β -isomer.¹¹⁴

(154)

(155)

(156)

Corwin and Straughn¹¹⁵ have shown that pyrrole acids, substituted at two or more of the other ring positions by electron withdrawing groups, may not undergo decarboxylation even at high temperatures. Under these circumstances, it has been found possible to effect decarboxylation by treatment with bromine in acetic acid. Displacement of the carboxyl group gives a bromopyrrole, which may be hydrogenated to an unsubstituted pyrrole.¹¹⁶ Iodine has been employed in a similar fashion for the decarboxylation of pyrrole acids.^{117,118} This is a simpler procedure than the Hunsdieker reaction, whereby silver carboxylates are degraded, with the elimination of carbon dioxide, to organic halides.¹¹⁹ A previous attempt to form silver salts from halogenated pyrrole carboxylic acids led to extensive degradation of material.

The mixture of 2-phenylpyrrole carboxylic acids (138) and (139), obtained from the alkaline hydrolysis of the pyrrole-diester (120), was heated in glycerol at 250°C. The product, which sublimed out, was identical with a sample of 2-phenylpyrrole (96) prepared by the route previously discussed.

When 2-(2'-methoxyphenyl)pyrrole-dicarboxylic acid (143) was heated in digel at 220°C, 2-(2'-methoxyphenyl)pyrrole (152) was obtained in low yield. Also, heating the crude mixture of pyrrole acid (143) and half ester (150), obtained as the bicarbonate soluble fraction

from the incomplete methylation of the diacid (143) with diazomethane, gave a mixture of the pyrrole ester (151) and the pyrrole (152). A route to O-methylpseudilin is hereby established.

The structure of the ester (151) was established by n.m.r. spectroscopy. The pyrrole protons resonated as triplets centred at τ 3.3 and 3.6. This suggested that the protons were on adjacent ring positions, i.e. 4 and 5, with the ester group present at the 3-position of the pyrrole ring and that $J_{1,2} = J_{2,3} = J_{4,5}$. The assignment was consistent with the observation that in other 2,3-disubstituted pyrroles, the pyrrole protons resonated as triplets, due to approximately equal coupling constants of the N-H with the other ring protons,⁴⁵ while in contrast the pyrrole protons of methyl 2-phenylpyrrole-4-carboxylate (147) appeared as quartets. It follows from the assignment of (151) as methyl 2-(2-methoxyphenyl)pyrrole-3-carboxylate, that the half-ester (150) from which it was derived by decarboxylation must be methyl 2-(2'-methoxyphenyl)pyrrole-3-carboxylate-4-carboxylic acid.

2-(3',5'-Dibromo-2'-methoxyphenyl)pyrrole-diacid (144) was decarboxylated by heating at 250 C. in digol, to give a low yield of 2-(3,5-dibromo-2-methoxyphenyl)pyrrole (35), identified by its mass spectrum m/e 329:331:333 (50:100:52% M^+). The n.m.r. spectrum showed a singlet at τ 6.26 for the three protons of the methoxy group, while the pyrrole protons resonated as multiplets

at τ 3.22, 3.52 and 3.8. The two aromatic protons resonated as doublets at τ 2.46 and 2.65. The ultraviolet spectrum showed an absorption maximum at 301 m μ . These spectra were identical with those of a sample of material prepared by other means.²¹

The 2-(3',5'-dichloro-2'-methoxyphenyl)pyrrole-diacid (146) underwent decarboxylation at a lower temperature than its bromo analogue in the presence of powdered soda glass and 1 equivalent of alkali. Heating the mixture at 170 C. in digel gave the dichloropyrrole (153) with spectral characteristics similar to those of the dibromo analogue (35). Also obtained in low yield as a side product from the reaction was 2-(3',5'-dichloro-2'-hydroxyphenyl)pyrrole (162), formed by displacement of the ether group by hydroxyl.

(35) X=Y=Br

(152) X=Y=H

(98) X=H Y=Br

(153) X=Y=Cl

(99) X=H Y=Cl

O-Methylpseudilin has been prepared together with several bromo and chloro analogues bearing substituents in the phenyl ring, by two different routes. Halogenation of pyrrole rings unsubstituted by electron withdrawing groups usually give mixtures of products. In an attempt

2 3

OF/DE

to obtain analogues, which were selectively halogenated in the pyrrole ring, the-decarboxylations of the 5-bromopyrrole half esters (141) and (145) were investigated. On heating in glycerol at 200°C. degradation of the starting materials occurred, but none of the desired bromopyrrole esters could be isolated.

ix) Halogenation of some O-methylpseudilins.

O-Methylpseudilin (152) and its 5'-bromo- (98) and 5'-chloro- (99) analogues were found to be unstable, undergoing autoxidation in a photocatalysed reaction. In contrast the presence of the second halogen atom in the phenyl ring of compounds (35) and (153) resulted in greatly increased stability. With the hope of producing a more stable system and since it had not been found possible to prepare compounds selectively halogenated in the pyrrole ring by other means, attempts were made to halogenate the pyrrole rings of 5'-bromo- (98) and 5'-chloro- O-methylpseudilins (99) directly.

Benzoylpyrroles have been selectively chlorinated in the pyrrole ring to give mono and dichlorinated pyrroles, related to the pyoluteorin antibiotics (12).^{15,16,24} Cyclopropyl 2-pyrrolyl-ketone on treatment with bromine in ethanol gave di and tribromopyrrolyl derivatives.¹²⁰ In the absence of a suitable electron withdrawing group selective halogenation of the pyrrole ring is difficult

to control. Hannessian and Kaltenbronn²¹ brominated dibromo-0-methylpseudilin (35) to obtain the pentabromo-0-methylpseudilin (154), substituted at all the pyrrole ring positions, which was then readily converted by demethylation with boron trichloride to a product identical with a sample of the naturally occurring antibiotic (13).

Treatment of 2-(5'-chloro-2'-methoxyphenyl)-pyrrole (99) with 3 moles of sulphuryl chloride gave 2-(5'-chloro-2'-methoxyphenyl)-3,4,5-trichloropyrrole (155). Bromination of 2-(5'-bromo-2'-methoxyphenyl)-pyrrole (98) gave the tetrabromo compound (156).

(154) R=CH ₃ X=Y=Br	(160) R=CH ₃ X=Y=Cl
(155) R=CH ₃ X=H Y=Cl	(163) R=X=H Y=Cl
(156) R=CH ₃ X=Y=Cl	(164) R=H X=Y=Cl

Similarly chlorination of 2-(3',5'-dichloro-2'-methoxyphenyl)pyrrole (153) using three moles of sulphuryl chloride gave the pentachloropyrrole (160).

In view of the low stability of 0-methylpseudilin (152) and its 5'-bromo and 5'-chloro analogues no attempt was made to demethylate these compounds to phenolic pseudilins, which it was anticipated might show further instability. Demethylation of the more stable tetrachloro-0-methylpseudilin (155) with boron trichloride gave

tetrachloropseudilin (163), which was however, also found to be unstable at room temperature.

The pentachloro-0-methylpseudilin (160) on demethylation gave 3',5',3,4,5-pentachloropseudilin (164), the chloro analogue of the natural product. The presence of a second halogen atom in the phenyl ring resulted in greatly increased stability over the tetrachloropseudilin (163) and this observation was consistent with the increase in stability with increased halogen substitution previously noted with 2-(5'-chloro-2'-methoxyphenyl)-pyrrole (99) and 2-(3',5'-dichloro-2'-methoxyphenyl)-pyrrole (153).

x) Oxidation of halogenated pyrroles.

Pyrroles are known to undergo oxidation by a photochemical process in the presence of air.¹²² The 2,5 addition of oxygen gives oxides, which are further converted to maleimide derivatives.¹²¹ Wasserman et al have investigated the photo-oxidation of 2,3,4,5-tetra-phenylpyrrole, isolating products in which cleavage of the 2-3 bond of the pyrrole ring had occurred following oxygen addition.¹³⁹ Lightner and co-workers have shown that alkylpyrroles on photo-oxidation generate a number of 2,5-oxygenated¹⁴⁰ as well as 2,3-oxygenated products.¹⁴¹ Tetra-alkylpyrroles are also reported to

undergo 2-3 bond cleavage to amido-ene-ones.¹⁴²

In this context of pyrrole oxidation it is of interest to note that Murphy and Williams¹⁴³ have shown that the in vivo biological inactivation of the 3-phenylpyrrole antibiotic, pyrrolnitrin also occurs with the formation of maleimides and other metabolites oxygenated at the 2- and 5- ring positions.

The tetrabromopyrrole (156) slowly decomposed on standing to give the aryl keto-ene-amide (158). The mechanism of this reaction would appear to involve an initial autoxidation to give the bridged 2,5-oxide, which on debromination yields an intermediate hydroxy- Δ^3 -pyrrolin-5-one and this undergoes ring opening to the acyclic product (158) by a 1-2 bond cleavage, rather than the 2-3 bond cleavage observed in other systems.

Some aspects of the oxidation, which occurs by the use of excess chlorinating agent over that required to substitute all vacant positions in the pyrrole ring of several systems have already been mentioned (p.50)¹⁰⁷⁻¹⁰⁹ in the context of the formation of the "overchlorinated" Δ^3 -pyrrolin-5-one, which was assigned the structure of the ethyl ether of (157). The mass spectra of (158) and (159) showed molecular ion peaks at m/e 439:441:443:445 and 467:469:471:474 respectively, with isotopic ratio abundance patterns consistent with the presence of three

bromine atoms. The infrared spectrum of (158) showed absorption at 3450 cm^{-1} and double carbonyl bands at 1725 (ketone) and 1695 cm^{-1} (amide). The infrared spectrum of (159) showed only a single carbonyl absorption at 1710 cm^{-1} , while its n.m.r. spectrum showed peaks at τ 6.6 and 8.8 consistent with the presence of an ethyl group. On the basis of these spectral characteristics the compounds were assigned the structures (157) and (158).

The formation of the ether (159) lends support to the proposed mechanism, via a hydroxypyrrolin-5-one intermediate for the decomposition of the bromopyrrole (156) to the aryl keto-amide (158). The dichloro-methoxyphenylpyrrole (153) on treatment with sulphuryl chloride in excess of three moles also gave an oxygenated product, which on the basis of its mass spectrum and infrared spectrum was assigned the structure of an aryl keto-amide (165), a chloro analogue of (158).

xi) The Spectra of 2-phenyl and 2-(2'-methoxyphenyl)-pyrroles.

The infrared spectra of 2-phenylpyrrole and its 2'-methoxy and halogenated derivatives all show absorption bands in the range $3450 - 3500 \text{ cm}^{-1}$ even when recorded in nujol. The absence of any significant lowering in the N-H absorption bands suggest that no intermolecular or intramolecular hydrogen bonding occurs between the pyrrole N-H and the lone pairs of electrons on the methoxy group oxygen even in the solid phase.

The ultraviolet spectra of a series of poly-halogenated 2-(2'-methoxyphenyl)pyrroles show distinct absorption bands with respect to their substitution patterns. (see Appendix Table 6). 2-Phenylpyrrole (96) itself shows $\lambda_{\text{max}} 287 \text{ m}\mu^{145}$, while the substitution of a 2'-methoxy substituent into the phenyl ring (152) results in a complex spectrum with maxima at 230, 284 and 306 $\text{m}\mu$. A further 5'-halogen substituent (98) and (99) results in a bathochromic shift of each of these bands to 241, 290 and 318 $\text{m}\mu$. Substitution of halogen atoms into the pyrrole ring, to give a tetrahalogen compound (155) and (156) results in a simplification of the spectra into two absorption bands at similar wavelengths to the two longer wavelength bands of the unhalogenated 2-(2'-methoxyphenyl)pyrrole (152). The presence of a

second halogen atom in the phenyl ring giving a 2'-(2',5'-dihalogen-2'-methoxyphenyl)pyrrole results in two low intensity bands at 242 and 248 m μ and a third band at 300 m μ . Further halogen substitution in the pyrrole ring, 3',5',3,4,5-pentachloro compound (160), shows a simplified spectrum, with a single absorption band at λ_{max} 288, which resembles that of 2-phenylpyrrole.

The 3',5'-dichlorophenols (162) and (164) show spectra which resemble apart from a small bathochromic shift, the corresponding methoxy compounds (99) and (155), substituted only by a single chlorine atom at the 5'-position of the phenyl ring, i.e. (162) shows a similar spectrum to (99) and (164) to (155). They show a marked bathochromic shift on the addition of alkali.

The mass spectrum of 2-phenylpyrrole closely resembles that of 1-phenylpyrrole, in which a 1 $\rightarrow$ 2 phenyl migration has been postulated as an initial step¹⁰⁸ in the fragmentation process. Loss of HCN, (M-27)⁺ and subsequent proton loss or the reverse processes give a peak at m/e 115, (M-28)⁺. An alternative fragmentation, which also gives rise to ions of this mass is a loss of C₂H₄ from the molecular ion. These fragmentations are supported by the presence of metastable peaks and are outlined in Scheme IV.

Scheme IV The Mass Spectral fragmentation pathways of 2-phenylpyrrole.

In contrast the main fragmentation pathway of 2-(2'-methoxy-phenyl)pyrrole (152) involves the loss of the ether group

in two steps as a methyl radical, $(M-15)^+$ followed by carbon monoxide to peaks at $(M-43)^+$. Subsequent loss of HCN leads to a peak at $(M-70)^+$. The mass spectra of a number of halogenated 2-(2'-methoxyphenyl)pyrroles have been analysed and a generalised fragmentation pathway involving halogen loss is outlined in Scheme (V).

When X and $2X$ are substituted in the pyrrole ring

From Dihalogen Substituted compounds.

Scheme V The Main Mass Spectral fragmentation pathways in Halogenated 2-(2'-methoxyphenyl)pyrroles.

The major fragmentations are again supported by metastable peaks, which are detailed in Appendix Table 7. The spectra of polyhalogenated compounds show complex isotopic abundance patterns with approximate intensities corresponding to the statistically expected distribution patterns¹⁴⁷, however overlap of series of isotopic peaks from different fragmentation processes may lead to abundance intensity patterns which appear to deviate from those predicted. Again the overlap of series of isotopic peaks together with the presence of doubly charged species from higher mass fragments, which are not readily discernable, make unreliable the assignment of breakdown pathways to the large numbers of ions at lower mass numbers.

xii) Microbiological activities of 2-benzoyl and phenyl-polychlorinated pyrroles.

The antimicrobial spectrum of pentachloropseudilin appears to compare favourably with other chlorinated 2-benzoylpyrroles. The results of biological testing are summarised in Appendix table 8 (p. 192), in which the activity of pentachloropseudilin is compared with pyoluteorin (12) and several synthetic deoxypyoluteorins (166)-(168)²⁴ as well as denitro-pyrrolnitrin (169).²⁷

Pentachloropseudilin appears to be particularly active against the Gram ⁺ve bacteria Staph aureus and species of fungi (Tricophyton). The sensitivity to autoxidation of other chloropseudilins (162) and (163), with reduced substitution in either the phenyl or pyrrole rings, precluded their biological evaluation and potential utility.

Summary

In an effort to devise viable routes to the less accessible 2-phenylpyrroles, two new syntheses have been developed.

- (i) The first route represents a simple new pyrrole synthesis from pyrrolidines. para-Halogenated anisoles were converted to 2-phenylpyrrolines via cyclopropyl aryl ketones and pyrrolidines by literature methods. 2-Phenylpyrrolines on treatment with N-bromosuccinimide give the previously unreported 3-Bromo-2-phenylpyrrolines, which on dehydrobromination with base gave pyrroles.

A number of mono and tetrahalogenated O-methyl-pseudilines, 2-(2'-methoxyphenyl)pyrroles, have been prepared and characterised. They are light sensitive and unstable at room temperature.

- (ii) The use of oxazolin-5-ones substituted only at the 2-position in 1,3 dipolar addition with substituted acetylenes offers a previously undeveloped route to less substituted pyrroles otherwise difficult to obtain. 2-Phenyl-oxazoline-5-ones and diethyl acetylene dicarboxylate gave pyrrole-3,4 diesters. These were hydrolysed and decarboxylated to produce 2-substituted pyrroles.

This route has been exploited to prepare 2-(3,5'-dibromo-2'-methoxyphenyl)pyrrole, an intermediate

in a previous synthesis of the antibiotic pentabromopseudilin and hence represents a new formal synthesis of this compound.

Pentachloropseudilin, the chloro analogue of the naturally occurring antibiotic has also been prepared by this route. 2,5-Oxygenated products were produced by the treatment 2-phenylpyrrole with "excess" halogenating agent.

The microbiological evaluation of pentachloropseudilin compares favourably with those of halogenated 2-benzoylpyrroles (Deoxypvoluteorins). Other chloropseudilins with reduced substitution in the phenyl or pyrrole rings were prepared but were not sufficiently stable to permit evaluation.

EXPERIMENTAL

General Experimental Details

Infrared Spectra.

Infrared spectra were recorded on a Unicam S.P. 200 and Perkin-Elmer 237 spectrophotometers. Unless otherwise stated the spectra were run as nujol mulls.

Ultraviolet Spectra.

Ultraviolet spectra were recorded on a Unicam S.P. 800 spectrophotometer, using 1 cm cells and refer to solutions in ethanol.

Nuclear Magnetic Resonance Spectra.

Spectra were recorded using a Jeol C-60HL and Varian Associates T-60 spectrometers. Unless otherwise specified in the text, deuteriochloroform, containing tetramethylsilane (τ 10) as an internal standard was used as solvent.

All signals are singlets, unless otherwise stated, when the following abbreviations are applied: d = doublet, t = triplet, q = quartet and m = unresolved multiplet. These appear in brackets together with integration analysis for each signal following the value for the chemical shift.

Mass Spectra.

Mass spectra were measured with an A.E.I. MS12 mass spectrometer, at an electron beam energy of 70 eV,

by direct insertion probe at temperatures below the melting point of the compound. Percentage abundance relative to the base peak (100%) are reported in brackets after the m/e values.

Melting Points.

Melting points were determined on a Koffler hot stage apparatus and are uncorrected.

Elemental Analyses.

Elemental analyses were carried out by Pascher and Pascher, Bonn, Germany, and A. B. Gygli, Toronto.

Chromatography.

Preparative thin layer chromatography was carried out using 1 mm thick plates of Kieselgel HF 254 (Fluka). Detection of bands was by shortwave u.v. light.

Column chromatography was performed on Silica gel (Grace), mesh size 60-200.

γ -Chloropropyl Phenyl Ketone (66).

Anhydrous aluminum chloride (26 g., 0.2 moles) was suspended in 50 ml of ice cold CS_2 . A mixture of benzene (15 g., 0.19 moles) and γ -chlorobutyryl chloride (23.5 g., 0.16 moles) was added dropwise with vigorous stirring over half an hour at 0°C . The soluble complex which formed was stirred for an additional 3 hrs., during which time the temperature of the mixture was allowed to rise to room temperature. CS_2 was removed under reduced pressure and the residual oil poured onto crushed ice. Extraction with ether, drying over MgSO_4 and evaporation gave 29 g. (95%) of crude liquid chloroketone (66).

B.pt. 113°C (2 mm.)

Infrared (liquid film): ν_{max} 1680 (carbonyl), 1600, 1580, 1450, 1225, 740, 680 cm^{-1} .

Nuclear magnetic resonance: τ 2.55 (m, 2), 3.0 (m, 3), 6.8 (t, 2, $J=6\text{cps}$), 7.4 (t, 2, $J=6\text{cps}$), 8.3 (quint., 2).

Mass spectrometry: m/e 182:184 (6:2% M^+), 146 (7.5%), 120 (13%), 105 (100%), 77 (45%), 51 (18%). ($T = 30^\circ\text{C}$).

Cyclopropyl Phenyl Ketone (67).

23 g. of ketone (66) were dissolved in 75 mls of 10% KOH in methanol and allowed to react over half an hour with occasional shaking. The methanol was removed under reduced pressure, the residue taken up in ether

and washed with water. After drying over MgSO_4 , evaporation of the ether gave 20 g. of a pale amber liquid. Fractional distillation of the crude product gave 13.1 g. (71%) of ketone (67). B.pt. 86°C . (1 mm.), $n_D^{20} = 1.5535$. Mariella and Raube¹²³ reported b.pt. 102°C . (7 mm.), $n_D^{20} = 1.5514$. Infrared (liquid film): ν_{max} 1670 (carbonyl), 1600, 1580, 1450, 1380, 1225, 990, 705 cm^{-1} . Nuclear magnetic resonance: τ 2.05 (m, 2), 2.55 (m, 3), 7.35 (m, 1), 8.95 (m, 4). Mass spectrometry: m/e 146 (40% M^+), 105 (100%), 77 (35%). (T = 35°C).

γ -Chloropropyl 5-Bromo-2-methoxy-phenyl Ketone (68).

Anhydrous aluminum chloride (9 g., 0.068 moles) was dissolved in 20 ml of ice cold nitrobenzene. A mixture of p-bromoanisole (10 g., 0.054 moles) and γ -chlorobutyryl chloride (8.3 g., 0.059 moles) was added dropwise with vigorous stirring over $\frac{3}{4}$ hr. while the temperature was maintained below 10°C . Further stirring of the mixture was continued for 3 hrs., during which time the temperature of the mixture was allowed to rise to room temperature. The mixture was poured onto crushed ice and the nitrobenzene removed by steam distillation. Extraction with ether, drying over MgSO_4 and evaporation gave 14.7 g. of crude product. Chromatography on silica

gel gave a fraction eluted with benzene/ether (80/20%) which yielded 7 g. (45%) of the ketone (68) as an oil.

Infrared (liquid film): $\nu_{\max}$ 1680 (carbonyl), 1590, 1480, 1400, 1270, 1180, 1030, 860 cm^{-1} .

Nuclear magnetic resonance: τ 2.26 (d, 1, $J_{4,6}=3\text{cps}$), 2.55 (q, 1, $J_{3,4}=9\text{cps}$, $J_{4,6}=3\text{cps}$), 3.25 (d, 1, $J_{3,4}=9\text{cps}$), 6.1 (s, 3), 6.4 (t, 2, $J=6\text{cps}$), 6.93 (t, 2, $J=6\text{cps}$), 7.9 (quint, 2, $J=6\text{cps}$).

Mass spectrometry: m/e 290:292:294 (7:9:2% M^+), 254:256 (1:1%), 228:230 (8:8%), 213:215 (98:100%), 198:200 (5:5%), 170:172 (25:24%), 155:157 (16:17%), 134 (10%), 63 (72%), 62:64 (22:7%), 41 (60%). ($T = 65^\circ\text{C}$).
Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{BrClO}_2$: C, 45.3; H, 4.2; Br, 27.4; Cl, 12.2.

Found: C, 45.4; H, 4.2; Br, 27.0; Cl, 11.4.

γ -Chloropropyl 5-Bromo-2-hydroxy-phenyl Ketone (69).

A mixture of γ -chlorobutyryl chloride (6 g., 0.045 moles) and p-bromoanisole (7.5 g., 0.041 moles) was added to anhydrous aluminum chloride (7.5 g., 0.057 moles) in 15 ml of nitrobenzene as previously described for ketone (68). After stirring for 2 hrs. the mixture was heated on a water bath at 50°C for a further 2 hrs. The nitrobenzene was removed by distillation under vacuum. The residue was poured into water, extracted with ether, dried over MgSO_4 .

and evaporated to give 5.9 g. (51%) of crystalline Ketone (69). Recrystallisation from ethanol/water gave needles m.pt. 48-49°C., which gave a +ve ferric chloride test.

Infrared: $\nu_{\max}$ 1650, 1610, 1570, 1420, 1340, 1300, 1270, 1215, 1190, 1010, 850, 810 cm^{-1} .

Nuclear magnetic resonance: τ 2.23 (d, 1, $J_{4,6}=3\text{cps}$), 2.5 (q, 1, $J_{3,4}=9\text{cps}$, $J_{4,6}=3\text{cps}$), 3.16 (d, 1, $J_{3,4}=9\text{cps}$), 6.36 (t, 2, $J_{\beta,\gamma}=6\text{cps}$), 6.8 (t, 2, $J_{\alpha,\beta}=6\text{cps}$), 7.83 (quint., 2, $J_{\beta,\gamma}=J_{\alpha,\beta}=6\text{cps}$).

Mass spectrometry: m/e 276:278:280 (7:27:21%), 227:229 (16:16%), 214:216 (11:11%), 199:201 (100:97%), 171:173 (11:10%), 148 (26%), 143:145 (16:16%), 63 (46%), 53 (21%), 41 (23%). (T = 40°C).

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{BrClO}_2$: C, 43.3; H, 3.6; Br, 28.8; Cl, 12.8.

Found: C, 43.4; H, 3.6; Br, 29.1, Cl, 12.5.

5-Bromo-2-methoxy-phenyl Cyclopropyl Ketone (70).

Method A: 3 g. of ketone (68) were dissolved in 7.5 ml of 10% KOH in methanol and allowed to stand for half an hour with occasional shaking. The methanol was removed under reduced pressure, the residue taken up in ether and washed with water. After drying over MgSO_4 , evaporation

of the ether yielded 2.3 g. (88%) of the crystalline ketone (70). Recrystallisation from methanol gave colourless plates m.pt. 66-67°C., which gave no reaction with ferric chloride.

Infrared: $\nu_{\max}$ 1655, 1590, 1410, 1275, 1255, 1200, 1190, 1135, 1050, 1030, 1010, 880, 825 cm^{-1} .

Nuclear magnetic resonance: τ 2.45 (d, 1, $J_{4,6}=3\text{cps}$), 2.6 (q, 1, $J_{3,4}=9\text{cps}$, $J_{4,6}=3\text{cps}$), 2.9 (d, 1, $J_{3,4}=9\text{cps}$), 6.15 (s, 3), 7.36 (m, 1), 8.95 (m, 4).

Mass spectrometry: m/e 254:256 (54:54%), 226:228 (31:29%), 213:215 (100:100%), 198:200 (7:7%), 183:185 (5:5%), 170:172 (21:20%), 155:157 (16:16%), 113:115 (7:7%), 76 (19%), 75 (23%), 69 (43%), 63 (47%), 41 (46%). (T = 60°C).

Anal. Calcd for $\text{C}_{11}\text{H}_{11}\text{BrO}_2$: C, 51.8; H, 4.4; Br, 31.3.

Found: C, 51.9; H, 4.2; Br, 31.5.

Method B: A mixture of cyclopropyl carbonyl chloride (5.2 g., 0.05 moles) and bromoanisole (9.5 g., 0.05 moles) was added to anhydrous aluminum chloride (6.8 g., 0.05 moles) in 40 ml of nitrobenzene under conditions previously described for the preparation of ketone (68). After workup, chromatography on silica gel gave a fraction eluted with petroleum ether/ether (95/5%) which yielded 6.0 g. (47%) of a product identical, by t.l.c. and infrared with the ketone (70).

Method C: Anhydrous aluminum chloride (6.8 g.) was suspended in 25 ml of ethylene dichloride at 0°C. Cyclopropyl carbonyl chloride (5.2 g.) and p-bromoanisole (9.5 g.) were added and the mixture stirred for 3 hrs. After pouring onto crushed ice, ether extraction with drying over MgSO_4 , the solvents were evaporated under reduced pressure and the residue chromatographed as in method B to yield 5.6 g. (44%) of ketone (70).

Method D: A combination of procedures, essentially the same as those described for the ketones (68) and (70) by method A, was employed. Crude unchromatographed ketone (68) (~15 g.), prepared as previously described was dissolved in 10 ml of methanol and treated with 40 ml of 10% KOH in methanol. After half an hour the methanol was removed under reduced pressure and the residue extracted with ether and water. The ether extract was dried over MgSO_4 and evaporated. The resulting oil was chromatographed on silica gel using a benzene/ether mixture as the eluting system to yield the following fractions:

(i) eluted with ether/benzene (5/95%), 0.25 g. crystalline ketone (71).

(ii) eluted with ether/benzene (20/80%), 6.2 g. (45%) of ketone (70), identical by t.l.c., infrared and n.m.r. with previously prepared samples.

(iii) eluted with ether, 2.2 g. (16%) of crystalline product, (78).

(iv) eluted with ether as an oil, 0.4 g. (3%) of compound (79).

1-(ω -Hydroxyethyl)-2-(5'-bromo-2'-methoxyphenyl)-3-(5''-bromo-2''-methoxybenzoyl)cyclopentene. (78).

Isolated as fraction (iii) above. m. pt. 54-55°C.

Infrared: $\nu_{\max}$ 3500, 1650, 1595, 1400, 1250, 1020, 815 cm^{-1} .

Nuclear magnetic resonance: τ 2.9-3.75 (m, 6), 4.6 (t, 1, $J=7.5\text{cps}$), 5.6 (t, 2, $J=9\text{cps}$), 6.28 (s, 3), 6.5 (t, 2, $J=6\text{cps}$), 6.95 (t, 2, $J=9\text{cps}$), 7.9 (q, 2, $J=7.5\text{cps}$, $J=6\text{cps}$), 8.35 (s broad, 1).

Mass spectrometry: m/e 508:510:512 (15:30:16 M^+), 477:479:481 (12:22:10), 213:215 (100:100%).

Anal. Calcd. for $\text{C}_{22}\text{H}_{22}\text{Br}_2\text{O}_4$: C, 51.79; H, 4.35; Br, 31.33.

Found: C, 51.38; H, 4.33;

3-(5'-Bromo-2'-methoxybenzoyl)propanol (79).

Isolated as fraction (iv) above.

Infrared: $\nu_{\max}$ 3500, 1675, 1595, 1400, 1270, 1250, 1175 1030, 815 cm^{-1} .

Nuclear magnetic resonance: τ 2.35 (d, 1), 2.55 (q, 1), 3.22 (d, 1), 6.15 (s, 3), 6.27 (s, 1), 6.41 (t, 2), 7.03 (t, 2), ~~8.18~~ (quint., 2).

Mass spectrometry: m/e 272:274 (5:4% M^+), 255:257 (58:53%), 254:256 (34:38%), 228:230 (13:14%), 213:215 (100:95%),

212:214 (37:40%), 183:185 (19:19%), 170:172 (18:18%),
155:157 (21:21%), 135 (31%).

Anal. Calcd. for $C_{11}H_{13}BrO_2$: C, 51.4; H, 5.1, Br, 31.1.

This compound did not give satisfactory analysis.

The aqueous extract was acidified with conc. hydrochloric acid and extracted with ether. After washing with 5% $NaHCO_3$ solution and drying over $MgSO_4$, evaporation of the ether gave 0.8 g. of a product identical with that obtained from fraction (i).

Combination of these gave 1.05 g. (10%) of

5-bromo-2-hydroxyphenyl cyclopropyl ketone (71).

Recrystallisation from ethanol/water gave needles m.pt.

106-107°C, which gave a +ve ferric chloride test.

Infrared: ν_{max} 1635, 1605, 1475, 1405, 1280, 1180, 1055, 1000, 895, 840, 800 cm^{-1} .

Nuclear magnetic resonance: τ 1.9 (d, 1, $J_{4,6} = 3cps$), 2.43 (q, 1, $J_{3,4} = 9cps$, $J_{4,6} = 3cps$), 3.1 (d, 1 $J_{3,4} = 9cps$), 7.36 (m, 1,), 8.76 (m, 4).

Mass spectrometry: m/e 240:242 (100:100% M^+), 225:227 (26:25%), 211:213 (100:07%), 171:173 (15:15%), 161 (100%), 143:145 (18:18%), 115 (12%), 69 (36%), 63 (53%) 53 (24%), 41 (43%). (T=125°C).

Anal. Calcd. for $C_{10}H_9BrO_2$: C, 49.8; H, 3.8; Br, 33.2.

Found: C, 49.9; H, 3.6; Br, 33.2.

3-(5'-Bromo-2'-hydroxybenzoyl)propanol (80).

500 mg. of ketone (69) in 5 ml of methanol was treated with 2.5 ml of 0.1N NaOH solution. After 15 mins. at room temperature the solvent was removed and the residue extracted with ether and water. The ether extract was washed with dil. acid, concentrated and chromatographed on silica gel thin-layer plates using ether/hexane (50/50%) as solvent. A band at R_f 0.9 yielded 80 mg. (18%) of the phenolic ketone (71), while that at R_f 0.8 gave 250 mg. (50%) of unreacted starting material. The bottom band at R_f 0.2 gave 20 mg. (4%) of product (80), as an oil.

Infrared: $\nu_{\max}$ 3400, 1640, 1280, 1185, 1060, 835 cm^{-1} .

Nuclear magnetic resonance: 2.1 (d, 1), 2.45 (q, 1), 3.11 (d, 1), 6.1 (s, 1), 6.23 (t, 2), 6.86 (t, 2), 8.0 (quint., 2), 8.24 (s, 1).

Mass spectrometry: m/e 241:243 (95:90%), 240:242 (90:95%), 199:201 (100:95%). No molecular ion peak observed. This compound was not fully characterised by elemental analysis.

5-Chloro-2-methoxyphenyl Cyclopropyl Ketone (73).

Methods used are those previously described for the bromo-keto analogue (70).

Method B: A mixture of cyclopropyl carbonyl chloride (5.2 g., 0.05 moles) and p-chloroanisole (8 g., 0.055 moles) was added to anhydrous aluminum chloride (6.8 g.) in 40 ml

of nitrobenzene. After workup, 4.18 g. (40%) of ketone (73) was obtained. Recrystallisation from ethanol/water gave needles m.pt. 53-54°C.

Infrared: $\nu_{\max}$ 1655, 1595, 1410, 1270, 1200, 1185, 1130, 1045, 1030, 1015, 885, 825 cm^{-1} .

Nuclear magnetic resonance: τ 2.48 (d, 1, $J_{4,6}=3\text{cps}$), 2.65 (q, 1, $J_{3,4}=9\text{cps}$, $J_{4,6}=3\text{cps}$), 3.13 (d, 1, $J_{3,4}=9\text{cps}$), 6.1 (s, 3), 7.3 (m, 1) 8.85 (m, 4).

Mass spectrometry: m/e 210:212 (45:13% M^+), 182:184 (18:6%), 169:171 (100:29%), 154:156 (6:2%), 139:141 (6:2%), 126:128 (15:5%), 111:113 (14:5%), 75 (10%), 69 (18%), 63 (13%), 41 (19%). ($T=60^\circ\text{C}$).

Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{ClO}_2$: C, 62.9; H, 5.3; Cl, 16.9.

Found: C, 62.5; H, 5.2; Cl, 16.8.

Method C: A mixture of cyclopropyl carbonyl chloride (5.2 g.) and p-chloroanisole (7.1 g., 0.05 moles) was added to anhydrous aluminum chloride (6.8 g. in 25 ml of ethylene dichloride. Workup and chromatography yielded 5.86 g. (56%) of the ketone (73), identical by t.l.c., infrared and n.m.r. with previously prepared material.

Method D: A mixture of γ -chlorobutyryl chloride (10.5 g., 0.075 moles) and p-chloroanisole (11.75 g., 0.082 moles) was added to anhydrous aluminum chloride (10 g., 0.076 moles) in 75 ml of nitrobenzene. Workup gave a crude yield of the phenyl γ -chloropropyl ketone (10 g.).

Treatment of 6.26 g. of this mixture with 3 g. of KOH in 20 ml of methanol gave after workup and chromatography on silica gel using ether/petroleum ether as eluting solvents three fractions: (i) eluted with ether/petrol (2/98%), 170 mg. of ketone (74). (ii) eluted with ether/petrol (5/95%), 300 mg. of ketone (73). (iii) eluted with ether, product (75).

5-Chloro-2-hydroxyphenyl Cyclopropyl Ketone (74).

Isolated from fraction (i) above. Recrystallisation from ethanol/water, m.pt. 77-78°C., gave a +ve ferric chloride test.

Infrared: $\nu_{\max}$ 1630, 1600, 1470, 1395, 1340, 1275, 1235, 1175, 1050, 995, 895, 835, 790, 765 cm^{-1} .

Nuclear magnetic resonance: τ 2.11 (d, 1, $J_{4,6}=3\text{cps}$), 2.6 (q, 1, $J_{3,4}=9\text{cps}$, $J_{4,6}=3\text{cps}$), 3.1 (d, 1, $J_{3,4}=9\text{cps}$), 7.4 (m, 1), 8.8 (m, 4).

Mass spectrometry: m/e 196:198 (100:28% M^+), 181:183 (26:8%), 168:170 (20:7%), 161 (85%), 155:157 (100:30%), 99 (22%), 69 (24%), 63 (21%), 41 (27%). ($T=75^\circ\text{C}$).

Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{ClO}_2$: C, 61.1; H, 4.6; Cl, 18.0.

Found: C, 60.8; H, 4.5, Cl, 17.7.

1-(ω -Hydroxyethyl)-2-(5'-chloro-2'-methoxyphenyl)-3-(5''-chloro-2''-methoxybenzoyl)cyclopentene (75).

Isolated as fraction (iii) from method D above.

Recrystallised from ethanol/water, m.pt. 126-128°C.

Infrared: $\nu_{\max}$ 3750, 1645, 1490, 1470, 1405, 1235, 1025, 815 cm^{-1} .

Nuclear magnetic resonance: τ 2.98-3.72 (m, 6), 4.55 (t, 1, $J=7.5\text{cps}$), 5.56 (t, 2, $J=9\text{cps}$), 6.3 (s, 6), 6.53 (t, 2, $J=6\text{cps}$), 6.95 (t, 2, $J=9\text{cps}$), 7.98 (q, 2, $J=6\text{cps}$, $J=7.5\text{cps}$), 8.2 (s, exchanged by D_2O).

Mass spectrometry: m/e 420:422:424 (13:9:2 M^+), 389:391:393 (19:13:3), 374:376:378 (12:12:5), 169:171 (100:33), 155:157 (25:8), 126:128 (60:26), 111:113 (42:19), 115 (30), 77 (27), 75 (23), 63 (28), 51 (15), 43 (20), 41 (13). ($T=160^\circ\text{C}$).

Anal. Calcd. for $\text{C}_{22}\text{H}_{22}\text{Cl}_2\text{O}_4$: C, 62.9; H, 5.3; Cl, 16.9

Found: C, 62.9; H, 5.0; Cl, 16.7.

1-Formyl-2-phenylpyrrolidine (83).

1-Formyl-2-arylpyrrolidines were prepared according to the method of Breuer and Stein⁷³.

Cyclopropyl phenyl ketone (67) (13 g., 0.09 moles), formamide (24.5 g., 0.5 moles) and magnesium chloride (1.7 g., 0.02 moles) were refluxed for six hours under nitrogen at 180°C. Workup and subsequent distillation gave 7.1 g. (46%) of pyrrolidine (83). B.pt. 145°C.

(1 mm), n_D^{20} 1.5589. Breuer and Stein⁷³ b.pt. 160°C. (6 mm).
 Infrared: (liquid film), $\nu_{\max}$ 1670, 1385, 750, 695 cm^{-1} .
 Nuclear magnetic resonance: τ 1.63, 1.93 (2s, 1),
 2.73 (s, 5). 5.15 (t, 1, $J=6\text{cps}$), 6.35 (t, 2, $J=7\text{cps}$),
 7.5-8.5 (m, 4).
 Mass spectrometry: m/e 175 (100% M^+), 174 (70%), 147 (95%),
 146 (43%), 130 (34%), 118 (50%), 104 (55%), 98 (30%),
 91 (50%), 77 (27%), 51 (17%). ($T=50^\circ\text{C}$).

1-Formyl-2-(5'-bromo-2'-methoxyphenyl)pyrrolidine (84).

Cyclopropyl phenyl ketone (70) (3 g., 0.012 moles),
 formamide (4 g., 0.09 moles) and magnesium chloride
 (0.35 g., 0.002 moles) were heated together under con-
 ditions described above. Workup and subsequent
 chromatography on silica gel using benzene/ether as eluting
 solvents gave a fraction with 60% benzene/40% ether
 containing 2.2 g. (66%) of pyrrolidine (84).
 Recrystallisation from benzene/light petroleum gave
 m.pt. 89-91°C.

Infrared: $\nu_{\max}$ 1660, 1380, 1250, 1125, 1030 810 cm^{-1} .
 Nuclear magnetic resonance: τ 2.76, 2.0 (2s, 1), 2.6-
 3.4 (m, 3), 4.9 (m, 1), 6.13 (s, 3), 6.4 (t, 2, $J=6\text{cps}$),
 7.6-8.4 (m, 4).
 Mass spectrometry: m/e 283:285 (90:86% M^+), 252:254:256
 (34:100:70%), 226:228 (12:9%), 212:214 (15:11%), 204 (16%),
 176 (18%), 132 (16%), 118 (16%), 102 (15%), 98 (25%).

77 (14%), 70 (24%), 63 (15%), 41 (21%). (T=110°C).

Anal. Calcd. for $C_{12}H_{14}NBrO_2$: C, 50.7; H, 5.0; N, 4.9, Br, 28.1.

Found: C, 50.6; H, 4.9; N, 5.0; Br, 28.2.

1-Formyl-2-(5'-chloro-2'-methoxyphenyl)pyrrolidine (85).

Cyclopropyl phenyl ketone (73) (8.4 g., 0.04 moles), formamide (12.5 g., 0.27 moles) and magnesium chloride (1 g., 0.006 moles) heated together as previously described gave on workup 7.7 g of crude material. Chromatography on silica gel using ether/petroleum ether as the solvent gave a fraction eluted with 40% ether/60% petroleum ether which yielded 4.6 g. (48%) of pyrrolidine (85). Recrystallisation from benzene/petroleum ether gave m.pt. 81-83°C.

Infrared: $\nu_{\max}$ 1655, 1495, 1475, 1425, 1395, 1255, 1130, 1040, 825 cm^{-1} .

Nuclear magnetic resonance: τ 1.66, 1.92 (2s, 1), 2.7-3.35 (m, 3), 4.85 (m, 1), 6.15 (s, 3), 6.35 (t, 2), 7.5-8.3 (m, 4).

Mass spectrometry: m/e 239:241 (98:32% M^+), 208:210:212 (45:100:28%), 204 (14%), 182:184 (13:4%), 176 (11%), 168:170 (20:6%), 155:157 (15:4%), 125 (13%), 98 (21%), 77 (12%), 70 (22%), 41 (22%). (T=50°C).

Anal. Calcd. for $C_{12}H_{14}NClO_2$: C, 60.3; H, 5.9; N, 5.9; Cl, 14.8.

Found: C, 60.0, H, 5.9, N, 6.0; Cl, 14.6

2-Phenylpyrrolidine (86).

1 g. of 1-formyl-2-phenylpyrrolidine was refluxed with 7 ml of 10% dilute sulphuric acid for 2 hrs. Neutralisation of the solution with NaOH, saturation with sodium chloride and extraction with ether (5x50 ml), gave after drying over Na_2SO_4 and evaporation of the ether 775 mg. (88%) of pyrrolidine (86) as an oil. Picrate, m.pt. 150-151°C. Gabriel and Colman reported¹²⁴ m.pt. 148-149°C.

Infrared (liquid film): ν_{max} 3350, 1620, 1445, 1330, 1090, 1050, 760, 690 cm^{-1} .

Nuclear magnetic resonance: τ 2.76 (s, 5), 6.0 (broad m, 1), 6.95 (broad m, 2), 7.7-8.7 (m, 4).

mass spectrometry: m/e 146 (43 M^+), 145 (39%), 144 (25%), 119 (34%), 118 (100%), 117 (69%), 104 (20%), 91 (48%), 77 (22%), 70 (42%), 51 (16%), 41 (18%). (T=40°C).

2-(5'-Bromo-2'-methoxyphenyl)pyrrolidine (87).

2 g. of 1-formyl-2-arylpyrrolidine (84) was refluxed with 5 ml of 10% sulphuric acid for 2 hrs. Neutralisation with NaOH and extraction with ether, gave after drying over MgSO_4 and evaporation of the solvent, 1.5 g. (83%) of an oily product (87).

Infrared (liquid film): ν_{max} 3325, 2960, 1485, 1250, 1030, 805, 755 cm^{-1} .

Nuclear magnetic resonance: τ 2.41 (d, 1, $J_{4,6}=2-3\text{cps}$),
 2.83 (q, 1, $J_{3,4}=9\text{cps}$, $J_{4,6}=2-3\text{cps}$), 3.43 (d, 1, $J_{3,4}=9\text{cps}$),
 5.75 (broad t, 1), 6.26 (s, 3), 7.0 (broad m, 2), 7.7-
 9.1 (m, 4), 8.03 (s, 1).

Mass spectrometry: m/e 255:257 (70:63% M^+), 254:256
 (49:43%), 227:229 (72:65%), 226:228 (49:43%), 212:214
 (11:13%), 176 (63%), 148 (57%), 133 (15%), 118 (17%),
 70 (100%), 41 (26%). ($T=35^\circ\text{C}$),

Analysed as its picrate, recrystallised from benzene
 m.pt. 178-180°C.

Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_4\text{BrO}_8$: C, 42.1; H, 3.5; N, 11.6;
 Br, 16.5.

Found: C, 42.1; H, 3.5; N, 11.4;
 Br, 16.8.

2-(5'-Chloro-2'-methoxyphenyl)pyrrolidine (88).

4.35 g. of 1-formyl-2-arylprrrolidine (85) was
 refluxed with 25 ml of 10% sulphuric acid for 3 hrs.
 Workup as previously outlined gave 3.35 g. (80%) of the
 pyrrolidine (88) as an oil.

Infrared (liquid film): ν_{max} 3350, 2950, 1490, 1250,
 1035, 815 cm^{-1} .

Nuclear magnetic resonance: τ 2.66 (d, 1, $J_{4,6}=3\text{cps}$),
 2.98 (q, 1, $J_{3,4}=10\text{cps}$, $J_{4,6}=3\text{cps}$), 3.41 (d, 1, $J_{3,4}=10\text{cps}$),
 5.75 (t, 1, $J=9\text{cps}$), 6.26 (s, 3), 7.0 (m, 2), 7.8-8.7 (m, 4).

Mass spectrometry: m/e 211:213 (82:26% M^+), 210:212 (50:27%), 183:185 (100:31%), 182:184 (80:34%), 176 (36%), 168:170 (20:9%), 153:155 (22:12%), 152:154 (17:12%), 148 (58%), 141:143 (15:6%), 125:127 (16:7%), 77 (18%), 70 (94%), 41 (38%). ($T=60^\circ\text{C}$).

Analysed as the picrate, recrystallised from methanol m.pt. $163-165^\circ\text{C}$.

Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_4\text{ClO}_8$: C, 46.3; H, 3.9; N, 12.7; Cl, 8.1.

Found: C, 46.3; H, 4.0; N, 12.7;

Cl, 8.2.

2-Phenylpyrroline (90).

3 g. of 2-phenylpyrrolidine were dissolved in 50 ml of 2.5% aqueous acetic acid and the solution cooled in ice. 25 ml of 6% sodium hypochlorite solution were added dropwise and the solution stirred for 2 hrs. Extraction with ether, followed by evaporation yielded an oil, which was dissolved in 25 ml of ethanol and cooled below 20°C . 1.25 g. of KOH in 25 ml of ethanol was added dropwise and the solution stirred overnight. Evaporation of the ethanol under reduced pressure, followed by ether extraction of the residue gave after drying over MgSO_4 and evaporation of the solvent 2.1 g. (71%) of 2-phenylpyrroline as an oil.

Picrate, m.pt. 196°C . Gabriel and Colman reported m.pt. 198°C . recrystallised from ethanol.¹²⁵

Infrared (liquid film): $\nu_{\max}$ 1615, 1570, 1490, 1440, 1335, 1045, 1025, 860, 690 cm^{-1} .

Ultraviolet: $\lambda_{\max}$ 249 m μ .

Nuclear magnetic resonance: τ 2.26 (m, 2), 2.71 (m, 3), 6.03 (m, 2), 7.16 (m, 2), 8.1 (quint., 2).

Mass spectrometry: m/e 145 (50% M^+), 117 (100%), 104 (15%), 77 (20%). (T=140°C).

Method B: 1-Formyl-2-arylpyrrolidine (83) (2 g., 0.011 moles) was refluxed with N-bromosuccinimide (4.5 g., 0.025 moles) in 50 ml of 60% aqueous dioxan for 2 hrs. under nitrogen, during which time the yellow colour of the solution was discharged. The solvent was removed under reduced pressure and the residue taken up in ether, washed with saturated sodium bicarbonate solution, dried over MgSO_4 and evaporated to give an oil which was chromatographed on silica gel using mixtures of benzene/ether as the eluting solvents. The fraction eluted with benzene/ether (80/20%) yielded 288 mg. (17%) of an oil, identical by infrared, n.m.r. and t.l.c. with a sample of the pyrroline (90) prepared by method A.

Method C: 1-Formyl-2-arylpyrrolidine (83) (500 mg., 0.003 moles) was refluxed with N-bromosuccinimide (1 g., 0.006 moles) in 20 ml of CCl_4 plus 2 drops of 30%

hydrogen peroxide for 15 hrs. After workup as described under method B, the residual oil was chromatographed on silica gel thin layer plates using ether/hexane (65/35%) as the solvent. The product extracted from the band at R_f 0.3 was shown to be identical with a sample of the pyrroline (90). A band at R_f 0.4 yielded the bromo-phenylpyrroline (93) as the major product from the reaction.

Method D: 2-Phenylpyrrolidine (83) (294 mg., 0.002 moles) was stirred overnight with N-bromosuccinimide (360 mg., 0.002 moles) in 10 ml of methylene chloride. Evaporation of the solvent, followed by workup and chromatography as outlined under method C gave the same two products. The band at R_f 0.3 gave 131 mg. (45%) of the pyrroline (90), while the band at R_f 0.4 yielded 25 mg. (6%) of the bromo compound (93).

2-(5'-Bromo-2'-methoxyphenyl)pyrroline (91).

2.5 g. of the arylpyrrolidine (87) were dissolved in 100 ml of anhydrous ether and dry HCl bubbled through the solution until precipitation of the pyrrolidine hydrochloride salt (2.65 g.) was completed. 2.0 g. of the salt in 20 ml of water were treated with 13 ml of 6% sodium hypochlorite solution at 0°C. Ether extraction and evaporation gave an oil, which was taken up in 10 ml of ethanol. After cooling below 20°C., 0.65 g. of KOH in

20 ml of ethanol was added dropwise to the ethanolic solution and stirring continued overnight. Evaporation of the ethanol under reduced pressure, followed by extraction of the residue with ether gave after drying over MgSO_4 and evaporation of the solvent 830 mg. (48%) of the pyrroline (91). Recrystallised from light petroleum, m.pt. 84°C .

Infrared: ν_{max} 1605, 1485, 1410, 1270, 1180, 1140, 1030, 810, 790 cm^{-1} .

Ultraviolet: λ_{max} 242 m μ ., 305 m μ .

Nuclear magnetic resonance: τ 2.1 (d, 1, $J_{4,6}=3\text{cps}$), 2.7 (q, 1, $J_{3,4}=9\text{cps}$, $J_{4,6}=3\text{cps}$), 3.33 (d, 1, $J_{3,4}=9\text{cps}$), 6.18 (m, 2), 6.25 (s, 3), 7.13 (t, 2), 8.15 (quint., 2).

Mass spectrometry: m/e 253:255 (27:26% M^+), 252:254 (20:26%), 224:226 (41:32%), 225:227 (39:33%), 211:213 (21:15%), 197:199 (35:27%), 196:198 (25:27%), 118 (100%), 103 (26%), 102 (22%), 89 (34%), 77 (30%), 76 (27%), 75 (28%), 63 (38%), 51 (26%), 41 (28%). ($T=55^\circ\text{C}$).

Analysed as the picrate, recrystallised from ethanol m.pt. $177-179^\circ\text{C}$.

Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{N}_4\text{BrO}_8$: C, 42.3; H, 3.1; N, 11.6; Br, 16.5.

Found: C, 42.4; H, 3.1; N, 11.3;

Br, 16.6.

2-(5'-Chloro-2'-methoxyphenyl)pyrroline (92).

2.2 g. of the arylpyrrolidine (88) were converted to the hydrochloric salt as described for compound (91). The salt was dissolved in 25 ml of water and treated with 14 ml of 6% sodium hypochlorite solution at 0°C, stirring being continued for 2 hrs. Ether extraction followed by evaporation gave a crystalline solid, which was taken up in ethanol (20 ml) and cooled below 20°C. 0.65 g. of KOH in 20 ml of ethanol was added dropwise and the solution stirred overnight. Isolation of the product by the procedures previously outlined gave 1.9 g. (86%) of compound (92). Recrystallization from light petroleum m.pt. 51-52°C.

Infrared: $\nu_{\max}$ 1605, 1495, 1470, 1420, 1280, 1190, 1145, 1030 cm^{-1} .

Ultraviolet: $\lambda_{\max}$ 242 m μ ., 305 m μ ..

Nuclear magnetic resonance: τ 2.3 (d, 1, $J_{4,6}=3\text{cps}$), 2.76 (q, 1, $J_{3,4}=9\text{cps}$, $J_{4,6}=3\text{cps}$), 3.25 (d, 1, $J_{3,4}=9\text{cps}$), 6.08 (m, 2), 6.2 (s, 3), 7.05 (m, 2), 8.05 (quint., 2).

Mass spectrometry: m/e 209:211 (100:32% M^+), 208:210 (66:32%), 181:182 (71:22%), 180:182 (70:25%), 167:169 (32:9%), 153:155 (75:25%), 152:154 (55:27%), 125:127 (55:18%), 89 (20%), 75 (25%), 70 (24%), 63 (22%), 51 (24%), 41 (42%).

(T=65°C)

Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{NClO}$: C, 63.0; H, 5.8; N, 6.7; Cl, 16.9.

Found : C, 63.3; H, 6.0; N, 6.3;

Cl, 16.6.

Picrate derivative, recrystallised from methanol m.pt.

153-155°C.

Anal. Calcd. for $C_{17}H_{15}N_4ClO_8$: C, 46.5; H, 3.5; N, 12.8;
Cl, 8.1.

Found: C, 46.5; H, 3.6; N, 12.5;

Cl, 8.1

3-Bromo-2-phenylpyrroline (93).

2-Phenylpyrroline (90) (2.1 g., 0.015 moles) was dissolved in 50 ml of CCl_4 and N-bromosuccinimide (2.8 g., 0.016 moles) added. The mixture was stirred overnight at room temperature and then the insoluble succinimide formed during the reaction was filtered off. Evaporation of the solvent gave 3.15 g. (97%) of the pyrroline (93) as an oil.

Infrared (liquid film): ν_{max} 1610, 1575, 1445, 1130, 1020, 770, 690 cm^{-1} .

Nuclear magnetic resonance: τ 2.05 (m, 2), 2.6 (m, 3), 4.76 (m, 1), 5.6 (m, 2), 7.53 (m, 2).

Ultraviolet: λ_{max} 252 m μ .

Mass spectrometry: m/e 223:225 (20:21% M^+), 144 (19%), 143 (20%), 117 (100%), 115 (44%), 104 (16%), 91 (26%), 77 (24%), 63 (12%), 51 (20%), 41 (30%). (T=55°C).

Analysed as the picrate, recrystallised from benzene m.pt. 160-162°C.

Anal. Calcd. for $C_{16}H_{13}N_4BrO_7$: C, 42.4; H, 2.9; N, 12.4;
Br, 17.6.

Found: C, 42.3; H, 2.9; N, 12.2;

Br. 17.7.

2-(5'-Bromo-2'-methoxyphenyl)-3-bromopyrroline (94).

The arylpyrroline (91) (1.53 g., 0.006 moles) and N-bromosuccinimide (1.3 g., 0.007 moles) in 150 ml of CCl_4 were stirred together for 36 hrs. at room temperature. Removal of the solvent under reduced pressure followed by extraction of the residue with hot petroleum ether gave on evaporation 2.0 g., (quantitative yield) of crystalline product (94), m.pt. 92-94°C.

Infrared: ν_{max} 1590, 1580, 1460, 1380, 1265, 1240, 1175, 1020, 980, 815 cm^{-1} .

Nuclear magnetic resonance: τ 2.02 (d, 1, $J_{4,6}=3\text{cps}$), 2.61 (q, 1, $J_{3,4}=9\text{cps}$, $J_{4,6}=3\text{cps}$), 3.27 (d, 1, $J_{3,4}=9\text{cps}$), 4.5 (broad t, 1), 6.02(m, 2), 6.13 (s, 3), 7.53 (m, 2).

Mass spectrometry: m/e 331:333:335 (18:34:17% M^+), 252:254 (100:100%), 225:227 (59:51%), 211:213 (37:31%), 197:199 (35:35%), 196:198 (20:22%), 173 (23%), 157 (25%), 158 (21%), 130 (28%), 129 (25%), 118 (75%), 115:117 (42:38%), 103 (33%), 102 (50%), 77 (42%), 76 (35%), 75 (39%), 89 (27%), 63 (50%), 51 (42%), 50 (28%), 43 (60%), 41 (80%). (T=30°C.

Analysed as the picrate, recrystallised from benzene m.pt. 135-137°C.

Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_4\text{Br}_2\text{O}_8$: C, 36.3; H, 2.5; N, 10.0; Br, 28.5.

Found: C, 36.5; H, 2.5; N, 10.0;

Br, 28.0

3-Bromo-2-(5'-chloro-2'-methoxyphenyl)pyrroline (95).

The arylpyrroline (92) (600 mg., 0.003 moles), and N-bromosuccinimide (550 mg., 0.004 moles) in 20 ml of CCl_4 were stirred together for 48 hrs. at room temperature. Insoluble succinimide was filtered off and the solvent removed. Extraction of the residue with boiling petroleum ether followed by evaporation of the extract gave 810 mg. (98%) of crystalline product (95), m.pt. dec. 65°C .

Infrared: ν_{max} 1595, 1420, 1270, 1240, 1175, 1135, 1020, 990, 820, 680 cm^{-1} .

Ultraviolet: λ_{max} 247 m μ ., 309 m μ ..

Nuclear magnetic resonance: τ 2.21 (d, 1), 2.70 (q, 1), 3.18 (d, 1), 4.44 (broad t, 1), 5.98 (m, 2), 6.15 (s, 3), 7.52 (m, 2).

Mass spectrometry: m/e 287:289:291 (16:20:5% M^+), 208:210 (100:35%), 207:209 (93:52%), 181:183 (55:18%), 180:182 (26:16%), ($T=85^\circ\text{C}$).

Analysed as the picrate, recrystallised from ethanol/water m.pt. $139-141^\circ\text{C}$.

Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{ClBrN}_4\text{O}_8$: C, 39.4; H, 2.7; N, 10.8; Br, 15.4; Cl, 6.9.

Found: C, 39.7; H, 2.8; N, 10.8;

Br, 15.4; Cl, 6.8.

2-Phenylpyrrole (96).

A solution of the bromopyrroline (93) (1 g., 0.0045 moles) in 10 ml of methanol was refluxed with 200 mg. of NaOH in 40 ml of methanol for half an hour on a waterbath. After evaporation of the solvent, the residue was taken up in ether, washed with water, dried over MgSO_4 and evaporated to give 475 mg. (74%) of 2-phenylpyrrole.

Recrystallisation from water m.pt. 125-128°C. Pictet and Crépieux reported 129°C. ³⁵

Infrared: ν_{max} 3550, 1110, 1070, 1030, 760, 730, 695 cm^{-1}

Ultraviolet: λ_{max} 287 m μ .

Nuclear magnetic resonance: τ 2.56 (, 5), 1.55 (broad 1), 3.10 (m, 1), 3.43 (m, 1), 3.63 (m, 1).

Mass spectrometry: m/e 143 (100% M^+), 115 (37%). (T=90°C).

3-Methoxy-2-phenylpyrroline (97).

When the bromopyrroline (93) (500 mg.) in methanol was treated with NaOH (100 mg.) in 20 ml of methanol at room temperature, after workup as outlined above, two major products were isolated by thin layer chromatography. Using silica gel and ether/petroleum ether (60/40%) as the solvent system, extraction of a band at R_f 0.5 gave 115 mg. (28%) of 2-phenylpyrrole. A band at R_f 0.3 yielded 30 mg. (8%) of the methoxypyrroline (97) as an oil. Infrared (liquid film): ν_{max} 1615, 1440, 1095, 1005, 770, 690 cm^{-1} .

Ultraviolet: λ_{max} 242 m μ .

Nuclear magnetic resonance: τ 2.15 (m, 2), 2.70 (m, 3),
5.15 (m, 1), 6.05 (m, 2), 6.76 (s, 3), 8.0 (m, 2).

Mass spectrometry: m/e 175 (17% M^+), 117 (52%), 104 (35%),
77 (35%), 72 (100%), 71 (30%), 57 (35%), 51 (30%),
41 (15%). (T=70°C).

Analysed as the picrate derivative, recrystallised from
benzene m.pt. 149-152°C.

Anal. Calcd. for $C_{17}H_{16}N_4O_8$: C, 50.5; H, 4.0; N, 13.9.

Found: C, 50.4; H, 3.9; N, 14.0.

2-(5'-Bromo-2'-methoxyphenyl)pyrrole (98).

A mixture of the bromopyrroline (94) (1.6 g.,
0.005 moles) in 25 ml of methanol and NaOH (500 mg.)
in 50 ml of methanol was refluxed on a waterbath for
half an hour. The solvent was removed under reduced
pressure and the residue taken up in ether. After washing
with water, drying over $MgSO_4$ and passage of the solution
through a silica gel column, evaporation gave 0.96 g. of
the pyrrole (98), as an oil at room temperature.

Infrared (liquid film): ν_{max} 3600, 1585, 1485, 1265,
1225, 1110, 1040, 1020, 805, 720 cm^{-1} .

Ultraviolet: λ_{max} 242 m μ ., 292 m μ ., 319 m μ .

Nuclear magnetic resonance: τ 2.26 (d, 1, $J_{4,6}=3\text{cps}$),
2.85 (q, 1, $J_{3,4}=9\text{cps}$), $J_{4,6}=3\text{cps}$), 3.27 (d, 1, $J_{3,4}=9\text{cps}$),
3.16 (m, 1), 3.42 (m, 1), 3.72 (m, 1), 6.13 (s, 3).

Mass spectrometry: m/e 251:253 (100:90% M^+), 236:238 (55:45%), 208:210 (55:52%), 172 (32%), 157 (80%), 141 (18%), 129 (90%), 128 (77%), 115 (32%), 102 (75%), 101 (30%), 91 (35%), 87 (35%), 75 (82%), 74 (72%), 63 (90%), 51 (78%), 50 (76%), 41 (66%). ($T=70^\circ\text{C}$).

Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{BrNO}$: C, 52.4; H, 4.0; N, 5.6;
Br, 31.7

Found: C, 52.6; H, 4.0; N, 5.6;

Br, 31.2.

2-(5'-Chloro-2'-methoxyphenyl)pyrrole (99):

The bromopyrroline (95) (0.5 g., 1.7 moles) in 10 ml of methanol and NaOH (350 mg.) in 10 ml of methanol were refluxed together on a waterbath for half an hour. The solvent was removed under reduced pressure and the residue taken up in ether, washed with water and dried over MgSO_4 . After passage of the solution through a silica gel column, evaporation gave 345 mg. of the pyrrole (99), an oil at room temperature.

Infrared (liquid film): ν_{max} 3525, 1595, 1495, 1235, 1120, 1050, 1030, 815, 725 cm^{-1} .

Ultraviolet: λ_{max} 241 $\text{m}\mu$., 290 $\text{m}\mu$., 318 $\text{m}\mu$..

Nuclear magnetic resonance: τ 0.33 (s broad, 1), 2.46 (d, 1, $J_{4,6}=2.5\text{cps}$), 2.97 (q, 1, $J_{3,4}=9\text{cps}$, $J_{4,6}=2.5\text{cps}$), 3.25 (d, 1, $J_{3,4}=9\text{cps}$), 3.23 (m, 1), 3.45 (m, 1), 3.75 (m, 1), 6.13 (s, 3).

Mass spectrometry: m/e 207:209 (100:28% M^+), 192:194 (63:18%), 164:166 (21:8%), 157 (10%). ($T=110^\circ\text{C}$).

The pyrrole (99) rapidly decomposed and no satisfactory elemental analysis could be obtained.

Methyl 3,5-Dibromo-2-methoxybenzoate (102).

Methylation of 3,5-dibromosalicylic acid was carried out according to the method of Bickoff *et al.*⁹⁵ The salicylic acid (14.8 g., 0.05 moles) and potassium carbonate (7.6 g., 0.077 moles) in 200 ml of anhydrous acetone were vigorously stirred together at room temperature during the dropwise addition of dimethyl sulphate (14 g., 0.11 moles). The mixture was refluxed for 5 hrs., with addition of small quantities of 10% KOH in methanol to maintain alkalinity. The solvent was evaporated and the product taken up in ether, washed with water and the solution dried over MgSO_4 . Evaporation of the ether gave 14.7 g. (91%) of the ester (102). $M.pt.$ $51-53^\circ\text{C}$. Leulier and Pinet reported $m.pt.$ 53°C .¹²⁶ The ester gave no ferric chloride reaction.

Infrared: ν_{max} 1730, 1415, 1270, 1230, 1195, 990 cm^{-1} .

Mass spectrometry: m/e 322:324:326 (32:63:30% M^+), 289:291:293:295:297 (28:95:100:50:10%). ($T=75^\circ\text{C}$).

Methyl 3,4-Dichloro-2-methoxybenzoate (103).

3,5-Dichlorosalicylic acid (20.7 g., 0.1 moles) and sodium hydroxide (10 g., 0.25 moles) were dissolved in 250 ml of water and stirred at room temperature during the dropwise addition of dimethyl sulphate (28 g., 0.22 moles). The mixture was refluxed for 2 hrs., then cooled and extracted with ether. After drying over MgSO_4 , evaporation of the ether gave 7.4 g. (32%) of the ester (103). Recrystallised from ethanol/water m.pt. 33°C . Infrared: ν_{max} 1730, 1420, 1280, 1235, 1000, 985, 800 cm^{-1} . Mass spectrometry: m/e 234:236:238⁺ (52:31:5% M^+), 201:203:205:207:209 (50:100:58:14:1%). (T= 50°C). Anal. Calcd. for $\text{C}_9\text{H}_6\text{O}_3\text{Cl}_2$: C, 46.0; H, 3.4; Cl, 30.2. Found: C, 45.9; H, 3.4; Cl, 30.2.

Methyl 5-Bromo-2-methoxybenzoate (100).

5-Bromosalicylic acid (15 g., 0.07 moles) and potassium carbonate (12 g.) in 200 ml of anhydrous acetone when treated with dimethyl sulphate (19 g.) under the conditions previously described gave 11.9 g. (70%) of the ester (100). M.pt. 35°C . Literature value m.pt. $39-40^\circ\text{C}$.

Infrared: ν_{max} 1730, 1595, 1495, 1400, 1300, 1105, 1030, 975, 820 cm^{-1} .

Mass spectrometry: m/e 244:246 (44:43% M^+), 211:213:215 (34:100:72%), 198:200 (8:8%), 183:185 (13:14%), 170:172 (21:19%), 155:157 (16:15%), 63 (50%).

Methyl 5-Chloro-2-methoxybenzoate (101).

5-Chlorosalicylic acid (17 g., 0.1 moles) and sodium hydroxide (12.5 g.) in 125 ml of water were treated with dimethyl sulphate (40 g.). After refluxing for 3 hrs. and workup 12.5 g. (63%) of the ester (101) were obtained as an oil.

Infrared (liquid film): $\nu_{\max}$ 1730, 1495, 1305, 1120, 1085, 1030, 820 cm^{-1} .

Mass spectrometry: m/e 200:202 (45:13% M^+), 167:169:171 (40:100:35%), 154:156 (7:2%), 139:141 (12:6%), 126:128 (21:7%), 111:113 (17:7%), 63 (19%).

Anal. Calcd. for $\text{C}_9\text{H}_9\text{O}_3\text{Cl}$: C, 53.9; H, 4.5; Cl, 17.7.

Found: C, 54.1; H, 4.6; Cl, 17.5.

3,5-Dibromo-2-methoxybenzoic acid (106).

The ester (102) (14 g., 0.43 moles) in 25 ml of ethanol was refluxed with NaOH (5.25 g., 0.13 moles) in 200 ml of water for 3 hrs. After cooling unhydrolysed material was removed by ether extraction. Acidification of the aqueous solution with conc. hydrochloric acid, resulted in the precipitation of 13.1 g. (98%) of the acid (106).

Recrystallisation from ethanol/water m.pt. 189-191°C.

Literature value given as m.pt. 193-194°C.

Infrared: $\nu_{\max}$ 1670, 1295, 1230, 990, 880, 795, 710 cm^{-1} .

3,5-Dichloro-2-methoxybenzoic acid (107).

The ester (103) (8 g., 0.034 moles) in 15 ml of ethanol was refluxed with NaOH (4 g., 0.1 mole) in 150 ml of water for 3 hrs. Workup as described for acid (106) gave on filtration of the product 7.3 g. (97%) of acid (107).

Recrystallisation from ethanol/water m.pt. 166-167°C.

Literature value reported as m.pt. 166.5-167°C.¹²⁹

Infrared: $\nu_{\max}$ 1670, 1420, 1310, 1240, 1000, 890, 855, 810, 750 cm^{-1} .

5-Bromo-2-methoxybenzoic acid (104).

The methyl benzoate (100) (11 g., 0.045 moles) in 100 ml of 10% aqueous ethanol was refluxed with NaOH (6 g., 0.15 moles) for 3 hrs. Workup as previously described gave 10.1 g. (97%) of the acid (104).

Recrystallised from water m.pt. 117-118°C. Literature value for the m.pt. 120-120.8°C.¹²⁸

Infrared: $\nu_{\max}$ 2650, 1705, 1495, 1280, 1250, 1020, 820 cm^{-1} .

5-Chloro-2-methoxybenzoic acid (105).

The methyl benzoate (101) (13.0 g., 0.065 moles) in 100 ml of 10% aqueous ethanol was refluxed with NaOH (8 g., 0.2 moles) for 3 hrs. Workup as previously outlined gave 12.0 g. (99%) of the acid (105).

Recrystallisation from water m.pt. 97-98°C. Literature value for the m.pt. 81-82°C.¹²⁹

Infrared: $\nu_{\max}$ 2650, 1705, 1495, 1280, 1260, 1020, 820 cm^{-1} .

2-Methoxybenzoylglycine (110).

10 g. of o-methoxybenzoic acid were reacted with 15 ml of thionyl chloride until the evolution of gas had ceased. Excess thionyl chloride was removed under reduced pressure. Small portions of the crude acid chloride were added to a solution of 5 g. of glycine in 40 ml of 15% aqueous NaOH, which was agitated vigorously in a glass stoppered bottle. The mixture was allowed to stand overnight and then acidified with conc. hydrochloric acid. Filtration of the precipitated acid gave 8.1 g. (59%) of the acid (110).

Infrared: $\nu_{\max}^{\circ}$ 3450, 1720, 1620, 1550, 1245, 1225, 1030, 955, 770, 665 cm^{-1} .

Mass spectrometry: m/e 209 (5% M^+), 165 (30%), 164 (20%), 135 (100%), 105 (10%), 92 (25%), 77 (50%), 64 (12%), 63 (10%), 51 (10%). (T=110°C).

Recrystallisation from benzene gave needles m.pt. 113-114°C.

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{NO}_4$: C, 57.4; H, 5.3; N, 6.7.

Found: C, 57.5; H, 5.3; N, 6.7.

Recrystallisation from water gave needles m.pt. 50-60°C. with dec.

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{NO}_4 \cdot \text{H}_2\text{O}$ ($\text{C}_{10}\text{H}_{13}\text{NO}_5$):

C, 52.9; H, 5.8; N, 6.2.

Found: C, 53.1; H, 5.8; N, 6.2.

3,5-Dibromo-2-methoxybenzoylglycine (111).

The dibromobenzoic acid (106) (7 g., 0.023 moles)

was refluxed with 6.5 ml of thionyl chloride in 10 ml of benzene for 1 hr. Excess thionyl chloride was removed under reduced pressure. Small portions of the crude acid chloride were added to a solution of glycine (1.9 g., 0.025 moles) in 20 ml of water previously cooled to 0°C. Simultaneously small volumes of NaOH solution (2.25 g. in 40 ml of water) were added to maintain the alkalinity of the mixture which was mixed vigorously. After standing overnight the mixture was acidified with conc. hydrochloric acid and filtered to give 6.0 g. (72%) of the acid (111).

Recrystallisation from dioxan/water gave needles

m.pt. 204-206°C.

Infrared: $\nu_{\max}$ 3450, 1735, 1625, 1555, 1420, 1230, 990, 885, 800, 705, 675 cm^{-1} .

Mass spectrometry: m/e 365:367:369 (6:11:6% M^+), 320:322:324 (2:4:2%), 291:293:295 (32:58:27%), 290:292:294 (12:25:16%), 276:278:280 (7:11:6%), 76 (100%). (T=115°C).

Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{NBr}_2\text{O}_4$: C, 32.7; H, 2.4; N, 3.8; Br, 43.5.

Found: C, 32.9; H, 2.5; N, 4.0;

Br, 43.3.

3,5-Dichloro-2-methoxybenzoylglycine (112).

The dichlorobenzoic acid (107) (4.4 g., 0.02 moles) was refluxed with 4.5 ml of thionyl chloride in 10 ml of benzene to give the crude acid chloride. Addition of the

acid chloride to glycine (1.65 g., 0.022 moles) in 15 ml of water, together with NaOH (1.75 g. in 30 ml of water) at 0°C. gave after acidification of the solution with conc. hydrochloric acid 3.3 g. (59%) of the acid (112). Recrystallisation from benzene gave needles m.pt. 182-184°C.

Infrared: $\nu_{\max}$ 3450, 1740, 1625, 1555, 1425, 1245, 1230, 990, 850, 810, 720, 690 cm^{-1} .

Mass spectrometry: m/e 277:279:281 (11:7:1% M^+), 232:234:236 (7:5:1%), 203:205:207 (100:65:10%), 202:204:206 (25:23:9%), 188:190:192, (19:12:2%), 173:175:177 (12:9:2%), 145:147:149 (12:8:2%), 97:99 (17:6%), 76 (78%). (T=110°C).

Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{NCl}_2\text{O}_4$: C, 43.2; H, 3.3; N, 5.0; Cl, 25.5.

Found: C, 43.1; H, 3.2; N, 5.1; Cl, 25.5.

5-Bromo-2-methoxybenzoylglycine (113).

5-Bromo-2-methoxybenzoic acid (104) (9.5 g., 0.041 moles and 12 ml of thionyl chloride in 20 ml of benzene were refluxed together. The resultant crude acid chloride was added to glycine (4 g., 0.053 moles) in 50 ml of water, while the mixture was kept alkaline by the addition of NaOH (4.5 g. in 50 ml of water). After standing overnight, the mixture was acidified with conc. hydrochloric acid. Filtration of the precipitated

acid gave after extraction of unreacted benzoic acid (104) with boiling benzene, 3.75 g. (32%) of the product (113). Recrystallisation from ethanol/water gave plates m.pt. 162-164°C.

Infrared: $\nu_{\max}$ 3400, 2600, 1720, 1610, 1550, 1285, 1255, 1130, 1020, 870, 820, 690 cm^{-1} .

Mass spectrometry: m/e 287:289 (14:14% M^+), 242:244 (11:11%), 213:215 (100:95%), 170:172 (16:15%), 155:157 (14:14%), 76 (76%), 63 (31%). (T=110°C).

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{BrNO}_2$: C, 41.6; H, 3.5; N, 4.9; Br, 27.7.

Found: C, 41.7; H, 3.6; N, 4.9;

Br, 27.8.

5-Chloro-2-methoxybenzoylglycine (114).

5-Chloro-2-methoxybenzoic acid (105) (10 g., 0.054 moles) was refluxed with 13 ml of thionyl chloride in 20 ml of benzene. The resultant crude acid chloride was added to a solution of glycine (4.5 g., 0.06 moles) in 50 ml of water, while NaOH (5 g. in 50 ml of water) was added gradually to maintain alkalinity of the mixture. Standing overnight, followed by acidification with conc. hydrochloric acid gave on filtration 7.7 g. (59%) of the acid (114). Recrystallised from ethanol/water as needles m.pt. 166-168°C.

Infrared: $\nu_{\max}$ 3400, 1720, 1620, 1550, 1255, 1210, 1130, 1020, 830, 820 cm^{-1} .

Mass spectrometry: m/e 243:245 (11:4% M^+), 198:200 (12:5%), 169:171 (100:28%), 154:156 (11.4%), 126:128 (19.6%), 111:113 (18.7%), 76 (35%), 63 (16%). (T=105°C).

Anal. Calcd. for $C_{10}H_{10}ClNO_4$: C, 49.3; H, 4.1; N, 5.8; Cl, 14.0.

Found: C, 49.3; H, 4.3; N, 5.6;

Cl, 14.4.

Benzoylalanine (115).

To a solution of alanine (9 g., 0.1 moles in 40 ml of water) was added small portions of benzoyl chloride (14 g., 0.1 moles) and the mixture shaken vigorously. The alkalinity of the solution was maintained by the addition of small quantities of NaOH solution. After leaving to stand for 1 hr., the solution was acidified with conc. hydrochloric acid. The oil, which separated crystallised to give 13.8 g. (71%) of the acid (115), m.pt. 160-164°C. Literature value for the m.pt. 165-166°C.¹³⁰

Infrared: $\nu_{\max}$ 3400, 1695, 1625, 1530, 1210, 1120, 900, 720, 695 cm^{-1} .

Mass spectrometry: m/e 193 (8% M^+), 175 (1%), 148 (24%), 105 (100%), 77 (34%), 51 (12%). (T=105°C).

Hippuric acid (Benzoylglycine) (109).

Infrared: $\nu_{\max}$ 3400, 1740, 1605, 1570, 1185, 725 cm^{-1} .

Mass spectrometry: m/e 179 (5% M^+), 161 (1%), 135 (20%), 134 (11%), 105 (100%), 77 (46%), 51 (18%). (T=100°C).

2-Phenyl- Δ^2 -oxazolin-5-one (116).

A mixture of hippuric acid (10 g., 0.056 moles) and acetic anhydride (30 ml) was heated on a water bath with stirring until a clear solution resulted. The solvent was removed under reduced pressure to give a crystalline residue. Extraction of the residue with hot petroleum ether (65-100°C.) gave after cooling 4.5 g. (50%) of pink crystalline product (116).

M.pt. 89°C. Literature value m.pt. 91-92°C.^{99a}

Infrared: $\nu_{\max}$ 1820, 1660, 1230, 1035, 1020, 875, 690 cm^{-1} .

Ultraviolet: $\lambda_{\max}$ 241 m μ .

Nuclear magnetic resonance: τ 2.0 (m, 2), 2.5 (m, 3), 5.56 (s, 2).

Mass spectrometry: m/e 161 (97% M^+), 117 (57%), 105 (100%), 77 (100%), 51 (50%), 50 (22%). (T=70°C).

Method B: A mixture of hippuric acid (1 g., 0.0056 moles) and N,N'-dicyclohexyl carbodiimide (1.1 g., 0.0054 moles) in 40 ml of toluene was heated for 2 hrs. on a water bath. Filtration of the mixture to remove insoluble dicyclohexyl urea, formed during the reaction and evaporation of the solvent gave 0.88 g (97%) of 2-phenyl- Δ^2 -oxazolin-5-one (116), m.pt. 86°C. The product was shown to be identical with a previously prepared sample by infrared spectra and t.l.c. on silica gel.

4-Methyl-2-phenyl- Δ^2 -oxazolin-5-one (117).

A mixture of benzoylalanine (2 g., 0.01 moles) and N,N'-dicyclohexyl carbodiimide (2 g., 0.01 moles) in 50 ml of toluene was heated for one hour on a water bath. Filtration and evaporation gave 1.5 g. (83%) of crystalline material (117), m.pt. 35-37°C.

Literature value m.pt. 39°C.⁹⁸

Infrared: $\nu_{\max}$ 1815, 1650, 1455, 1325, 1210, 1115, 1010, 890, 700 cm^{-1} .

Mass spectrometry: m/e 175 (20%), 131 (15%), 105 (100%), 77 (60%), 51 (32%).

2-(3',5'-Dibromo-2'-methoxyphenyl)- Δ^2 -oxazolin-5-one (118).

3,5-Dibromo-2-methoxybenzoylglycine (111) (1.35 g., 3.8 moles) was heated with dicyclohexylcarbodiimide (1 g., 5 moles) in toluene on a water bath for 1 hr. Cooling and the addition of petroleum ether resulted in the precipitation of insoluble dicyclohexylurea, which was removed by filtration. Evaporation of the solvent gave 1.26 g. (95%) of the title compound (118) as a red oil. The compound was not fully characterised due to its unstable nature.

Infrared: $\nu_{\max}$ 1820 cm^{-1} .

Mass spectrometry: m/e 347:349:351 (M^+).

2-(3',5'-Dichloro-2'-methoxyphenyl)- Δ^2 -oxazolin-5-one (119).

3,5-Dichloro-2-methoxybenzoylglycine (112) (1.35 g., 5 mmoles) was heated with dicyclohexylcarbodiimide (1 g., 5 mmoles) in 40 ml of toluene for 1 hr. Removal of dicyclohexylurea as outlined previously left on evaporation of solvent 1.1 g. (83%) of crude product (119) as a red oil. This product was not fully characterised.

Infrared: $\nu_{\max}$ 1815 cm^{-1} .

Mass Spectrometry: m/e 259:261 (M^+).

Diethyl 2-Phenylpyrrole-3,4-dicarboxylate (120).

2-Phenyl- Δ^2 -oxazolin-5-one (116) (2 g., 0.012 moles) was refluxed with diethyl acetylene dicarboxylate (2.1 g., 0.012 moles) in 20 ml of chlorobenzene for 2 hrs. The solvent was removed under reduced pressure and the residue left to stand. Chromatography on silica gel using benzene/ether mixtures as eluting solvents gave 1.2 g. (33%) of crystalline product (120) eluted with benzene/ether (75/25%).

Method B: Hippuric acid (3 g., 0.017 moles) and diethyl acetylene dicarboxylate (2.85 g., 0.017 moles) were heated together with 12 ml of acetic anhydride on a water bath under nitrogen for half an hour. Solvent was removed by vacuum distillation and the residue chromatographed as described above. A fraction eluted with benzene/ether (80:20%) gave an oil, which was taken up in benzene, washed with sodium bicarbonate solution and dried. Evaporation of the solvent

gave 1.9 g. (41%) of the pyrrole (120), identical by t.l.c. on silica gel with the product of method A.

Recrystallisation from benzene/light petroleum gave needles m.pt. 129-131°C.

Infrared: $\nu_{\max}$ 3250, 1685, 1395, 1205, 1060, 775, 710, 695, cm^{-1} .

Ultraviolet: $\lambda_{\max}$ 277 m μ . ($\log \epsilon$ 4.11).

Nuclear magnetic resonance: τ 0.26 (broad s, 1), 2.75 (s, 5), 2.93 (d, 1), 5.81 (q, 4), 8.76 (sextet, 6).

Mass spectrometry: m/e 287 (100% M^+), 242 (49%), 214 (72%), 170 (11%), 169 (12%), 115 (14%), 58 (15%), 44 (30%), 43 (42%). (T=120°C).

Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}_4$: C, 67.0; H, 5.9; N, 4.8.

Found: C, 66.9; H, 6.0; N, 4.9.

Diethyl 2-(2'-methoxyphenyl)pyrrole-3,4-dicarboxylate (121).

2-Methoxybenzoylglycine (110) (6 g., 0.023 moles) was heated with 30 ml of acetic anhydride on a water bath under nitrogen until solution was effected. Diethyl acetylene dicarboxylate (7.5 g., 0.029 moles) was added to the yellow solution and heating continued for 1 hr. The solvent was removed and the residue chromatographed on silica gel using benzene/ether mixtures as the eluting solvent. The fraction eluted with benzene/ether (80/20%) gave an oil, which was taken up in ether, washed with sodium bicarbonate solution and dried over MgSO_4 . Evaporation of the solvent gave

5.2 g. (56%) of the pyrrole (121) as an oil, which could not be induced to crystallise.

Infrared: $\nu_{\max}$ 3325, 1710, 1295, 1260, 1180, 1060, 1025, 760 cm^{-1} .

Ultraviolet: $\lambda_{\max}$ 274 m μ . ($\log \epsilon$ 4.07), 293 m μ . ($\log \epsilon$ 4.02).

Nuclear magnetic resonance: τ 0.17 (broad s, 1), 2.55-3.3 (m, 4), 5.8 (q, 4), 2.76 (d, 1), 6.26 (s, 3), 8.75 (sextet, 6).

Mass spectrometry: m/e 317 (20% M^+), 272 (8%), 242 (90%), 213 (100%), 214 (19%), 197 (16%), 170 (19%), 169 (95%), 168 (14%), 142 (13%), 140 (10%), 135 (41%), 115 (14%), 85 (15%), 83 (23%), 44 (26%), 40 (21%). ($T=80^\circ\text{C}$).

Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{NO}_5$: C, 64.3; H, 6.0; N, 4.4.

Found: C, 64.5; H, 6.1; N, 4.3.

Diethyl 2-Methyl-5-phenylpyrrole-3,4-dicarboxylate (122).

A mixture of the oxazolin-5-one (117) (1.12 g., 0.0064 moles) and diethyl acetylene dicarboxylate (1.5 g., 0.0088 moles) was heated under nitrogen at 130-140°C. for half an hour. After cooling, the mixture was chromatographed on silica gel using mixtures of benzene/ethyl acetate as the eluting solvent. The fraction eluted with benzene/ethyl acetate (92/8%) gave 1.57 g. (82%) of crystalline pyrrole (122).

Recrystallisation from benzene/light petroleum gave m.pt. 98-100°C.

Infrared: $\nu_{\max}$ 3275, 1685, 1210, 1100, 695 cm^{-1} .

Ultraviolet: $\lambda_{\max}$ 283 $\text{m}\mu$. ($\log \epsilon$ 4.20).

Nuclear magnetic resonance: τ 0.46 (s broad, 1),

2.78 (m, 5), 5.83 (octet, 4), 7.65 (s, 3), 8.76 (sextet, 6).

Mass spectrometry: m/e 301 (85% M^+), 256 (70%), 255

(100%), 226 (85%), 227 (40%), 228 (75%), 199 (17%),

183 (43%), 155 (38%), 104 (80%). ($T=100^\circ\text{C}$).

Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{NO}_4$: C, 67.7; H, 6.4; N, 4.7.

Found: C, 67.8; H, 6.3; N, 4.7.

Diethyl 2-(2'-methoxy-3',5'-dibromophenyl)pyrrole-
3,4-dicarboxylate (123).

A mixture of the oxazolin-5-one (118) (1.26 g., 0.0036 moles) and diethyl acetylene dicarboxylate (0.7 g., 0.004 moles) was heated under nitrogen at 140°C . for half an hour. The product was chromatographed on silica gel using benzene/ethyl acetate mixtures as the eluting solvent. Benzene/ethyl acetate (95/5%) gave a fraction which yielded 330 mg. (19%) of the pyrrole (123).

Method B: The benzoylglycine (111) (3.3 g., 0.01 moles) in 10 ml of chlorobenzene was heated on a water bath with 10 ml of acetic anhydride until solution was effected.

Diethyl acetylene dicarboxylate (2 g., 0.012 moles) was added and the mixture heated under nitrogen at $130-140^\circ\text{C}$.

for 1½ hr. Solvent was removed under reduced pressure and the residue on cooling partially crystallised. The residue was taken up in ether (100 ml) and washed with sodium bicarbonate solution. After drying over MgSO_4 , the solution was concentrated to 25 ml. On standing the ether solution deposited 600 mg. (14%) of crystalline pyrrole, which was identical by t.l.c. and infrared with the material prepared by method A. Recrystallised from ether m.pt. 136-138°C.

Infrared: ν_{max} 3350, 1720, 1685, 1435, 1280, 1200, 1060, 990, 880, 785, 745 cm^{-1} .

Ultraviolet: λ_{max} 284 mμ. ($\log \epsilon$ 4.0).

Nuclear magnetic resonance: τ -0.15 (broad s, 1), 2.42 (d, 1, $J=3\text{cps}$), 2.55 (d, 1, $J=3\text{cps}$), 2.72 (d, 1), 5.8 (q, 4), 6.52 (s, 3), 8.73 (q, 6).

Mass spectrometry: m/e 473:475:477 (55:100:52% M^+), 442:444:446 (5:11:6%), 428:430:432 (26:48:25%), 398:400:402:404 (11:41:52:22%), 368:370:372 (38:70:44%), 341:343:345 (20:31:16%), 327:329:331 (12:16:8%), 326:328:330 (8:15:12%). ($T=130^\circ\text{C}$).

Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{NBr}_2\text{O}_5$: C, 43.0, H, 3.6; N, 3.0; Br, 33.6.

Found: C, 42.8; H, 3.7; N, 2.9;

Br, 33.6.

Diethyl 2-(3',5'-dichloro-2'-methoxyphenyl)pyrrole-
3,4-dicarboxylate (124).

The benzoylglycine (112) (1.3 g., 0.0047 moles) was heated together with acetic anhydride (4.5 ml) and diethyl acetylene dicarboxylate (1.0 g., 0.006 moles) under nitrogen on a water bath for 1 hour. The solvent was removed under reduced pressure and the residue chromatographed on silica gel using mixtures of benzene/ethyl acetate as the eluting solvent. The fraction eluted with benzene/ethyl acetate (99/1%) gave 620 mg. (34%) of the pyrrole (124). Recrystallised from ether/light petroleum m.p. 110-112°C.

Infrared: $\nu_{\max}$ 3300, 1710, 1685, 1290, 1175, 1125, 1075, 1000, 770, 760 cm^{-1}

Ultraviolet: $\lambda_{\max}$ 283 m μ . (log ϵ 4.0).

Nuclear magnetic resonance: τ 0.02 (broad s, 1), 2.62 (d, 1), 2.71 (s, 2), 5.78 (q, 4), 6.57 (s, 3), 8.72 (sextet, 6).

Mass spectrometry: m/e 385:387:389 (100:73:15% M^+), 354:356:358 (9:6:2%), 340:342:344 (55:37:7%), 310:312:314:316 (20:62:36:6%), 280:282:284 (78:60:20%), 253:255:257 (47:29:5%). (T=100°C).

Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{Cl}_2\text{NO}_5$: C, 52.9; H, 4.4; Cl, 18.4; N, 3.6.

Found: C, 52.9; H, 4.5; Cl, 18.3;

N, 3.6.

Diethyl 2-(5'-bromo-2'-methoxyphenyl)pyrrole-
3,4-dicarboxylate (125).

A mixture of the benzoylglycine (113) (2 g., 0.007 moles) and diethyl acetylene dicarboxylate (1.3 g., 0.008 moles) was heated with 5.5 ml of acetic anhydride on a water bath under nitrogen for 1 hr. The solvent was removed and the residue chromatographed on silica gel using mixtures of benzene/ethyl acetate as the eluting solvent. The fraction eluted with benzene/ethyl acetate (90/10%) yielded 900 mg. (33%) of the pyrrole (125). Recrystallised from benzene/light petroleum m.pt. 126-128°C. Infrared: $\nu_{\max}$ 3360, 1705, 1495, 1290, 1270, 1190, 1095, 1065, 825, 765 cm^{-1} .

Ultraviolet: $\lambda_{\max}$ 275 ($\log \epsilon$ 4.04), 305 ($\log \epsilon$ 3.96).

Nuclear magnetic resonance: τ 0.1 (broad s, 1), 2.58 (d, 1), 8.73 (sextet, 6), 2.70 (q, 1), 2.81 (d, 1), 3.33 (d, 1), 5.81 (octet, 4), 6.3 (s, 3).

Mass spectrometry: m/e 395:397 (100:98% M^+), 350:352 (40:40%), 320:322:324 (14:50:40%), 290:292 (30:30%), 263:265 (26:25%). ($T=100^\circ\text{C}$).

Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{BrNO}_5$: C, 51.5; H, 4.6; N, 3.5; Br, 20.2.

Found: C, 51.7; H, 4.7; N, 3.3;

Br, 20.5.

Diethyl 2-(5'-chloro-2'-methoxyphenyl)pyrrole-3,4-dicarboxylate (126).

The benzoylglycine (114) (2 g., 0.008 moles) and diethyl acetylene dicarboxylate (1.5 g., 0.009 moles) were heated together with 6.5 ml of acetic anhydride under nitrogen on a water bath for 1 hr. The solvent was removed under reduced pressure and the residue chromatographed on silica gel using mixtures of benzene/ethyl acetate as the eluting solvent. The fraction eluted with benzene/ethyl acetate (90/10%) gave 1.5 g. (53%) of the pyrrole (126). Recrystallised from benzene/light petroleum m.pt. 119-121°C.

Infrared: $\nu_{\max}$ 3350, 1705, 1495, 1290, 1265, 1185, 1065, 825, 765 cm^{-1} .

Ultraviolet: $\lambda_{\max}$ 273 m μ . (log ϵ 4.03), 304 m μ . (log ϵ 3.96).

Nuclear magnetic resonance: τ 0.03 (broad s, 1), 2.72 (d, 1), 2.74 (s, 1), 2.87 (q, 1), 3.27 (d, 1), 5.7 (octet, 4), 6.3 (s, 3), 8.73 (sextet, 6).

Mass spectrometry: m/e 351:353 (100:39% M^+), 306:308 (50:19%), 276:278:280 (16:57:20%), 246:248 (41:20%), 219:221 (33:13%), 204:206 (18:11%). (T=110°C).

Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{NClO}_5$: C, 58.0; H, 5.2; N, 4.0
Cl, 10.1.

Found: C, 58.6; H, 4.7; N, 4.0:

Cl, 10.2.

Diethyl 2-Bromo-5-phenylpyrrole-3,4-dicarboxylate (127).

The phenylpyrrole diester (120) (500 mg., 1.4 mmoles) was dissolved in 10 ml of chloroform and cooled to 0°C. Dropwise addition of bromine (0.3 g., 1.9 mmoles) in 10 ml of CCl_4 was carried out under nitrogen. The solution was stirred overnight and then the solvent removed under reduced pressure to yield 625 mg. (98%) of the pyrrole (127).

Recrystallised from benzene/light petroleum as prisms m.pt. 124-126°C.

Infrared: ν_{max} 3175, 1730, 1685, 1515, 1490, 1250, 1215, 1110, 1070, 1020, 780, 760 cm^{-1} .

Ultraviolet: λ_{max} 276 m μ . ($\log \epsilon$ 4.13).

Nuclear magnetic resonance: τ 0.56 (broad s, 1), 2.62 (s, 5), 5.74 (octet, 4), 8.74 (q, 6).

Mass spectrometry: m/e 365:367 (100:100% M^+), 320:322 (38:38%), 292:294 (53:48%), 214 (14%), 141 (16%), 140 (22%), 58 (100%), 43 (100%). (T=115°C).

Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{NBrO}_4$: C, 52.5; H, 4.5; N, 3.8; Br, 21.8.

Found: C, 52.9; H, 4.3; N, 3.9;

Br, 21.8.

o Diethyl 2-(5'-bromo-2'-methoxyphenyl)-5-bromopyrrole-3,4-dicarboxylate (128).

The pyrrole diester (121) (900 mg., 28. mmoles) in 20 ml. of chloroform was cooled to 0°C. and bromine

(1.75 g., 11 mmoles) in 20 ml of CCl_4 added dropwise.

The solution was stirred overnight and the solvent removed under reduced pressure. The residue was taken up in ether and washed with sodium thiosulphate and dilute sodium hydroxide solutions. After drying over MgSO_4 , the ether solution was concentrated and on standing deposited 725 mg. (68%) of the dibrominated pyrrole (128). Recrystallised from ether as prisms m.pt. $158.5-160.5^\circ\text{C}$.

Infrared: ν_{max} 3225, 1710, 1675, 1510, 1330, 1255, 1215, 1120, 1030, 825 cm^{-1} .

Ultraviolet: λ_{max} 275 m μ . ($\log \epsilon$ 3.94), 305 m μ . ($\log \epsilon$ 3.84).

Nuclear magnetic resonance: τ 0.44 (broad s, 1), 2.51 (d, 1), 2.66 (q, 1), 3.25 (d, 1), 5.74 (q, 4), 6.2 (s, 3), 8.7 (sextet, 6).

Mass spectrometry: m/e 473:475:477 (54:100:54% M^+), 428:430:432 (18:34:17%), 400:402:404 (29:49:24%), 368:370:372 (17:35:22%), 341:343:345 (28:49:24%). ($T=150^\circ\text{C}$).

Anal. Calcd. for $\text{C}_{11}\text{H}_{17}\text{Br}_2\text{NO}_5$: C, 43.0; H, 3.6; N, 3.0; Br, 33.6.

Found: C, 43.0; H, 3.6; N, 3.0;

Br, 33.7.

Method B: 50 mg. of the bromopyrrole diester (125) in 10 ml of chloroform was treated with 30 mg. of bromine in CCl_4 at 0°C . The reaction mixture was left to stand overnight and then the solvent removed. The residue was taken

up in ether and the solution concentrated. On standing 57 mg. (95%) of the pyrrole (128) was deposited as prisms. The product was shown by infrared and ultraviolet spectroscopy, behaviour on thin layer silica gel and m.pt. to be identical with the previously prepared material.

Diethyl 2-(3',5'-dibromo-2'-methoxyphenyl)-5-bromopyrrole-3,4-dicarboxylate (129).

To the pyrrole (123) (400 mg., 0.85 mmoles) in 10 ml of chloroform at 0°C. was added a solution of bromine (185 mg., 1.1 mmoles) in CCl₄. After stirring for 1 hr. the solvent was removed. The residue was taken up in ether, washed with sodium bicarbonate solution and dried over MgSO₄. Evaporation of the ether gave 450 mg. (97%) of the pyrrole (129). Recrystallised from benzene/hexane

Infrared: $\nu_{\max}$ 3250, 1715, 1690, 1500, 1290, 1200, 1070, 685 cm⁻¹.

Ultraviolet: $\lambda_{\max}$ 285 mμ. (log ε 3.96).

Nuclear magnetic resonance: τ 0.13 (broad s, 1), 2.42 (d, 1, J=3cps), 2.53 (d, 1, J=3cps), 5.77 (octet, 4), 6.42 (s, 3), 8.72 (q, 6).

Mass spectrometry: m/e 551:553:555:557 (38:100:100:40% M⁺), 506:508:510:512 (8:21:21:8%), 478:480:482:484 (11:20:17:7%), 446:448:450:452 (11:29:30:13%), 419:421:423:425 (8:13:12:4%). (T=90°C).

Anal. Calcd. for $C_{17}H_{16}NBr_3O_5$: C, 36.9; H, 2.9; N, 2.5; Br, 43.3.

Anal. Calcd. for $C_{17}H_{16}NBr_3O_5 \cdot \frac{5}{6} C_6H_6$: C, 42.7; H, 3.4; N, 2.3; Br, 38.7.

Found: C, 42.7; H, 3.6; N, 2.2; Br, 38.3.

Repeated analysis after careful drying showed that this compound crystallised with $\frac{5}{6}$ mole benzene.

Diethyl 2-Chloro-5-phenylpyrrole-3,4-dicarboxylate (130).

2-Phenylpyrrole diester (120) (601 mg., 2.1 mmoles) in 10 ml of $CHCl_3$, cooled to $0^\circ C$. was treated with sulphonyl chloride (350 mg., 2.6 mmoles) in 5 ml of $CHCl_3$. The solution was stirred overnight and the solvent removed. The crystalline residue was chromatographed on silica gel using benzene/ether mixtures as the eluting solvent, to yield 532 mg. (79%) of the pyrrole (130).

Recrystallised from benzene/light petroleum as prisms m.pt. $110-111^\circ C$.

Infrared: ν_{max} 3175, 1720, 160, 1515, 1485, 1215, 1110, 1070, 1020, 780, 755, 710, 685 cm^{-1} .

Ultraviolet: λ_{max} 275 m μ . ($\log \epsilon$ 4.12).

Nuclear magnetic resonance: τ 0.71 (broad s, 1), 2.63 (s, 5), 5.72 (octet, 4), 8.71 (q, 6).

Mass spectrometry: m/e 321:323 (100:29% M^+), 276:278 (29:10%), 248:250 (49:16%). ($T=120^\circ C$).

Anal. Calcd. for $C_{16}H_{16}NClO_4$: C, 59.7; H, 5.1; N, 4.4; Cl, 11.0.

Found: C, 59.5; H, 5.0; N, 4.3;

Cl, 10.9.

Diethyl 2-(2'-methoxyphenyl)-5-chloropyrrole-3,4
dicarboxylate (131).

The pyrrole diester (121) (125 mg., 0.4 mmoles) in 10 ml of CHCl_3 cooled to 0°C . was treated with sulphuryl chloride (60 mg., 0.44 mmoles) in 5 ml of CHCl_3 . After stirring overnight the solvent was removed and the residue chromatographed on thin layer silica gel using ether/petroleum ether (50/50%) as solvent. A band at R_f 0.25 yielded upon extraction 36 mg. (10%) of the required pyrrole (131). Recrystallised from ether/petroleum ether m.pt. $122-125^\circ\text{C}$.

Infrared: ν_{max} 3250, 1715, 1685, 1525, 1335, 1300, 1260, 1220, 1110, 1030, 765 cm^{-1} .

Ultraviolet: λ_{max} 274 m μ . ($\log \epsilon$ 3.90), 296 m μ . ($\log \epsilon$ 3.85).

Nuclear magnetic resonance: τ 0.7 (broad s, 1), 2.5-3.25 (m, 4), 5.75 (octet 4), 6.15 (s, 3), 8.76 (sextet, 6).

Mass spectrometry: m/e 351:353 (100:37% M^+), 306:308 (30:10%), 276:278:280 (7:26:9%); 246:248 (18:8%), 219:221 (13:5%), 170 (11%), 135 (17%). ($T=95^\circ\text{C}$).

Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{ClNO}_5$: C, 58.0, H, 5.2; N, 4.0; Cl, 10.1.

Found: C, 58.0; H, 5.3; N, 3.9;

Cl, 10.1.

Diethyl 3,4-dichloro-2-(2'-methoxyphenyl)pyrrolin-5-one-3,4-dicarboxylate (137).

500 mg. of the pyrrole-diester (121) in 10 ml of CHCl_3 was treated with 8 ml of chlorine in CCl_4 (0.96 N). Thin layer chromatography of the products on silica gel using ether/petroleum ether (50/50%) gave on isolation of the top band the compound (137) as an oil.

Infrared: ν_{max} 1750, 1730, 1670, 1600, 1030, 870, 770 cm^{-1} .

Nuclear magnetic resonance: τ 2.2-3.2 (m, 4), 6.2 (s, 3), 5.65 (m, 4), 8.7 (m, 6).

Mass spectrometry: m/e 401:403:405 (ratio 9:6:1% M^+).

No analysis was obtained for this compound.

Diethyl 2-(5'-chloro-2'-methoxyphenyl)-5-chloropyrrole-3,4-dicarboxylate (132).

The chloropyrrole diester (126) (202 mg., 0.58 mmoles) in 10 ml of CHCl_3 was treated with sulphuryl chloride (80 mg., 0.59 mmoles) in 10 ml of CCl_4 at 0°C . After stirring overnight the solvent was removed and the residue recrystallised from benzene to yield 182 mg. (82%) of the dichloro compound (132), m.pt. $153-155^\circ\text{C}$.

Infrared: ν_{max} 3250, 1710, 1675, 1520, 1335, 1265, 1220, 1130, 1030, 910, 825 cm^{-1} .

Ultraviolet: λ_{max} 274 m μ . ($\log \epsilon$ 3.91), 304 m μ . ($\log \epsilon$ 3.84).

Nuclear magnetic resonance: τ 0.35 (s broad, 1), 2.66 (d, 1), 2.82 (q, 1), 3.25 (d, 1), 5.75 (q, 4), 6.21 (s, 3), 8.71 (sextet, 6).

Mass spectrometry: m/e 385:387:389 (100:65:11% M^+), 340:342:344 (21:14:3%), 312:314:316 (20:12:3%), 280:282:284 (12:10:3%), 253:255:357 (8:6:1%). ($T=125^\circ\text{C}$).

Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{Cl}_2\text{NO}_5$: C, 52.9; H, 4.4; N, 3.6; Cl, 18.4.

Found: C, 52.9; H, 4.5; N, 3.7;

Cl, 18.0.

Diethyl 5-chloro-2-(3',5'-dichloro-2'-methoxyphenyl)-pyrrole-3,4-dicarboxylate (133).

The diester (124) (150 mg., 0.4 mmoles) in 10 ml of CHCl_3 was stirred with sulphuryl chloride (50 mg., 0.37 mmoles) in 5 ml of CHCl_3 at 0°C . for 2 hrs. The solvent was removed and the residue chromatographed on thin layer silica gel using ether/petroleum ether (50/50%) as solvent. The band at R_f 0.6 gave on extraction 75 mg., (46%) of the trichloropyrrole (133). Recrystallised from ether/petroleum ether, m.pt. $81-83^\circ\text{C}$.

Infrared: ν_{max} 3250, 1720, 1690, 1295, 1100, 1080, 1000, 885, 795 cm^{-1} .

Ultraviolet: λ_{max} 284 m μ . ($\log \epsilon$ 3.83).

Nuclear magnetic resonance: τ 0.15 (s broad, 1), 2.68 (s, 2), 5.75 (octet, 4), 6.38 (s, 3), 8.72 (sextet, 6).

Mass spectrometry: m/e 419:421:423:425 (100:97:32:4% M^+),
374:376:378:380 (25:25:8:1%), 346:348:350:352 (21:19:6:1%),
314:316:318:320 (25:25:10:4%), 287:289:291 (11:9:3%).
(T=85°C).

Anal. Calcd. for $C_{17}H_{16}Cl_3NO_5$: C, 48.5; H, 3.8; N, 3.3;
Cl, 25.3.

Found: C, 48.6; H, 3.9; N, 3.2;
Cl, 25.1.

Alkaline hydrolysis of Diethyl 2-phenylpyrrole-
3,4-dicarboxylate (12Q).

A mixture of the phenylpyrrole diester (2 g.,
7 mmoles) in 50 ml of ethanol and NaOH (6 g., 0.15 moles)
in 50 ml of water was refluxed for 4 hrs. The ethanol
was removed under reduced pressure and the aqueous solution
was acidified with hydrochloric acid and re-extracted with
ether. After drying over $MgSO_4$, the ether was removed
leaving 1.2 g. of crude material. Analytical t.l.c. on
silica gel using ether as solvent showed the presence
of two major components. Chromatography on silica gel
gave two fractions, (i) eluted with benzene/ether (25/75%)
yielded 0.65 g. (49%) of acid (138), (ii) eluted with
ether/acetic acid (95/5%) yielded 0.5 g. (31%) of the
pyrrole acid (139).

2-Phenylpyrrole-4-carboxylic acid (138).

Obtained as fraction (i) above, eluted with benzene/ether (25/75%). Recrystallised from acetone/light petroleum m.pt. dec. 170°C .

Infrared: ν_{max} 3375, 2600, 1645, 1220, 1135, 980, 760 cm^{-1} .

Ultraviolet: λ_{max} (0.05N Ethanolic HCl) 279 m μ . (log ϵ 4.33).

(Neutral ethanol) 283 m μ . (log ϵ 4.31).

(0.05N Ethanolic NaOH) 287 m μ . (log ϵ 4.33).

Mass spectrometry: m/e 187 (100% M^+), 170 (37%), 142 (5%), 115 (19%). (T= 150°C).

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{NO}_2$: C, 70.6; H, 4.9; N, 7.5.

Found: C, 70.0; H, 5.0; N, 7.7.

2-Phenylpyrrole-3,4-dicarboxylic acid (139).

Obtained as fraction (ii) above, eluted with ether/acetic acid (95/5%). Recrystallised from ethanol/water m.pt. dec. $228-230^{\circ}\text{C}$.

Infrared: ν_{max} 3200, 2700, 1695, 1640, 1220, 1155, 1140, 1060, 945, 770, 760, 690 cm^{-1} .

Ultraviolet: λ_{max} (0.05N Ethanolic HCl) 283 m μ . (log ϵ 3.95).

(Neutral ethanol) 285 m μ . (log ϵ 4.00).

(0.05N Ethanolic NaOH) 286 m μ . (log ϵ 4.19).

Mass spectrometry: m/e 231 (3% M^+), 213 (3%), 187 (100%), 170 (37%), 143 (7%), 142 (5%), 115 (22%), 85 (9%), 77 (7%), 63 (6%), 51 (6%), 44 (100%). (T= 140°C).

This compound did not give satisfactory elemental analysis.

Acid catalysed hydrolysis of Diethyl 2-phenylpyrrole-3,4-dicarboxylate.

A mixture of the phenylpyrrole (120) (280 mg., 1 mmole) and 1 ml of conc. sulphuric acid was stirred together at 60°C. for 4 hrs. and then poured into water. After ether extraction the ether fraction was re-extracted with sodium bicarbonate solution. Acidification of the bicarbonate extract with conc. hydrochloric acid followed by a second ether extraction, gave on evaporation of the ether 140 mg. of a mixture of acids. Chromatography on silica gel thin layer using ether/~~acetic~~ acid (90/10%) as solvent gave two fractions, (i) an acid with Rf 0.6, which was shown by its infrared spectrum to be identical with 2-phenylpyrrole-4-carboxylic acid (138). (ii) An acid with Rf 0.2 (140).

Ethyl 2-phenylpyrrole-4-carboxylate-3-carboxylic acid (140).

Obtained as fraction (ii) above. Recrystallised from acetone/petroleum ether m.pt. 170°C. dec.

Infrared: $\nu_{\max}$ 3300, 2650, 1710, 1620, 1330, 1200, 1070, 765 cm^{-1} .

Ultraviolet: $\lambda_{\max}$ 281 m μ .

Mass spectrometry: m/e 259 (95% M^+), 231 (3%), 214 (100%), 187 (11%), 170 (18%), 169 (12%), 115 (8%). (T=150°C.)

Anal. Calcd. for $\text{C}_{14}\text{H}_{13}\text{NO}_4$: C, 64.9; H, 5.1; N, 5.4.

Found: C, 65.2; H, 5.0.

Ethyl 2-bromo-5-phenylpyrrole-3 or 4-carboxylate-4 or 3-carboxylic acid (141).

The bromopyrrole diester (127) (256 mg., 0.7 mmoles) was refluxed in 5 ml of aqueous ethanol (20%) with NaOH (400 mg., 10 mmoles) for 2 hrs. The ethanol was removed and the aqueous solution extracted with ether. The aqueous residue was acidified with dilute hydrochloric acid and re-extracted with ether. This ether solution was dried over Na_2SO_4 and evaporated. The residue was chromatographed on thin layer silica gel and yielded 81 mg. (38%) of the pyrrole half ester (141), as well as unhydrolysed material. Recrystallised from toluene, m.pt. dec. 154°C . Infrared: ν_{max} 3200, 2700, 1680, 1620, 1510, 1320, 1250, 1075, 1015, 780, 770, 700 cm^{-1} .

Ultraviolet: λ_{max} (0.05N Ethanolic HCl) 280 m μ . (log ϵ 4.02).
 (Neutral ethanol) 292 m μ . (log ϵ 3.98).
 λ_{max} (0.05N Ethanolic NaOH) 252 m μ . (log ϵ 4.12).
 315 m μ . (log ϵ 3.97).

Mass spectrometry: m/e 337:339 (100:100% M^+). (T= 140°C).

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{NBrO}_4$: C, 49.7; H, 3.6; N, 4.1; Br, 23.6.

Found: C, 49.7; H, 3.6; N, 4.3;

Br, 23.6.

Ethyl 2-chloro-5-phenylpyrrole-3 or 4-carboxylate-4 or 3-carboxylic acid (142).

375 mg. of the chloropyrrole diester (130) was

refluxed in 10 ml of 50% aqueous ethanol containing 0.75 g. of NaOH for 2 hrs. The ethanol was removed under reduced pressure and the aqueous solution acidified with dilute hydrochloric acid. Ether extraction followed by evaporation gave 305 mg. of oil, which was chromatographed on thin layer silica gel using ether/hexane (60/40% as the solvent. A band at Rf. 0.6 yielded unhydrolysed starting material, while that at Rf 0.2 gave the pyrrole (142) as the major product from the reaction.

Recrystallised from ethanol/water m.pt. dec. 175°C.

Infrared: $\nu_{\max}$ 3200, 2600, 1675, 1615, 1520, 1495, 1330, 1260, 1225, 1080, 1020, 775, 700 cm^{-1} .

Ultraviolet: $\lambda_{\max}$ (0.05 Ethanolic HCl) 280 m μ . (log ϵ 4.08).
 (Neutral ethanol) 291 m μ . (log ϵ 4.04).
 (0.05N Ethanolic NaOH) 253 m μ . (log ϵ 4.12).
 316 m μ . (log ϵ 4.05).

Mass spectrometry: m/e 293:295 (30:10%), 248:250 (43:19%), 249:251 (45:15%), 221:223 (50:17%), 204:206 (100:31%).
 (T=160°C).

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{NClO}_4$: C, 57.3; H, 4.1; N, 4.8; Cl, 12.0.

Found: C, 57.1; H, 4.3; N, 4.7;

Cl, 12.1.

2-(2'-Methoxyphenyl)pyrrole-3,4-dicarboxylic acid (143).

The pyrrole diester (121) (3 g., 9.5 mmoles) was

refluxed with NaOH (9 g., 0.23 moles) in 100 ml of 50% aqueous ethanol for 4 hrs. The ethanol was removed and the aqueous residue extracted with ether. The aqueous fraction was acidified with conc. hydrochloric acid and re-extracted with ether. This ether extract was dried over MgSO_4 , evaporated and the residue chromatographed on silica gel. The fraction eluted with ether/acetic acid (90/10%) gave 1.5 g. (61%) of the pyrrole diacid (143). Recrystallised from acetic acid m.pt. dec. 143°C .

Infrared: ν_{max} 3300, 2600, 1680, 1640, 1595, 1340, 1295, 1255, 1220, 1065, 1035, 795, 755 cm^{-1} .

Ultraviolet: λ_{max} (0.05N Ethanolic HCl) 280 m μ . (log ϵ 4.07).
 (Neutral ethanol) 280 m μ . (log ϵ 4.05).
 (0.05N Ethanolic NaOH) 283 m μ . (log ϵ 4.39).
 301 m μ . (log ϵ 4.39).

Mass spectrometry: m/e 217 (100%), 202 (9%), 174 (10%), 173 (12%), 172 (10%), 158 (19%), 157 (10%), 130 (15%).
 (T= 110°C).

No molecular ion peak was observed.

No satisfactory analysis could be obtained for this compound.

Ethyl 2-(5'-bromo-2'-methoxyphenyl)-5-bromopyrrole-3 or 4-carboxylate-4 or 3-carboxylic acid (145).

The bromopyrrole diester (128) (2.8 g., 5.9 mmoles) was refluxed in 75 ml of 33% aqueous ethanol with NaOH (2.8 g., 0.07 moles) for 4 hrs. The ethanol was removed

and the aqueous residue extracted with ether. The aqueous solution was then acidified with conc. hydrochloric acid and re-extracted with ether. After drying this extract over MgSO_4 , it was concentrated and on standing deposited 2.2 g. (84%) of the pyrrole half ester (145). Recrystallised from acetone/light petroleum m.pt. dec. 185°C .

Infrared: ν_{max} 3400, 3200, 2600, 1680, 1610, 1510, 1310, 1255, 1135, 1020, 830, 780 cm^{-1} .

Ultraviolet: λ_{max} (0.05N Ethanolic HCl) 280 m μ . (log ϵ 3.91).
 305 m μ . (shoulder).
 (Neutral ethanol) 283 m μ . (log ϵ 3.87).
 305 m μ . (shoulder).
 (0.05N Ethanolic NaOH) 249 m μ . (log ϵ 4.11).
 319 m μ . (log ϵ 3.87).

Mass spectrometry: m/e 445:447:449 (15:29:15% M^+),
 400:402:404 (52:100:48%), 399:401:403 (8:22:24%), 356:358:
 360 (15:26:14%), 342:344:346 (12:17:8%), 441:443:445
 (12:24:13%), 313:315:317 (10:20:10%). ($T = 150^\circ\text{C}$).

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{NBr}_2\text{O}_5$: C, 40.3; H, 2.9; N, 3.1;
 Br, 35.7.

Found: C, 40.3; H, 3.0; N, 3.2;

Br, 35.1.

2-(3',5'-Dibromo-2'-methoxyphenyl)pyrrole-3,4-
dicarboxylic acid (144).

The pyrrole diester (123) (435 mg., 0.92 mmoles)

was refluxed with NaOH (2 g., 0.05 moles) in 40 ml of 50% aqueous ethanol for 4 hrs. After workup as outlined for previous ester hydrolyses, a yield of 320 mg. (83%) of the pyrrole diacid was obtained. Recrystallised from acetone/light petroleum m.pt. dec. 220°C.

Infrared: $\nu_{\max}$ 3375, 3150, 2600, 1670, 1630, 1525, 1420, 1210, 1070, 995, 880, 770 cm^{-1} .

Ultraviolet: $\lambda_{\max}$ (0.05N Ethanolic HCl) 273 m μ . (log ϵ 3.97).
(Neutral ethanol) 275 m μ . (log ϵ 3.89).
(0.05N Ethanolic NaOH) 303 m μ . (log ϵ 4.12).

Mass spectrometry: m/e 417:419:421 (5:11:5% M^+), 399:401:403: (7:14:7%), 386:388:390 (30:52:27%), 369:371:373:375:377 (12:23:48:60:28%), 368:370:372 (50:100:55%), 44 (100%). (T=160°C).

This compound did not give satisfactory elemental analysis.

2-(3',5'-Dichloro-2'-methoxyphenyl)pyrrole-3,4-dicarboxylic acid (146).

The pyrrole diester (124) (0.5 g., 1.3 mmoles) was refluxed with NaOH (2 g., 0.05 mole) in 40 ml of 50% aqueous ethanol for 4 hrs. Workup as outlined for previous ester hydrolyses yielded 375 mg. (88%) of the pyrrole diacid (146). Recrystallised from ether/light petroleum, m.pt. dec. 110°C.
Infrared: $\nu_{\max}$ 3400, 3150, 2500, 1675, 1640, 1525, 1420, 1260, 1210, 990, 875, 800, 760 cm^{-1} .

Ultraviolet: λ_{max} (0.05N Ethanolic HCl) 273 m μ . (log ϵ 3.69).
 (Neutral ethanol) 275 m μ . (log ϵ 3.62).
 (0.05N Ethanolic NaOH) 302 m μ . (log ϵ 3.87).

Mass spectrometry: m/e 329:331:333 (20:14:2% M^+),
 311:313:315 (11:8:2%), 298:300:302 (32:21:4%), 281:283:
 285:287:289 (16:15:23:13:3%), 280:282:284 (100:69:15%),
 45 (65%). (T=150°C).

This compound did not give satisfactory elemental analysis.

Methyl 2-Phenylpyrrole-4-carboxylate (147).

2-Phenylpyrrole carboxylic acid (138) (500 mg.,
 2.7 mmoles) in 5 ml of methanol was treated with diazo-
 methane (~200 mg., 5 mmoles) in 75 ml of ether.

Evaporation of the solvent and recrystallisation gave
 500 mg. (93%) of the pyrrole ester (147). Recrystallised
 as needles from benzene/light petroleum, m.pt. 170-172°C.

Infrared: ν_{max} 3300, 1675, 1355, 1280, 1220, 1130, 1000,
 775, 760 cm^{-1} .

Ultraviolet: λ_{max} 278 m μ . (log ϵ 4.20).

Nuclear magnetic resonance: (DMSO- d_6) τ -1.95 (broad s, 1),
 2.49 (q, 1 $J_{15}=3.0$ $J_{35}=1.4$), 2.25-2.9 (m, 5), 3.1 (q, 1
 $J_{13}=2.8$ $J_{35}=1.4$), 6.25 (s, 3).

Mass spectrometry: m/e 201 (80% M^+), 170 (100%), 115 (22%),
 85 (16%). (T=105°C).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.6; H, 5.5; N, 7.0.

Found: C, 71.5; H, 5.5; N, 7.1.

Dimethyl 2-Phenylpyrrole-3,4-dicarboxylate (148).

2-Phenylpyrrole dicarboxylic acid (139) (150 mg., 0.65 mmoles) in 5 ml of methanol was treated with diazomethane (~100 mg., 2.5 mmoles) in 25 ml of ether. Removal of solvent and recrystallisation gave 150 mg. of the pyrrole diester (148). Recrystallised from ether, m.pt. 103-105°C.

Infrared: $\nu_{\max}$ 3300, 1720, 1680, 1355, 1270, 1205, 1065, 780, 700 cm^{-1} .

Ultraviolet: $\lambda_{\max}$ 278 m μ . (log ϵ 4.11).

Nuclear magnetic resonance: τ 0.08 (broad s, 1), 2.73 (s, 5), 2.84 (s, 1) 6.25 (s, 6).

Mass spectrometry: m/e 259 (70% M^+), 228 (100%), 198 (8%), 196 (8%), 169 (7%), 170 (6%), 115 (9%), 114 (10%). (T=105°C).

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.9; H, 5.1, N, 5.4.

Found: C, 64.6; H, 5.1; N, 5.6.

Methylation of 2-(2'-Methoxyphenyl)pyrrole-3,4-dicarboxylic acid (143).

The pyrrole diacid (143) (700 mg., 2.7 mmoles) in 5 ml of methanol was treated with diazomethane (0.3 g., 7.5 mmoles) in 100 ml of ether. The solvent was evaporated and the residue taken up in benzene, washed with sodium bicarbonate solution and dried over $MgSO_4$. Removal of the benzene gave 480 mg. (61%) of the pyrrole diester (149).

Acidification of the bicarbonate washings with conc. hydrochloric acid, followed by ether extraction, drying over MgSO_4 and evaporation gave 270 mg. of pyrrole acids. This residue with an R_f 0.5 could not be resolved on thin layer silica gel using ether/acetic acid (95/5%) as solvent and showed similar mobility to the starting diacid (143). Fractional crystallisation from ethanol/water gave the pyrrole half ester (150).

Dimethyl 2-(2'-methoxyphenyl)pyrrole-3,4-dicarboxylate (149).

Obtained as the neutral fraction from the methylation above. Recrystallised from ether, m.pt. 116-118°C.

Infrared: ν_{max} 3300, 1725, 1685, 1505, 1350, 1265, 1205 1085, 1065, 760 cm^{-1} .

Ultraviolet: λ_{max} 274 m μ . ($\log \epsilon$ 4.02), 294 m μ . ($\log \epsilon$ 4.01).

Nuclear magnetic resonance: τ 0.21 (broad s, 1), 2.75 (s, 1), 2.63-3.36 (m, 4), 6.26 (s, 9).

Mass spectrometry: m/e 289 (100% M^+), 259 (16%), 258 (83%), 212 (26%), 201 (15%), 185 (10%), 170 (24%), 129 (14%), 115 (10%), 44 (20%). (T=100°C).

Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{NO}_5$: C, 62.3; H, 5.2; N, 4.8.

Found: C, 62.1; H, 5.3; N, 5.1.

Methyl 2-(2'-methoxyphenyl)pyrrole-3-carboxylate-4-carboxylic acid (150).

Obtained as a bicarbonate soluble component from the partial methylation of the pyrrole dicarboxylic acid

(143) above, after recrystallisation from ethanol/water had m.pt. dec. 162°C.

Infrared: $\nu_{\max}$ 3150, 2600, 1675, 1620, 1565, 1525, 1330, 1285, 1250, 1205, 1065, 775, 760 cm^{-1} .

Ultraviolet: $\lambda_{\max}$ (0.05N Ethanolic HCl) 281 m μ . (log ϵ 3.95).
 298 m μ . (shoulder).
 (Neutral ethanol) 281 m μ . (log ϵ 3.96).
 298 m μ . (shoulder).
 (0.05N Ethanolic NaOH) 282 m μ . (log ϵ 4.05).
 297 m μ . (log ϵ 4.06).

Mass spectrometry: m/e 275 (100% M^+), 244 (58%), 231 (10%), 217 (22%), 212 (13%), 200 (9%), 185 (18%), 171 (8%), 170 (14%), 157 (9%). (T=130°C).

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.16; H, 4.8; N, 5.1.

Found: C, 61.0; H, 4.8; N, 5.0.

Decarboxylation of the 2-Phenylpyrrole carboxylic acids (138) and (139).

500 mg. of the mixture of the pyrrole acids (138) and (139), obtained as the crude hydrolysis products of diethyl 2-phenylpyrrole dicarboxylate (120), were heated in 0.5 ml of glycerol at 250°C. for 10 mins. The product, which sublimed out was collected (21 mg.) and shown by infrared and ultraviolet spectroscopy, melting point and behaviour on thin layer silica gel to be identical with a sample of 2-phenylpyrrole (96) prepared by an alternative route.

Decarboxylation of the 2-(2'-Methoxyphenyl)pyrrole-carboxylic acids (143) and (150).

200 mg. of the mixture of pyrrole acids (143) and (150), obtained as the base soluble fraction from the incomplete methylation of the pyrrole diacid (143), were heated in 2 ml of glycerol at 180-200°C. for 2 hrs. After pouring into water and extraction with ether, drying of the ether extract over $MgSO_4$ and evaporation gave a mixture of products. Chromatography on thin layer silica gel using ether/petroleum ether as solvent (5/95%) gave a band at R_f 0.3, which yielded the pyrrole (152).

An extract of the baseline was rechromatographed on silica gel using ether as solvent to give a band at R_f 0.9, which yielded the pyrrole-ester (151).

Methyl 2-(2'-methoxyphenyl)pyrrole-3-carboxylate (151).

Obtained from the band at R_f 0.9 on chromatography of the decarboxylation products of acids (143) and (150) above. Recrystallised from ether m.pt. 135-137°C.

Infrared: ν_{max} 3375, 1685, 1275, 1140, 1025, 750, 740 cm^{-1} .

Ultraviolet: λ_{max} 283 m μ ., 295 m μ ..

Nuclear magnetic resonance: (DMSO- d_6) τ 2.7-3.2 (m, 4), 3.3 (t, 1), 3.6 (t, 1), 6.35 (s, 3), 6.5 (s, 3).

Mass spectrometry: m/e 231 (100% M^+), 200 (62%), 185 (41%), 172 (27%), 157 (16%), 138 (17%). (T=75°C).

No elemental analysis was obtained for this compound.

2-(2'-Methoxyphenyl)pyrrole (152).

70 mg. of the diacid (143) was heated in 2 ml. of digol at 220°C. for $\frac{1}{2}$ hr. After pouring into water and extraction with ether, the ethereal solution was concentrated and chromatographed on thin layer silica gel using ether/petroleum ether (5/95%) as solvent to give 10 mg. of the pyrrole (152).

This product was also obtained from the decarboxylation of the mixture of acids (143) and (150).

Infrared: $\nu_{\max}$ 3500, 1600, 1580, 1500, 1235, 1115, 1050, 1030, 760, 730 cm^{-1} .

Ultraviolet: $\lambda_{\max}$ 284 m μ ., 306 m μ ..

Nuclear magnetic resonance: τ 2.3-3.3 (m, 4), 3.18 (m, 1), 3.4 (m, 1), 3.71 (m, 1), 6.09 (s, 3).

Mass spectrometry: m/e 173 (100% M^+), 172 (15%), 158 (52%), 130 (21%), 77 (11%), 58 (16%), 43 (32%). (T=40°C).

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.3; H, 6.4; N, 8.1.

Found: C, 76.1; H, 6.7; N, 7.6.

2-(3',5'-Dibromo-2'-methoxyphenyl)pyrrole (35).

200 mg. of the diacid (144) was heated in 1 ml of digol at 250°C. for $\frac{1}{2}$ hr. After work-up as described for pyrrole (152), the product was chromatographed to yield 10 mg. of pyrrole (35).

Infrared $\nu_{\max}$ 3460, 1570, 1235, 1115, 1045, 985, 840
720 cm^{-1} .

Ultraviolet: $\lambda_{\max}$ 301 m μ .

Nuclear magnetic resonance: (CCl_4) τ 2.46 (d, 1), 2.65
(d, 1), 3.22 (m, 1), 3.52 (m, 1), 3.8 (m, 1), 6.26 (s, 3).

Mass spectrometry: m/e 329:331:333 (52:100:50 M^+),
314:316:318 (35:61:30%), 286:288:290 (7:12:7%), 235:237
(26:25%), 207:209 (10:9%), 141 (11%), 128 (36%),
64 (35%). (T=45°C).

2-(3',5'-Dichloro-2'-methoxyphenyl)pyrrole (153).

A mixture of 200 mg. of the diacid (146), 500 mg.
of powdered soda glass and 25 mg. of NaOH were heated
together in 2 ml of dipol at 170°C. for 1 hr. After
workup by the method previously outlined for other
decarboxylation products, 25 mg. of the pyrrole (153)
was obtained. Recrystallised from petroleum ether
m.pt. 107-108°C.

Infrared: $\nu_{\max}$ 3450, 1585, 1230, 1120, 1060, 1045, 975,
845, 740 cm^{-1} .

Ultraviolet: $\lambda_{\max}$ 300 m μ .

Nuclear magnetic resonance: τ 0.2 (s broad, 1), 2.66
(d, 1), 2.93 (d, 1), 3.25 (m, 1), 3.56 (m, 1), 3.9 (m, 1),
6.28 (s, 3).

Mass spectrometry: m/e 241:243:245 (100:70:9% M^+),
226:228:230 (90:60:8%), 198:200:202 (19:13:2%), 191:193
(15:5%), 128 (14%), 99 (11%). (T=70°C).

Anal. Calcd. for $C_{11}H_9NOCl_2$: Cl, 29.3

Found: Cl, 28.6.

2-(5'-Bromo-2'-methoxyphenyl)-3,4,5-tribromopyrrole (156).

100 mg of the pyrrole (98) in 15 ml of $CHCl_3$ was treated with 190 mg of bromine in 10 ml of $CHCl_3$ at $0^\circ C$. After stirring for 2 hrs. the solvent was removed and the residue chromatographed on silica gel thin layer using ether. Extraction of a band at R_f 0.7 gave 190 mg of the pyrrole (156). Recrystallised from petroleum ether, m.pt. $127-129^\circ C$.

Infrared: ν_{max} 3500, 1495, 1240, 1030, 970, 805 cm^{-1} .

Ultraviolet: λ_{max} 282 m μ , 307 m μ .

Nuclear magnetic resonance: τ 0.7 (s broad, 1), 2.0 (d, 1), 2.65 (q, 1), 3.22 (d, 1), 6.12 (s, 3).

Mass spectrometry: m/e 485:487:489:491:493 (20:70:100:: 65:17% M^+), 470:472:474:476:478 (1:3:4:2:1%), 391:393:395:397 (19:50:47:18%). ($T=100^\circ C$).

No analysis was obtained for this compound.

4-(5'-Bromo-2'-methoxyphenyl)-2,3-dibromo-4-oxo-but-2-enamide (158).

The tetrabromopyrrole (156) slowly decomposed on standing to give (158). Recrystallised from benzene, m.pt. $192-194^\circ C$.

Infrared: $\nu_{\max}$ 3450, 1725, 1695, 1270, 1105, 1050,
1020, 990, 920, 820 cm^{-1} .

Mass spectrometry: m/e 439:441:443:445 (29:88:85:28% M^+),
422:424:426:428 (3:10:10:3%), 360:362:364 (50:100:50%).

Anal. Calcd. for $\text{C}_{11}\text{H}_8\text{NO}_3\text{Br}_3$: C, 30.3; H, 1.9; Br, 53.6.

Found: C, 29.8; H, 2.0; Br, 53.4

2-(5'-Bromo-2'-methoxyphenyl)-3,4-dibromo-2-ethoxy-
 Δ^3 -pyrrolin-5-one (159).

500 mg of pyrrole (98) in 25 ml of CHCl_3 /ethanol
(4/1) were stirred overnight with 1.25 g. of bromine
(4 molar ratio) in 30 ml of CHCl_3 . After removal of
solvent and chromatography on silica gel thin layer,
compound (159) was obtained. Recrystallised from
benzene/petroleum ether, m.pt. dec. 180°C .

Infrared: $\nu_{\max}$ 3250, 3150, 1710, 1495, 1275, 1105,
820 cm^{-1} .

Nuclear magnetic resonance: τ 2.1 (d, 1), 2.6 (q, 1) 3.32
(d, 1), 6.3 (s, 3), 6.5 (2), 8.7 (3).

Mass spectrometry: m/e 467:469:471:473 (15:42:41:14 M^+),
422:424:426:428 (35:100:97:32%), 388:390:392 (13:24:13%),
360:362:364 (7:14:7%), 328:330:332 (4:8:4%), 254:256:258
(6:10:6%), 213:215 (35:30%). (T= 130°C).

Anal. Calcd. for $\text{C}_{13}\text{H}_{12}\text{NO}_3\text{Br}_3$: C, 33.3; H, 2.6; N, 3.0;
Br, 50.9.

Found: C, 33.1; H, 2.5; N, 3.2;

Br, 51.4.

2-(5'-Chloro-2'-methoxyphenyl)-3,4,5-trichloropyrrole (155).

100 mg of the pyrrole (99) in 10 ml of CCl_4 were treated with 200 mg of sulphuryl chloride in 10 ml of CCl_4 at 0°C , and stirred overnight. Removal of the solvent and chromatography on thin layer silica gel gave 70 mg of the tetrachloropyrrole (155). Recrystallised from petroleum ether, m.pt. $117-119^\circ\text{C}$.

Infrared: ν_{max} 3450, 1505, 1370, 1240, 1130, 1020, 980, 880, 805 cm^{-1} .

Ultraviolet: λ_{max} 281 m μ ., 307 m μ ..

Nuclear magnetic resonance: τ 0.6 (s broad, 1), 2.05 (s, 1), 2.82 (q, 1), 3.15 (d, 1), 6.08 (s, 3).

Mass spectrometry: m/e 309:311:313:315:317 (78:100:49:11:1% M^+), 294:296:298:300 (31:39:19:4%), 267:269:271:273 (32:41:20:7%), 259:261:263:265 (24:23:8:1%). ($T=130^\circ\text{C}$).

Anal. Calcd. for $\text{C}_{11}\text{H}_7\text{NOCl}_4$: C, 42.5; H, 2.3; N, 4.5; Cl, 45.6.

Found: C, 42.3; H, 2.2; N, 4.4;

Cl, 46.2.

2-(3'5'-Dichloro-2'-methoxyphenyl)-3,4,5-trichloropyrrole (166).

50 mg of the pyrrole (153) in 3 ml of CCl_4 were treated with 140 mg of sulphuryl chloride in 5 ml CCl_4 at room temperature, for two hours. Removal of the solvent and chromatography on silica gel thin layer (Ether/Petroleum ether 10:90) gave 25 mg of the pentachloropyrrole (160) at R_f 0.4 m.pt. $118-121^\circ\text{C}$.

Infrared: $\nu_{\max}$ 3450, 1495, 1420, 1370, 1235, 1130, 975, 855.

Ultraviolet: $\lambda_{\max}$ 288 m μ .

Mass Spectrometry: m/e 343:345:347:349:351 (64:100:65:22:2% M^+), 328:330:332:334:336 (49:75:49:15:2%), 300:302:304:306:308:310 (4:10:10:6:10:11), 301:303:305:307:309:311 (41:65:42:15:5:3), 293:295:297:299:301 (22:29:13:2:-). (T=100°C).

2-(3'5'-Dichloro-2'-hydroxyphenyl)-3,4,5-trichloropyrrole (164).

20 mg of pyrrole in 3 ml methylene dichloride treated with 0.5 ml 12% BCl_3 in methylene chloride at -60°C overnight. The organic layer was washed with water, dried and chromatographed on silica gel. A band at R_f 0.2 yielded 12 mg phenol. m.pt. 126-130°C.

Ultraviolet: $\lambda_{\max}$ 284 m μ , 309 m μ (in neutral ethanol)
283 m μ , 293 m μ , 349 m μ (in alkaline ethanol).

Mass Spectrometry: m/e 329:331:333:335:337 (62:100:64:21:3% M^+), 294:296:298:300:302 (52:66:32:7:17), 259:260:261:263 (19:20:12:10), 267:269:271:273 (47:55:25:5%).

High Resolution Mass Spectrometry:

Mass Calcd. for $\text{C}_{10}\text{H}_4\text{NO}^{35}\text{Cl}_5$: 328.8736

Found: 328.8750

Mass Calcd. for $\text{C}_{10}\text{H}_4\text{NO}^{37}\text{Cl}_2^{35}\text{Cl}_3$: 332.8687

Found: 332.8690

2-(5'-Chloro-2'-hydroxyphenyl)-3,4,5-trichloropyrrole (163).

To 30 mg of pyrrole (155) in 5 ml of methylene chloride at -60°C was added 0.5 ml 12% BCl_3 in methylene chloride. After 24 hrs the solution was washed with water. The organic layer was chromatographed on silica gel to give 16 mg of an oil.

Ultraviolet: λ_{max} 279, 286, 312 m μ (in neutral ethanol)
280, 288, 388 m μ (in alkaline ethanol)

Mass Spectrometry: m/e 295:297:299:301 (54:68:32:

10% M^+)

No satisfactory analysis was obtained for this compound.

4-(3',5'-Dichloro-2'-methoxyphenyl)-2,3-dichloro-4-oxo-but-2-enamide (165).

24 mg of pyrrole (153) in 4 ml CCl_4 was treated with 88 mg of sulphuryl chloride in 8 ml of CCl_4 at 0°C and stirred for 1 hr. Concentration and chromatography on thin layer silica gel (Ether/Petrol 1:1) gave 22 mg (115) ($R_f = 0.6$) m.p.

Infrared: λ_{max} 3400, 3300, 1725, 1690, 990, 840.

Nuclear Magnetic Resonance: ($\text{DMSO}-d_6$) τ 2.28 (s, 2),
6.36 (s, 3)

Mass Spectrometry: m/e 341:343:345:347:349 (80:100:
47:11:1% M^+), 306:308:310:312 (98:98:36:8%), 260:262:
264:266 (60:58:20:6%), 203:205:207 (95:58:11%), 166:
168:170 (100:67:14%)

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APPENDICES

Table 1.

The Infrared and Ultraviolet Spectra of Some
Diethyl 2-phenylpyrrole-3,4-dicarboxylates

	Infrared $\nu_{\max}$ (nujol)* cm^{-1}			N-H stretching		C=O stretching		Ultraviolet $\lambda_{\max}$ (ethanol) μ	
	Substitution	2'	3'	5'				$\lambda_{\max}$	$\log \epsilon$
(120)	H	H	H	H	3250	1685		277	4.11
(122)	CH_3	H	H	H	3275	1685		283	4.20
(127)	Br	H	H	H	3175	1730 1685		276	4.13
(130)	Cl	H	H	H	3175	1725 1680		275	4.12
(121)	H	OCH_3	H	H	3225	1710		274, 293	4.07 4.02
(131)	Cl	OCH_3	H	H	3250	1715 1685		274, 296	3.90 3.85
(126)	H	OCH_3	H	Cl	3350	1710		273, 304	4.03 3.96
(132)	Cl	OCH_3	H	Cl	3250	1710 1675		274, 304	3.91 3.84
(125)	H	OCH_3	H	Br	3360	1710		275, 305	4.04 3.96
(128)	Br	OCH_3	H	Br	3250	1710 1675		275, 305	3.96 3.84
(124)	H	OCH_3	Cl	Cl	3300	1710 1685		283	4.0
(133)	Cl	OCH_3	Cl	Cl	3250	1720 1690		284	3.83
(123)	H	OCH_3	Br	Br	3350	1715 1685		284	4.0
(129)	Br	OCH_3	Br	Br	3250	1715, 1690		285	3.96

* Infrared spectra of all compounds $\nu_{\max}$ (carbon tetrachloride)

3475 cm^{-1} (N-H stretching), 1710-1720 cm^{-1} (C=O)

Table 2.

The Infrared and Ultraviolet Spectra of Some

2-Phenylpyrrole Esters

Substitution			Infrared $\lambda_{\max}$ (nujol) cm^{-1}		Ultraviolet $\lambda_{\max}$ (ethanol) $\text{m}\mu$	
2'	3	4	N-H stretching C=O stretching		$\lambda_{\max}$	$\log \epsilon$
		5				
*	H	H	-	-	308	4.39
		COOC ₂ H ₅				
+	H	COOCH ₃	3270	1730, 1680	242, 276	4.38, 4.37
		COOCH ₃				
		COOCH ₃			294, 306	4.40, 4.41
(147)	H	COOCH ₃	3300	1675	278	4.20
(148)	H	COOCH ₃	3300	1720, 1680	278	4.11
(149)	OCH ₃	COOCH ₃	3300	1725, 1685	274, 294	4.02, 4.01

* S. Umio et al. Chem. Pharm. Bull., 17, 582 (1969)+ T. Sheradsky Tetrahedron Letters, 25, (1970)

Table 3. The N.m.r. Spectra of Diethyl 2-phenylpyrrole-3,4-dicarboxylates*

Compound	Phenyl ring					Pyrrole ring			
	2'	3'	4'	5'	6'	1	3	4 [†]	5
							CH ₃ CH ₂ } J=6.8 Hz		
(120)	← 2.75(s) →					0.26	8.75	8.8 (6) [‡]	2.93(d)
							5.81	5.81(4)	
(122)	← 2.78(s) →					0.46	8.75	8.78(6)	CH ₃
							5.82	5.83(8)	
(130)	← 2.63(s) →					0.71	8.76	8.66(4)	Cl
							5.70	5.63(8)	
(127)	← 2.62(s) →					0.56	8.76	8.63(4)	Br
							5.70	5.66(8)	
(121)	OCH ₃	← 2.55-3.3(m) →				0.17	8.72	8.78(6)	2.76(d)
	6.26(s)						5.8	5.8 (4)	
(131)	OCH ₃	← 2.5-3.25(m) →				0.7	8.8	8.73(6)	Cl
	6.15(s)						5.82	5.78(8)	
(126)	OCH ₃	3.27	2.87	Cl	2.72	0.03	8.75	8.78(6)	2.74(d)
	6.3(s)	(d)	(q)		(d)		5.70	5.72(8)	
(125)	OCH ₃	3.33	2.70	Br	2.58	0.01	8.70	8.74(6)	2.81(d)
	6.3(s)	(d)	(q)		(d)		5.77	5.81(8)	
(132)	OCH ₃	3.25	2.82	Cl	2.66	0.35	8.72	8.68(6)	Cl
	6.21(s)	(d)	(q)		(d)		5.75	5.75(4)	
(128)	OCH ₃	3.25	2.66	Br	2.51	0.44	8.72	8.68(6)	Br
	6.2(s)	(d)	(q)		(d)		5.74	5.74(4)	
(124)	OCH ₃	Cl	2.71	Cl	2.71	0.02	8.66	8.76(6)	2.62(d)
	6.57(s)		(s)		(s)		5.78	5.78(4)	
(123)	OCH ₃	Br	2.42	Br	2.55	-0.15	8.68	8.80(4)	2.72(d)
	6.52(s)		(d)		(q)		5.8	5.8 (4)	
(133)	OCH ₃	Cl	2.68	Cl	2.68	0.15	8.75	8.68(6)	Cl
	6.38(s)		(s)		(s)		5.78	5.72(8)	
(129)	OCH ₃	Br	2.42	Br	2.53	0.13	8.76	8.66(4)	Br
	6.42(s)		(d)		(d)		5.74	5.72(8)	

* Spectrum recorded in CDCl₃

† Somewhat arbitrary assignment to 3,4-protons

‡ numbers of lines in spectra of methyl and methylene groups of esters

Table 4.

Main Mass Spectral Fragmentation Pathways

in Diethyl 2-Phenylpyrrole-3,4-dicarboxylates		M/e (% Abundance)*						
		Associated metastable.						
2-Substituent	5-Substituent	M ⁺	(M-45) ⁺	(M-73) ⁺	(M-91) ⁺	(M-72) ⁺	(M-28) ⁺	(M-100) ⁺
(120)	Phenyl	287 (100)	242 (49)	214 (72)	196 (6)	215 (15)	259 (4)	187 (3)
			*204	*189	*179.5	*181	*233.6	*135
(127)	Phenyl	365:367 (100:100)	320:322 (38:38)	292:294 (53:48)	274:276 (9:10)	293:295 (15:13)	337:339 (3:3)	265:267 (4:4)
			*282.5	*266.5	*257	*235	*311	
(130)	Phenyl	321:323 (100:29)	276:278 (29:10)	248:250 (49:16)	230:232 (10:5)	249:251 (12:4)	293:295 (4:2)	221:223 (4:2)
			*237.3	*222.8	*213.3	*193	*269.5	*166.5

Fragmentation Pathway see Scheme I p 67

* Metastable peak associated with formation of ion peak.

For isotopic metastable peaks, only the lowest peak value is reported.

Table 5.

Main Mass Spectral Fragmentation Pathways

in Diethyl 2-(2'-Methoxyphenyl)pyrrole-3,4-dicarboxylates[†]

2-Substituent	5-Substituent	M ⁺	(M-45) ⁺	(M-73) ⁺	(M-91) ⁺	(M-105) ⁺	(M-119) ⁺	(M-132) ⁺
(121) 2'-Methoxyphenyl	H	317 (100)	272 (44) *233.3	244 (30) *219	226 (4) *209.3	212 (20) *184.5	198 (7)	185 (18)
(131) 2'-Methoxyphenyl	Cl	351:353 (100:37)	306:308 (30:10) *266.6	278:280 (26:9) *252:5 *243	260:262 (6:3) *243	246:248 (18:8) *217.5	232:234 (6:7) *207	219:221 (13:6)
(126) 5'-Chloro- 2'-methoxyphenyl	H	351:353 (100:39)	306:308 (50:19) *266.5	278:280 (52:20) *252.5	260:262 (4:4) *243	246:248 (41:20) *217.5	232:234 (6:8) *207	219:221 (33:13)
(125) 5'-Bromo- 2'-methoxyphenyl	H	395:397 (100:98)	350:352 (40:40) *310	322:324 (38:40) *296	304:306 (3:3) *287	290:292 (30:30) *261	263:265 (26:25)	
(132) 5'-Chloro- 2'-methoxyphenyl	Cl	385:387:389 (100:65:11)	340:342:344 (21:14:3) *300.3	312:314:316 (20:12:3) *286.3	294:296:298 (2:2:1) *277	280:282:284 (12:10:3) *251	266:268:276 (3:5:4) *240.5	253:255:257 (8:6:1) *228.5
(128) 5'-Bromo- 2'-methoxyphenyl	Br	473:475:477 (54:100:54)	428:430:432 (18:34:17) *387.5	400:402:404 (29:40:24) *374	382:384:386 (3:6:6) *365	368:370:372 (17:35:22)	354:356:358 (4:14:20)	341:343:345 (28:49:24)

[†] Fragmentation Pathways - Schm. III A69^{*} Metastable peaks associated with ion formation.

For isotopic metastable peaks, only the lowest peak value is reported.

Table 5 (cont.)

Main Mass Spectral Fragmentation Pathways in Diethyl-2-(2'-Methoxyphenyl)pyrrole-3,4-dicarboxylates [†]									
2-Substituent	5-Substituent	M ⁺	(M-43) ⁺	(M-73) ⁺	(M-91) ⁺	(M-105) ⁺	(M-119) ⁺	(M-132) ⁺	
(124) 3',5'-dichloro- 2'-methoxyphenyl	H	385:387:389 (100:73:15)	340:342:344 (55:37:17) *300.3	312:314:316 (52:35:16) *286.5	294:296:298 (51:5:5) *277	280:282:284 (78:60:20) *251	266:268:270 (15:15:12) *240.5	253:255:257 (47:29:5)	
(123) 3',5'-dibromo- 2'-methoxyphenyl	H	473:475:477 (55:100:52)	428:430:432 (26:48:25) *387.5	400:402:404 (22:40:22) *373.8	382:384:386 (21:6:6) *365	368:370:372 (38:70:44) *338.5	354:356:358 (8:14:14) *306	341:343:345 (20:31:16)	
(133) 3',5'-dichloro- 2'-methoxyphenyl	Cl	419:421:423 (425)	374:376:378 (380) *334	346:348:350 (352) *320	328:330:332 (334) *311	314:316:318 (320) *285	300:302:304 (306) *274	287:289:291 (293)	
(129) 3',5'-dichloro- 2'-methoxyphenyl	Br	551:553:555 (557)	506:508:510 (512) *464	478:480:482 (484) *451	460:462:464 (468) *431	446:448:450 (452) *405	432:434:436 (438) *375	418:420:422 (424) *345	
		(38:100:100 (40)	(8:21:21:8) *464	(11:20:17:7) *451	(11:3:4:3) *431	(11:29:30:13) *405	(3:4:5:6) *375	(8:13:12:4) *345	

[†] Fragmentation Pathway - Scheme III p 9

* Metastable peaks associated with ion formation.

For isotopic metastable peaks, only the lowest peak value is reported.

Table 6. The Ultraviolet Spectra of 2-phenyl and
2-(2'-methoxyphenyl)pyrroles (Pseudilin analogues)

<u>Compound</u>	<u>λ_{max} (ethanol)_{mμ}</u>	
	<u>neutral</u>	<u>alkali</u>
(96) 2-Phenylpyrrole	287	
(152) 2-(2'-methoxyphenyl)pyrrole	230, 284, 306	
(98) 2-(5'-bromo-2'-methoxyphenyl)pyrrole	242, 292, 319	
(99) 2-(5'-Chloro-2'-methoxyphenyl)pyrrole	241, 290, 318	
(35) 2-(3',5'-Dibromo-2'-methoxyphenyl)- pyrrole	244, 250, 301	
(153) 2-(3',5'-Dichloro-2'-methoxyphenyl)- pyrrole	242, 248, 300	
(156) 2-(5'-bromo-2'-methoxyphenyl)- 3,4,5-tribromopyrrole	282, 307	
(155) 2-(5'-Chloro-2'-methoxyphenyl)- 3,4,5-trichloropyrrole	281, 308	
(160) 2-(3',5'-Dichloro-2'-methoxyphenyl)- 3,4,5-trichloropyrrole	288	
(162) 2-(3',5'-Dichloro-2'-hydroxyphenyl)- pyrrole	243, 294, 322	255, 280, 283, 351
(163) 2-(5'-Chloro-2'-hydroxyphenyl)- 3,4,5-trichloropyrrole	279, 286, 312	280, 288, 338
(164) 2-(3',5'-Dichloro-2'-hydroxyphenyl)- 3,4,5-trichloropyrrole	284, 309	283, 293, 349

Table 7. The Main Mass Spectral Fragmentation Pathways of Some 2-(2-Methoxyphenyl)pyrroles.

Substitution																
	3'	5'	3	4	5	M ⁺	(M-15) ⁺	(M-43) ⁺	(M-70) ⁺	(M-B-X) ⁺	(M-43-X) ⁺	(M-70-X) ⁺	(M-2X) ⁺	(M-15-2X) ⁺	(M-43-2X) ⁺	(M-43-3X) ⁺
(152)	H	H	H	H	H	173(100)	158(52) *144.3	130(21) *107	(103(7))							
(98)	H	Br	H	H	H	251:253 (100:90)	236:238 (55:45) *222	208:210 (55:52) *183.5	181:183 (2:2)	157(80) *103.5	129(90)	102(75)				
(99)	H	Cl	H	H	H	207:209 (100:28)	192:194 (63:18) *178	164:166 (21:8) *140	137:139 (2:1)	157(10) *128.5	129(5)	102(8)				
(35)	Br	Br	H	H	H	329:331 :333 (52:100) :150)	314:316 :318 (35:60) :330) *299.5	286:288 :290 (7:12) :17)		235:237 (26:25) *175	207:209 (10:9) (2:2)	180:182	156(4)	128(36)		
(153)	Cl	Cl	H	H	H	241:243 :245 (100:70) :19)	226:228 :230 (90:60) :8) *212	198:200 :202 (19:13) :12) *173.3		191:193 (15:5) *163.3	163:165 (6:2) *134	136:138 (6:3)		128(14)		
(156)	H	Br	Br	Br	Br	485:487 :489:491 :493 (20:70) :100:65 :17)	470:472 :474:476 :478 (1:3:4) :2:1) *455	443:445 :446:448 :450 (3:4:2) :1) *455		391:393 :395:397 (19:50) :47:18) *325	363:365 :367:369 (2:5:5) :2) *297	406:408 :410:412 (6:10) :1) *339	312:314 :316 (3:6:3) *219	284:286 :288 (2:4:2) (5:5)	205:207	
(155)	H	Cl	Cl	Cl	Cl	309:311 :313:315 :317 (78:100) :49:11 :1)	294:296 :298:300 :302 (31:39) :19:4 :1) *279.5	266:268 :270:272 :274 (11:18) :10:5 :10) *279.5	267:269 :271:273 :275 (32:40) :20:7 :1) *228.3	259:261 :263:265 (24:23) :18:1) *228.3	231:233 :235:237 (3:3:11) :1) *199	274:276 :278:280 (10:8:3) :1) *243	224:226 :228 (4:3:1) (3:2:-)	196:198 :200		
(160)	Cl	Cl	Cl	Cl	Cl	343:345 :347:349 :351:353 (64:100) :65:22 :121-)	328:330 :332:334 :336:338 (49:75) :49:15 :121-) *313.5	300:302 :304:306 :308:310 (4:10:10) :16:10 :11) *313.5	301:303 :305:307 :309:311 (41:65) :42:15 :15:13) *276.5	293:295 :297:299 :301 (22:29) :13:2 :1-)	265:267 :269:271 :273 (7:10:5) :2:5) *276.5	308:310 :312:314 :316 (10:11:5) :3:1-)	273:275 :277:279 :316 (5:4:4:3) :3:-)	230:232 :234:236 (11:10: :3:-)	195:197 :199	

Table 8. Comparison of Microbiological Activities of
2-Benzoyl and Phenyl-polychlorinated Pyrroles.

Complete Inhibition ($\mu\text{g/ml}$)^{*}

	(12) ²⁴	(168) ¹⁴⁹	(166) ²⁴	(167) ²⁴	(164)	(169) ²⁷
<u>Staph. aureus</u> 20g-P	6.2	-	3.1	0.4	<1.5	10
<u>Staph. aureus</u> (resistant)	6.2	-	3.1	0.8	<1.5	-
<u>E. coli</u> NIHJ	-	-	-	-	25	20
<u>Shig. flexneri</u> 2a	6.2	-	>100	-	25	-
<u>Shig. flexneri</u> 1b (resistant)	6.2	-	>100	-	25	-
<u>Pseud. aeruginosa</u>	-	-	-	-	25	-
<u>Candida albicans</u>	-	-	>100	-	6.2	1
⁺ <u>Tricophyton asteroides</u>	50	6.2	6.2	<1.5	<1.5	-
⁺ <u>Tricophyton interdigitale</u>	50	6.2	12.5	<1.5	<1.5	1
⁺ <u>Tricophyton rubrum</u>	50	6.2	3.1	<1.5	<1.5	-

* Plate method, solvent acetone (maximum concentration 10%) nutrient agar medium, culture temperature 37 and 27°C, incubation time 18 hrs.

⁺ S. Agar, incubation time 7 days.

(12) R=OH X=H Y=Cl

(166) R=X=H Y=Cl

(167) R=H X=Y=Cl

(168) R=X-Y=Cl

(164)

(169)

END

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