THE PREPARATION AND SOME REACTIONS OF BROMINATED PYRROLE DERIVATIVES

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Brominated Pyrrole Derivatives   .

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PREFACE

The author would like to express her sincere thanks to Dr. Hugh J. Anderson for his valuable and patient guidance throughout the course of this work.

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Shu-fan Lee

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PART I

Discussion

Section I

Bromination of methyl 2-pyrrolecarboxylate and 2-pyrrolecarboxaldehyde.

(a) Introduction:

Methyl 2-pyrrolecarboxylate was prepared using a modification of the method of Maxim, et al, (1) as described by Anderson and Hopkins (2). The preparation of 2-pyrrolecarboxaldehyde followed the procedure described by Silverstein, et al. (3).

The methods of bromination of methyl 2-pyrrolecarboxylate and 2-pyrrolecarboxaldehyde fall into three main classes. These are brominations by molecular bromine or other neutral species, by positively charged brominating species and free radical bromine.

Owing to the charge separation, the resonance structures of type (1) b, are more important than those of type (1) c for pyrrole itself.

(I)
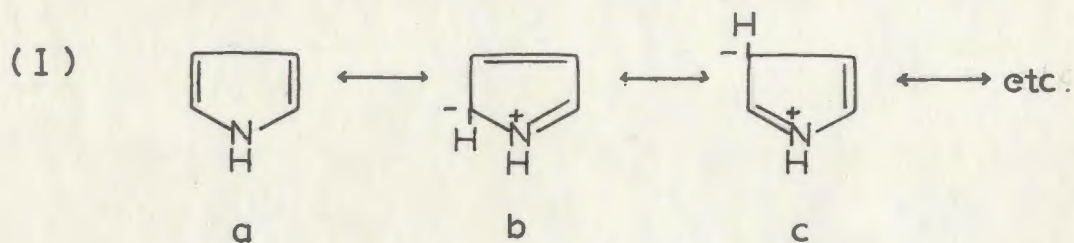
It is well known that an electrophilic reagent will attack the α-position of the pyrrole ring if that position is open. However, in the presence of an electron-withdrawing group at the 2-position, such as 2-COOCH$_3$ or 2-CHO, this situation may be altered substantially. When the reaction occurs, the combined "meta"-directing influence of the electron-withdrawing group at 2-position as well as the α-directing influence of the hetero nitrogen should be considered.

(II)

    a   b   c
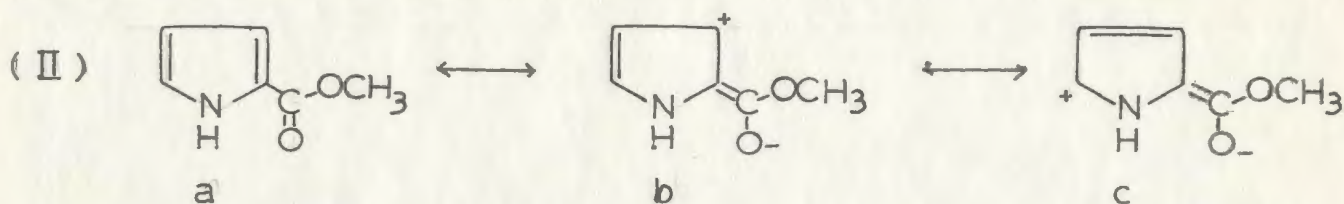
The whole ring system is deactivated to electrophilic substitution. The 3- and 5- positions are deactivated to a greater extent than the 4- position. If any electrophilic substitution occurs, both 4- and 5- positions would be expected to be attacked and 3- position is left to the last. It was reported by Anderson (4) that only 6-7 % of 3-nitropyrrole was formed along with 93-94% of 2-isomer in the nitration of pyrrole itself, whereas the nitration of 2-acetyl-pyrrole following the same procedure lead to about two parts of 2-acetyl-4-nitropyrrole to one of the 5- nitro isomer (5). The nitration of 2-pyrrolecarboxaldehyde leads to equal amounts of 4- and 5- substituted products (6).

Brominations of furfural and methyl 2-acetyl furan were found by Nazarova and Gol'dfarb (7-8) to produce the 5-bromo isomer predominantly. In contrast, the bromination of 2-acetothienone (9) and 2-pyrrole ester or 2-pyrrole aldehyde have produced mixtures of 4-, 5-, and

4,5-dibromo isomers. This indicates that the α-directing effect of the hetero sulphur or nitrogen in thiophene or pyrrole during bromination is less than that of the oxygen in furan.

In the preparative bromination of methyl 2-pyrrole-carboxylate and 2-pyrrolecarboxaldehyde, the former gave a better yield than the latter and 4-substitution pre-dominated. Similar results were obtained from the isopropy-lation of 2-pyrrole ester (2), 2-pyrrole ketone, 2-pyrrole aldehyde (10) and 2-thienyl ketone (11). Sub-stitution in the 5-position still occurred to a consider-able extent which depended on the temperature of reaction. There was no evidence for the presence of the 3-bromo derivatives. This suggested that the 2-aldehyde group has a stronger electron-withdrawing effect on the pyrrole ring than the 2-ester group and that the "meta"- directing group in the 2-position of pyrrole overcomes the directive influence of the nitrogen atom of the nucleus.

The two mono-bromo derivatives obtained on treat-ment of the starting material with one mole of brominating reagent are the 4- and 5- isomers. Using an excess of brominating reagent under the same conditions gave the 4,5-dibromo and 3, 4, 5-tribromo derivatives in very high yield.

The ratios of isomers of the reaction mixtures were evaluated by triangulation of the peak areas drawn by the recorder in gas-liquid partition chromatography. Stand-ardization against a series of mixtures of known proportions showed that this method gave results accurate to about 2%.

(b)   Structure determination of the bromo-pyrrole derivatives:

Nuclear magnetic resonance spectroscopy was applied primarily for determination of the orientation of bromine function in the reaction products. The relative positions of α- and β - hydrogens of pyrrole are unchanged in any kind of solvent. The fact that resonance of the α- hydrogens occurs at lower field than that of the β- hydrogens in pyrrole has been ascribed by Jackman (12) to lower electron density of the α - hydrogens. However, in the presence of a diamagnetically anisotropic carbonyl function in the 2-position, the electron-withdrawing effect from the 3- and 5- positions, in accordance with resonance forms (II) [a, b, c] is evident from the shifts toward lower field of the resonances of the 3- and 5- hydrogens, whilst the 4-hydrogen shifts only slightly, (Table II). For the same reason, an electron donating group at the 2-position will cause shifts toward higher field especially of the 3- and 5- hydrogens. It is evident from chemical shift data that the influence of a substituent on the electron density of the ring protons can be studied. However, it is difficult to correlate the chemical shifts of pyrrole derivatives with chemical reactivity since ring currents and solvation are also involved.

The chemical shifts of methyl 2-pyrrolecarboxylate and 2-pyrrolecarboxaldehyde are recorded in Table I, the hydrogens at the 4-position of 5-bromopyrrole derivatives are readily recognised as the highest field ones, but the hydrogens at 3- and 5- positions in the 4-bromo compounds can not be distinguished from each other by chemical shifts.   The

two absorptions at lower field could be due to hydrogens in either 3- or 5- position. The introduction of a bromine substituent into pyrrole ring, as in other systems (12-13), only causes minor shifts in the resonance frequencies of the remaining hydrogens. The 4, 5-dibromo structures were established by the absence of the 4- hydrogens signal of highest field and the presence of only one signal at lower field. The structures of 4-bromo derivatives were clearly defined by their n. m. r. spectra in which both ring protons appeared in the same low field region, and the characteristic resonances of 4-hydrogens were absent. It was rather difficult to verify the 5-bromo structures, as the absorptions at lower field could be the signal of 3- or 5- hydrogens, however, from their further bromination to 4, 5-dibromo derivatives, the 5-substituted structures were identified.

The resonances of the remaining hydrogens of the deuterated derivatives which were prepared from bromo derivatives by deuteration showed very little difference from those of the bromo derivatives. There was no splitting of the proton of the aldehyde group in the n. m. r. spectrum of 5-bromo- or 5-deutero-2-pyrrolecarboxaldehyde. This proved that the 5- hydrogen atom or bromo- or deutero-pyrrole aldehyde was displaced by bromine or deuterium, otherwise the coupling of the 5-hydrogen and the proton of the aldehyde group must occur as observed in 4-bromo or 4-cyano-2-pyrrolecarboxaldehyde (see Table I). Thus the chemical shifts of the parent compounds were further established.

An investigation of the n. m. r. spectra of the unsubstituted pyrrole derivatives, 6 monosubstituted and 4 disubstituted bromo- and deutero- pyrrole derivatives (Table I) showed that 5-, 3-, and 4- hydrogens had resonances centered at δ = 6.90-7.19; 6.79 - 6.98; 6.17-6.30, whilst the coupling constants fell in five distinct regions: J_{13} = 2.80 - 2.86; J_{15} = 3.04; J_{34} = 3.85 - 3.92; J_{35} = 1.40 - 1.50; J_{45} = 2.44 - 2.56; J CHO/5 = 1.10. The chemical shifts of bromo-2-pyrrole esters agreed with those obtained by Rickards (14).

By direct comparison of methyl 5-cyano-2-pyrrole-carboxylate III synthesised from the corresponding mono-bromo-2-ester (A) as well as by an unequivocal route (B), the structure of methyl 5-bromo-2-pyrrolecarboxylate was further established:
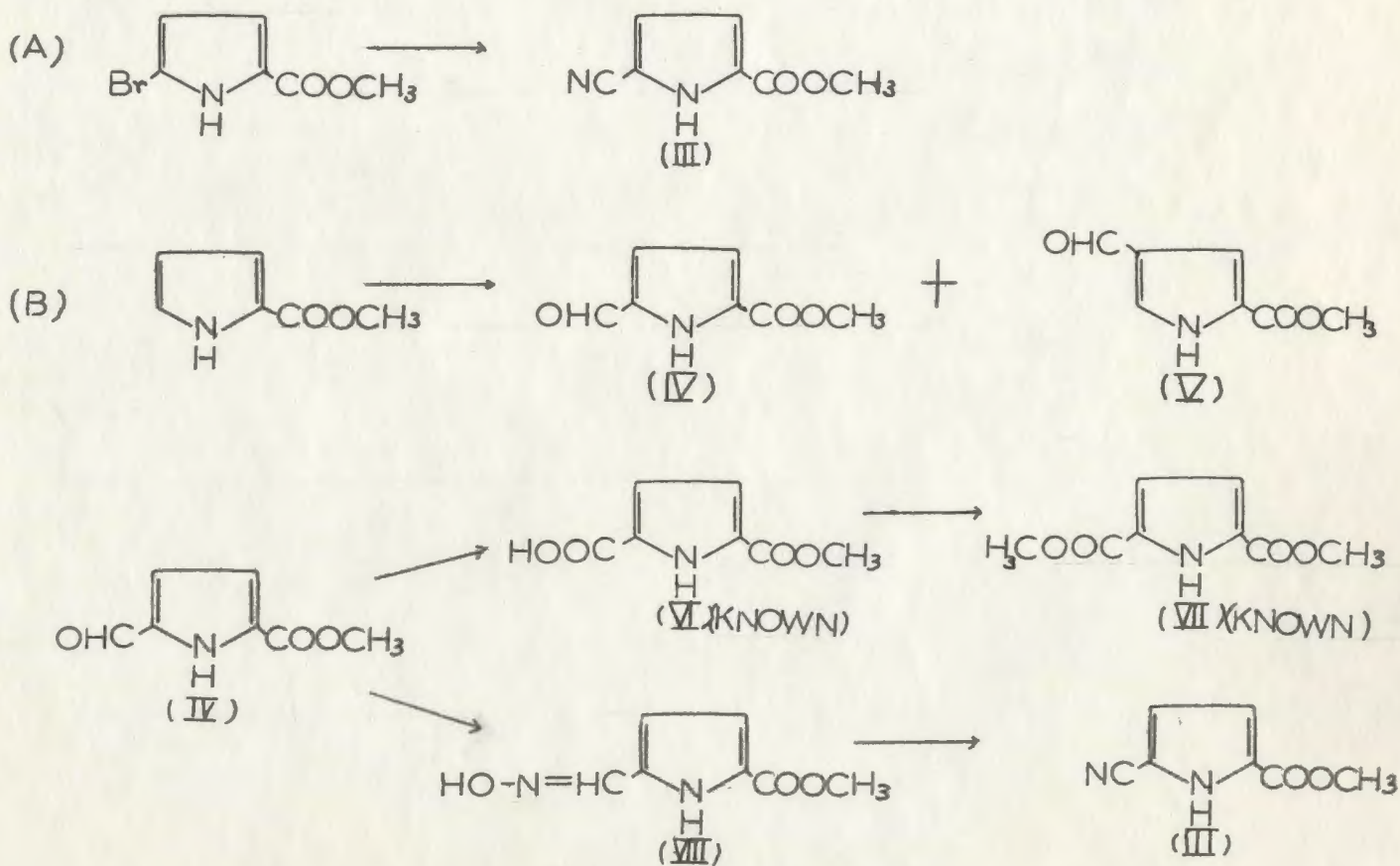
Formylation of methyl 2-pyrrolecarboxylate with phosphorus oxychloride and dimethylformamide (3) afforded two isomeric aldehyde products. Methyl 5-formyl-2-pyrrolecarboxylate (IV) was separated by fractional distillation in vacuo from corresponding 4-isomer (V). The structure of (IV) was confirmed by oxidizing it to the known acid (VI) and was further established by converting the acid to the known methyl 2,5-pyrroledicarboxylate (VII); (15). The corresponding oxime of methyl 5-formyl-2-pyrrolecarboxylate (VIII) obtained from the reaction of the aldehyde with hydroxylamine hydrochloride and sodium acetate (16-17) and the methyl 5-cyano-2-pyrrolecarboxylate (III) prepared through the dehydration of the oximes of the aldehyde (17). The infrared spectrum of this resultant cyano-2-pyrrole ester was identical with that of the specimen obtained from the corresponding bromo-2-pyrrole ester as discussed in Section IV. The mixed melting point was not depressed. Thus the methyl 5-bromo-2-pyrrolecarboxylate was firmly established. The structure of methyl 4-bromo-2-pyrrolecarboxylate was also proven by procedures similar to that described above.

4-Bromo, 5-bromo and 4,5-dibromo-2-pyrrolecarboxaldehyde were oxidised with alkaline silver oxide (18). Treatment of the corresponding acids in ether solution with diazomethane (19) gave the already proven methyl bromo-2-pyrrolecarboxylates in high yield. Mixed melting points of the products with their authentic specimens prepared by the bromination of methyl α -pyrrolecarboxylate were undepressed. The structures were also confirmed by their infrared spectra compared with those of their authentic specimens.

(c)   Bromination with molecular bromine.

The heterolytic bromination of pyrrole derivatives
with molecular bromine in the polar solvent glacial acetic
acid, and the non-polar solvent carbon tetrachloride with
aluminum chloride or iodine as catalyst was attempted.

In general, aromatic bromination (20), like bromine
addition, may be formulated as a two stage process. The first
stage is an electrophilic attack by a bromine molecule polar-
ized by a polar surface, a solvent dipole, or by a second
molecule of bromine to join with the pyrrole ring forming an
intermediate _sigma_ complex; the second stage is the removal
of a bromide ion from this addition compound with the simul-
taneous separation of a hydrogen atom as hydrogen bromide.
The mechanism of 4-substitution presumably is as follows:
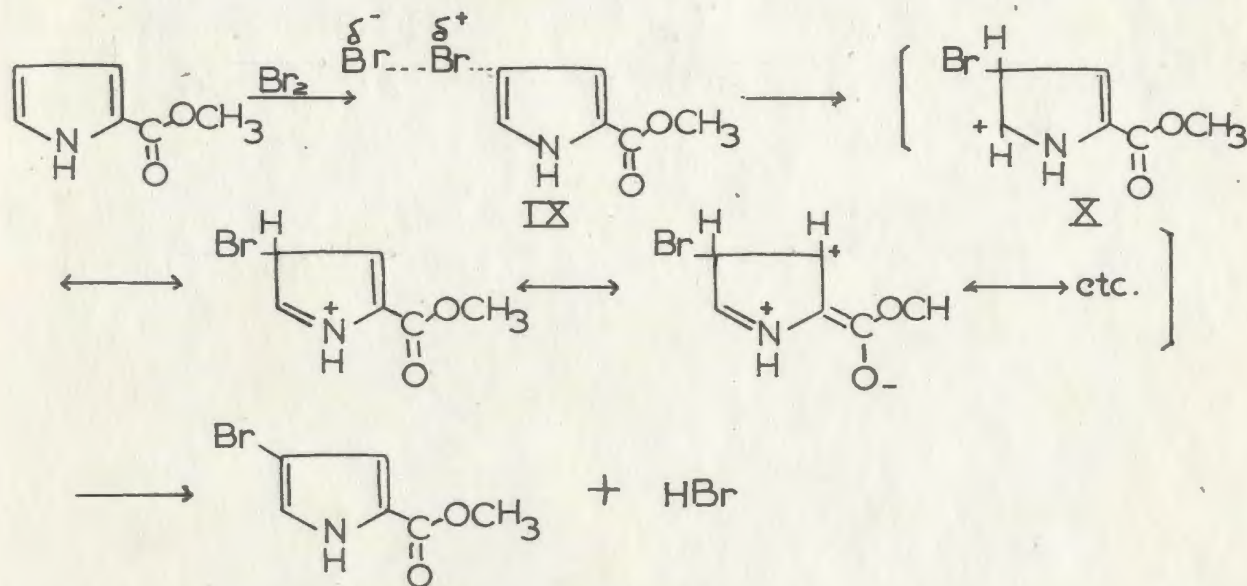
where (IX) represents the transition state and (X)
represents the intermediate.

Andrews (21) showed that the kinetic picture of electro-
philic aromatic bromination is altered with an increase in
the polarity of the medium. Robertson (22) and coworkers
have reported extensively on the kinetics of aromatic halo-

genation in acetic acid and they suggested that sodium acetate has a "salt effect" in the reaction, and is not a catalyst in the reaction.

The molecular bromination of methyl 2-pyrrolecarboxylate in acetic acid was reported by Rinkes (23) and Rickards (14) and 4-, 5-, 4, 5-dibromo esters were obtained. This experiment was repeated by stirring the pyrrole ester at $60^{\circ}C$ for 20 minutes with one mole of bromine in glacial acetic acid containing sodium acetate. It was found that reaction occurred with evident preference for attack at the 4- position but the 4, 5-dibromo ester was formed in a large amount and therefore a fairly large amount of starting ester was left. A small amount of 5-bromo ester also formed, but no 3-bromo ester was found.

Using iodine in bromination reactions suggests the initial step must be electrophilic attack by the catalyst on the bromine atom, causing the polarization of a bromine molecule. The first to make a kinetic study of the reaction of iodine as a catalyst in bromine substitution was Bruner (27). A further investigation of the nature of iodine catalysis of bromination for aromatic compounds was made by Price (28). It was suggested that iodine tribromide and iodine bromide acted as catalysts in the reaction.

IBr is not greatly dissociated under the reaction conditions, and it takes the place of one or more molecules of bromine in breaking the Br-Br bond in the complex. The iodine may also act in the reaction to remove the proton from the active intermediate.

$$\left[\overset{\delta^-}{Br}\text{--}\overset{\delta^+}{Br} \cdots \underset{\overset{|}{H}}{N}\text{-pyrrole-}\overset{O}{\underset{}{C}}\text{-OCH}_3\right] + IBr \longrightarrow \left[\text{intermediates} \right]$$

$$\longrightarrow etc. \Bigg] \;+\; \left[IBr_2\right]^-$$
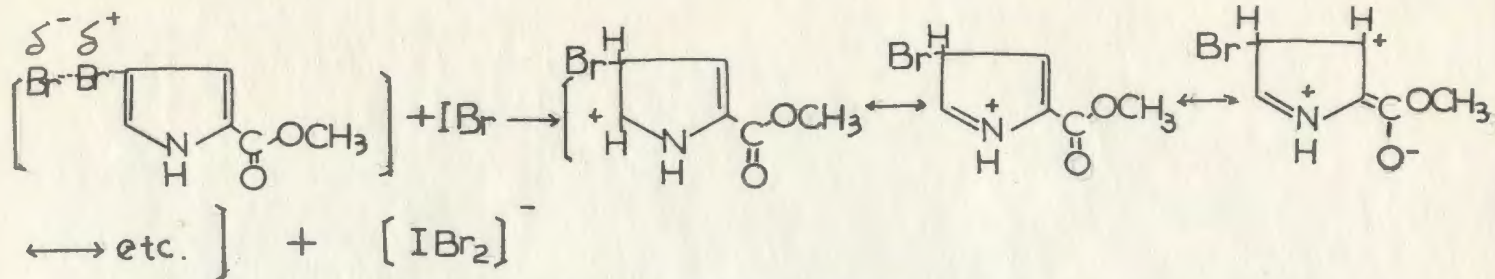
Since the molecular bromination of pyrrole deri-
vatives in carbon tetrachloride with iodine as a catalyst
showed all the possible products and gave very good yields,
a series of reactions (Table III & IV) was carried out under
different reaction conditions for the investigation of the
course of this reaction.

It was observed from Table III and IV that increasing
the proportion of bromine to two moles relative to the start-
ing material gave high yields of the 4, 5-dibromopyrrole deri-
vatives. Using molecular brominating reagents attack at
the 3- position finally occurs only when both the 4- and
5- positions are occupied, so, by using a large excess of
bromine, the 3, 4, 5-tribromo derivatives were formed in
very high yield, however, this was usually avoided in our
experiments. The 4-substituted compounds were predominant
at lower reaction temperature, and the percentage of con-
version of starting material was as high as 83% for 2-
pyrrole ester; 62 % for 2-pyrrole aldehyde. As the reaction
temperature was raised to the refluxing temperature of the
solvent, the amount of 5-substitution increased.

The bromination of methyl-2-pyrrolecarboxylate in carbon tetrachloride using excess aluminum chloride as a catalyst was undertaken. It was suggested by Pearson (24) that the swamping catalyst effect entails bromination by the aluminum chloride complex with a highly reactive brominating species, either Br^+ itself, or the ion pair, $Br^+Al^-Cl_3Br$. He also suggested that the brominating species can not be obtained unless an excess of equivalents of aluminum chloride is used (25). The brominations of methyl 2-furyl ketone and of 2-thienyl ketone in the presence of excess aluminum chloride were carried out by Gol'dfarb (26) and Vol'kenstein (8), 4,5-dibromo-2-furyl methyl ketone, 4-bromo-2-acetothienone and 4,5-dibromo-2-acetothienone were obtained. However, 4- and 5-bromo pyrrole esters in almost equal amount and a small amount of 4,5-dibromo pyrrole ester was obtained in our bromination of pyrrole ester using excess aluminum chloride, and little selectivity was found.

(d)   Bromination with positively charged bromine.

The electron-deficient halogenonium ions, I_3^+, $BrOH_2^+$, Br_3^+ and Cl_3^+ would be expected to be the most effective species in aromatic halogenation (29). Positively charged brominating species Br_3^+, or $BrOH_2^+$, can be derived from silver nitrate, nitric acid, and bromine; bromine with bromic acid and sulphuric acid; bromine with silver sulphate and sulphuric acid; bromine, silver perchlorate, and perchloric acid; or mercuric oxide and bromine.

Hypobromous acid is an effective brominating reagent especially in acid solutions, a rapid reversible reaction with hydrogen ion occurs to give either free bromine cations:

$$H_3^+O + HOBr \rightleftharpoons 2H_2O + Br^+$$
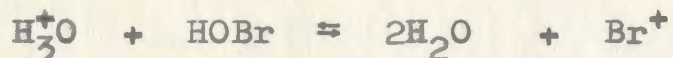
or the complex hydrated bromine cation which is the con-
jugate acid of the weak base HOBr

$$H_3O^+ + HOBr \rightleftharpoons (BrOH_2)^+ + H_2O$$

Using positive bromine, Derbyshire and Waters (30)
successfully carried out the bromination of benzene, bromo-
benzene etc. in an acidic media. They suggested that small
concentrations of bromates present in the reaction mixture
should be exceedingly effective as a catalyst owing to the
removal of the bromine anion.

$$H_3^+O + HOBr \rightarrow (BrOH_2)^+ + H_2O$$

$$2H_2O + Br_2 \rightleftharpoons HOBr + H_3^+O + Br^-$$

$$5H_3^+O + 5Br^- + HBrO_3 \rightleftharpoons 8H_2O + 3Br_2$$
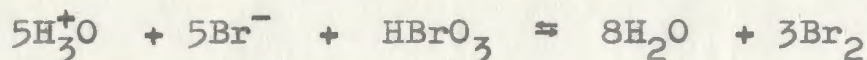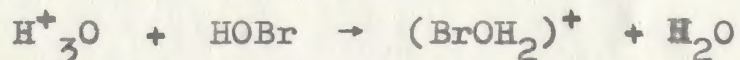
A number of workers (31-34) have given detailed dis-
cussions about hypobromous acid, and mentioned that bromine
water does not display such reactivity. Gould (35) also
suggested that brominonium ion, is a more powerful bromin-
ating agent than the corresponding bromine molecules, since
bromination with the latter requires an extra measure of
activation energy to break the $Br^{-\delta}$ ---- $Br^{+\delta}$ bond.

However, hypobromous acid can behave as a brominating
agent in the same way as nitric acid behaves as a nitrating
agent (36), so the steps in bromination are analogous to
those comprising the usual nitration mechanism. This in-
volves addition of a positive bromine ion to the aromatic
nucleus, followed by elimination of a hydrogen ion from
the intermediate to yield the substitution product.

$$BrOH \overset{+H^+}{\underset{-H^+}{\rightleftharpoons}} BrOH_2^+ \longrightarrow$$

[Reaction scheme showing bromination of the pyrrole derivative methyl pyrrole-2-carboxylate, with resonance structures of the brominated intermediate, leading via $-H^+$ to the 5-bromo product.]
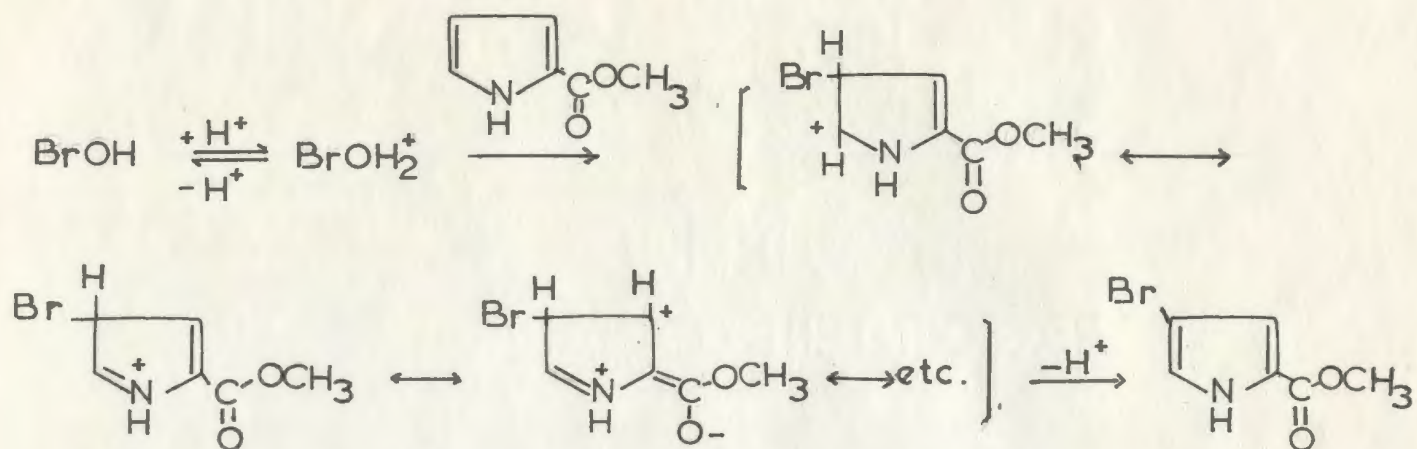
An attempt was made to brominate the pyrrole deri-
vatives with the bromonium ion. However, it was a failure
since considerable starting material remained unreacted and
only small amounts of bromo derivatives were formed. Per-
chloric acid was then added to the reaction mixture as a
catalyst, but the yields were still poor. It is possible
that the activated intermediate was destroyed by the strong
oxidizing action of hypobromous acid. It is apparent that
a further study should be made before any conclusion may be
drawn.

(e)   Bromination with free radical bromine.

In nonpolar solvent, polar catalysts and high reacti-
vity of the substrate, N-bromosuccinimide, N-bromophthalimide,
N-bromoacetamide and related compounds can be used in the
nuclear bromination of aromatics.

Djerassi (37) gave detailed discussions about the al-
lylic bromination with N-bromosuccinimide and related com-
pounds. It can be seen that various investigations have
presented indirect evidence to favor a free radical mech-
anism for the Wohl-Ziegler reaction with N-bromosuccinimide.

Brominations by N-bromosuccinimide may be catalysed
photochemically or by the addition of peroxides or azonitriles
(38). Following the ideas of Bloomfield (39), the mechanism
for the bromination of pyrrole derivatives is probably that
the substrate is initially attacked by the succinimide radi-
cal, then the carbon radical of pyrrole derivative is formed,
and it reacts with a second molecule of N-bromosuccinimide.
The exchange of hydrogen and bromine in the reaction is
then a chain process.
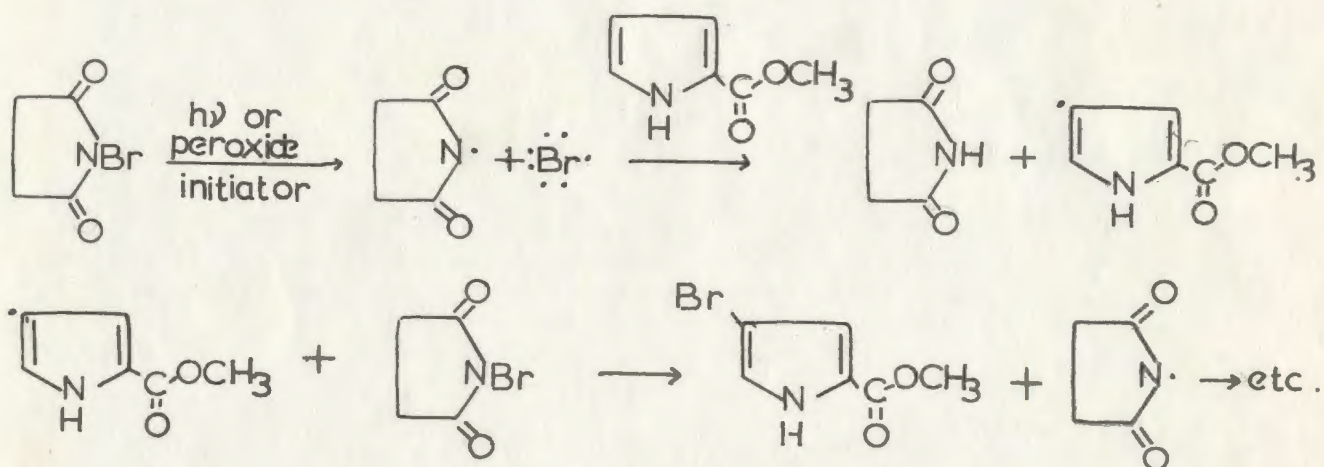
The attacking bromine atom, besides being a radical
is an electrophilic species that attacks the pyrrole ring.

Carbon tetrachloride and chloroform are widely used
solvents. In certain cases, benzene has added advantages
since N-bromosuccinimide is more soluble in benzene than
in carbon tetrachloride and benzene is not attacked by
N-bromosuccinimide in the presence of peroxide under ordi-
nary circumstances. Petroleum ether and heptane have been
used occasionally in the literature, but do not seem to
offer any obvious advantages.

As with many other free radical halogenations which yield a mixture of isomeric products the free radical bromination was expected to be less selective (40) so that 3-bromo-pyrrole derivatives might be obtained. The bromination of pyrrole derivatives with N-bromosuccinimide as the brominating reagent and carbon tetrachloride as solvent was carried out in the presence of benzoyl peroxide at 60°C. The reaction mixture of brominated methyl 2-pyrrolecarboxylates was analyzed by gas-chromatography and there was an extra peak found along with those for 4-, 5- and 4,5-dibromo derivatives. Column chromatography and the fractional crystallization from petroleum petane were applied to isolate the extra product. White crystals of pure succinimide itself were obtained. This was confirmed by the mixed melting point with the authentic specimen and the n. m. r. spectra. So no methyl 3-bromo-2-pyrrolecarboxylate was formed in the reaction.

(f)   Bromination with other brominating agents.

The bromination of pyrrole derivatives was effected with several other brominating reagents. Cupric bromide and lithium bromide with dimethylformamide as solvent (41); dibromodioxane (42) with dioxane or carbon tetrachloride as solvent; pyridinium bromide perbromide in pyridine (43); sodium hypobromite; and p-nitro-N-bromoacetanilide (44) were used in bromination. The details of the reaction paths followed are still uncertain in many of the reagents.

Starting material and 4-bromo derivatives were predominant in the reaction mixtures. 5-, and 4,5-dibromo derivatives were also formed in small amounts, no 3-bromo

derivatives were found through all the reactions using these different brominating reagents. By increasing the moles of brominating reagents, dibromo-, and tribromo-derivatives were increased in amount. Tables V and VI give the isomer ratios of the reaction mixtures from bromination using different brominating reagents. None of the brominating reagents was very selective, however molecular bromination in carbon tetrachloride with iodine as catalyst gave the best yields of all reagents investigated.

Section II:

Some reactions of methyl monobromo-2-pyrrolecarboxy-
lates and methyl dibromo-2-pyrrolecarboxylate.

(a) Carbonation of the Grignard reagent.

As carbon dioxide is useful in the synthesis of acids
from the Grignard reagent

$$RMgX \; + \; \overset{\overset{\displaystyle O}{\|}}{C=O} \; \rightarrow \; \overset{\overset{\displaystyle O}{\|}}{RC}-OMgx \; \rightarrow \; \overset{\overset{\displaystyle O}{\|}}{RC} - OH$$
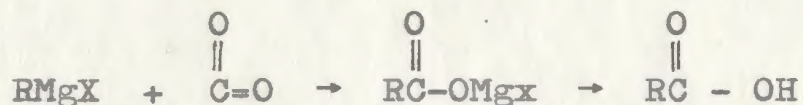
the carbonation of Grignard reagents from bromo-pyrrole
esters was attempted. In the presence of anhydrous ether
a bromo-pyrrole ester might react with magnesium to form an
ether solution of organomagnesium halide, carbon dioxide
or "Dry Ice" might then react with this Grignard reagent
and an acid group enter.
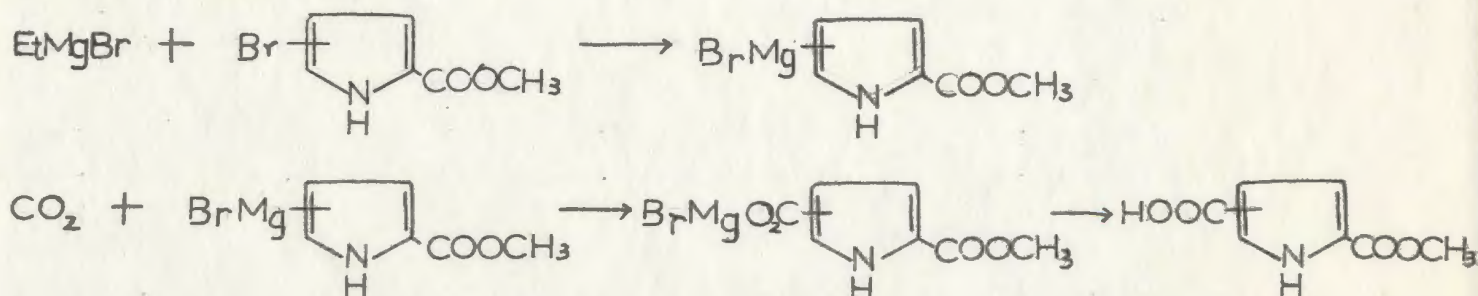
This could be considered as either nucleophilic
addition to carbon dioxide or an electrophilic substit-
ution of carbon dioxide for magnesium.

"Dry Ice" was chosen for this reaction, since it not
only furnishes the carbon dioxide, but acts as a refrig-
erant as well to maintain a more favorable concentration
of the reactant. A small amount of iodine and ethyl bro-
mide was added to initiate the formation of Grignard re-
agent, both ether and tetrahydrofuran were tried as sol-

vents for the Grignard reaction. Gas-chromatographic analysis showed that a large amount of starting material was left in the reaction mixture each time. In order to confirm the result of the reaction, the reduction of methyl 4, 5-dibromo-2-pyrrolecarboxylate in tetrahydro-furan using Grignard technique was carried out, and it was found that 45% of the starting material did reduce to monobromo-pyrrole esters, thus the Grignard reagent must have been formed (see section lll a). It is apparent that larger scale reaction should be tried again in order to isolate the expected acids, or highly activated mag-nesium-copper alloy, which was used for the Grignard re-action of 2-bromofuran (45-46), should be applied instead of ordinary magnesium for Grignard reaction in order to get better yields.

(b) Hydrolysis.

The hydrolysis of bromo-pyrrole esters was carried out in aqueous methanolic solution containing potassium hydro-xide. These reactions are bimolecular and involve acyl-oxygen bond cleavage,
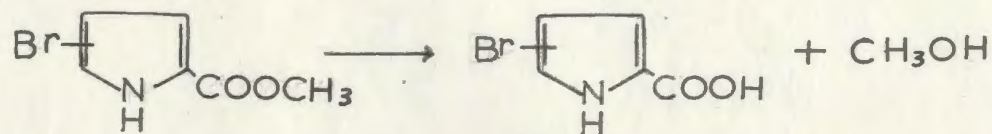
although methanol which was used for hydrolysis might repress the reaction or bring about the formation of a new ester, it helped the esters to dissolve.

4-Bromo, 5-bromo and 4, 5-dibromopyrrole esters were hydrolyzed in this manner. 4-Bromo and 4, 5-dibromo acids were obtained, but the 5-bromo acid decomposed by standing in air. These acids were purified by sublimation and fractional crystallization from pentane. They decomposed and carbon dioxide was evolved while taking the melting points. Sharp melting points could not be obtained.

(c)   Decarboxylation.

Although sharp melting points for 4-bromo and 4,5-dibromo-2-pyrrolecarboxylic acids were not obtained, the decarboxylation of these acids was attempted, (47).

Heating the bromo-pyrrole acids in an organic base such as quinoline in the presence of copper powder (48) dry distillation of the acids mixed with copper powder, or copper bronze; pyrolysis of the acids with soda-lime, were tried in order to decarboxylate these acids. However, pyrolysis of the acids caused only decomposition and sublimation of unchanged material, and decarboxylation seemed best effected by heating in quinoline with copper powder. This had been used successfully for decarboxylation of bromo furoic acids and bromo thiophenecarboxylic acids (46), (49). Gas-chromatographic analysis of the product showed several peaks. A bromination of pyrrole was carried out in order to identify those decarboxylated products, but this did not give information. The reaction mixture of brominated pyrroles was a dark brown solid, and the reaction was not considered to be a successful one. The decarboxylated products gave positive Erlich's reagent tests, but failed to react with phenyl isothiocyanate to give crystalline products (50).

A further study should be made of these decarboxylations.

Section III.

Reduction of bromo-pyrrole derivatives.

(a)   Replacement of halogen by hydrogen.

Bromine may be replaced by hydrogen using a variety of procedures. The methods include reduction with active metals; catalytic hydrogenation and via the Grignard reaction.

Zinc dust and glacial acetic acid had little action on bromo-pyrrole derivatives. A reduction was carried out with methyl 4, 5-dibromo-2-pyrrolecarboxylate and glacial acetic acid in the presence of zinc dust (51). Only 8 % of starting material was reduced to the 2-pyrrole ester and 92 % of dibromo-pyrrole ester was left unreduced in the reaction mixture.

Reduction of 4, 5-dibromo-pyrrole ester by addition of water to the Grignard reagent was attempted
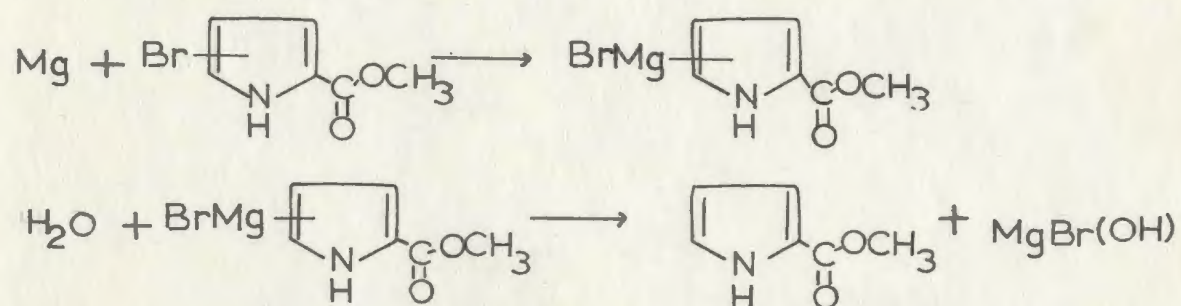
Forty-five percent of the dibromo-pyrrole ester was reduced to a mixture of unsubstituted ester and the monobromo esters, when this method was applied.

However, the bromopyrrole derivatives can be reduced by hydrogen (Pd charcoal) in glacial acetic acid buffered with anhydrous sodium acetate.

The catalytic hydrogenations were successful for both
the reactions which were carried out under low pressure
(3 atm.) and 60°C and those at atmospheric pressure of
hydrogen and room temperature. The apparatus for low hydro-
gen pressure was described by Gilman (52), whilst for atmos-
pheric pressure the apparatus for hydrogenation similar to
that described by Linstead (53) was used. It was observed
that the bromo-pyrrole esters underwent dehalogenation fas-
ter than the corresponding bromo-aldehydes. However,
it might be explained by the fact that pyrrole esters were
more soluble in glacial acetic acid than the corresponding
aldehydes.

It was found that 5-bromo atoms were easier to dis-
place by hydrogen that the 4-bromo atoms. However, as the
5- position has lower electron density than the 4- position
(Section Ia), it is fairly reasonable that the 5- position
should be more reactive toward nucleophilic substitution.

(b)   Replacement of halogen by deuterium.

In order to further prove the structures of bromo-
pyrrole derivatives by nuclear magnetic resonance spectro-
scopy (See Section Ib) the preparation of pure, deuterated
pyrrole derivatives was attempted. The method of prepar-
ation of deuterated species of thiophene was described by
Hoffman (54) and by Christensen (55), in which Grignard
technique and zinc dust reduction were used for the pre-
paration of 2-deutero-thiophene. However, since both Grig-
nard technique and zinc dust reaction were not very success-
ful for reduction of bromo-pyrrole derivatives and only
catalytic reduction was very effective, the method of cata-

lytic deuteration of bromo-pyrrole derivatives was used.
The apparatus was the same as that used for hydrogenation
under atmospheric pressure described in the last paragraph.

Acetic acid-d containing the mild base anhydrous
sodium acetate was used as solvent, and the mixture of sol-
vent and palladium/charcoal catalyst was stirred under one
atmosphere of deuterium for 30 minutes before adding the sa-
mple in order to avoid the possible occurrence of undesired
deuterium-hydrogen exchange. Then the sample was deuter-
ated under the same conditions.

Both gas-chromatographic and nuclear magnetic res-
onance spectra confirmed that pure 5-deutero- and 4, 5-
dideutero-pyrrole esters and aldehydes had been obtained.

Section IV:

Nucleophilic substitution of bromo-pyrrole derivatives.

The nucleophilic substitution reaction between cup-
rous cyanide and bromo-pyrrole derivatives as a preparative
method for the corresponding nitriles was attempted. This
synthesis is one involving replacement of an aromatically
bound bromine by cyanide group and the expected general mech-
anism of this reaction was given by Friedman and Schechter (56).

$$2Ar-X + Cu_2CN_2 \rightarrow [Ar-CN]_2 CuX + CuX \quad (1)$$

$$[Ar-CN]_2 CuX \rightarrow 2 Ar-CN + CuX \quad (2)$$
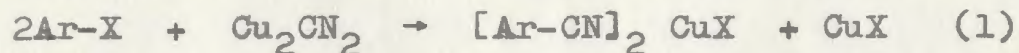
This reaction might be taking place between two
phases, solid and liquid, as the substrate forms a com-
plex with cuprous cyanide. Usually dimethylformamide (56),

was used as a solvent and pyridine or quinoline was used
as catalyst. Aqueous ferric chloride and ethylenediamine
(57-57) were used to destroy the reaction complexes formed
in dimethylformamide after finishing the reaction. This
procedure failed when bromo-pyrrole derivatives were used
as starting materials and dimethylformamide or pyridine
was used as the solvent.

After several experiments dimethylsulfoxide was at
last chosen as a solvent for this reaction. Although the
yields of the corresponding nitriles were very low and the
isolation of nitrile from the reaction mixture was diffi-
cult and laborious, the products were obtained and analyzed.
Cuprous cyanide was soluble in dimethylsulfoxide at temp-
eratures above 80°C, and the reaction mixture turned to
dark brown gradually as the reaction proceeded. The com-
plex formed from the nitrile and cuprous bromide was sol-
uble, whereas the copper, uncomplexed copper bromide, and
excess cuprous cyanide remained as precipitates. Dilute
ammonium chloride solution was used to decompose the com-
plexes and ether was used to extract the reaction mixture.

It was found that bromo-pyrrole esters gave better
yields than the corresponding aldehyde. However, as the
overall conversions for both kinds of starting materials
were so low, it is difficult to draw any conclusion from
the expected trend based on the electronegativity of the
groups which are attached to the pyrrole ring. It is
apparent that the synthesis of nitriles from this method
does not seem capable of wide application, and an improved
preparative method should be investigated. It was men-

tioned in Section I.b. that 5-cyano-2-pyrrolecarboxylate
had been prepared through the dehydration of the oxime of
the corresponding 5-formyl-2-ester and gave a good yield
of the product. Methyl 4-cyano-2-pyrrolecarboxylate had
also been obtained from the corresponding aldehyde-2-ester
under the same reaction conditions. This is certainly
a good method for the preparation of nitriles from methyl
2-pyrrolecarboxylate.

It is known that for bromo-furan and bromo-thiophenes
sodium methoxide brings about the removal of bromine
fairly easily (59, 60). An attempt was made to replace
the bromo group of the bromo-pyrrole derivatives with
methoxy group. This reaction was carried out by refluxing
the bromopyrrole ester with sodium methoxide in methanol
and a trace of cupric oxide was used as a catalyst. How-
ever, the bromo groups of both methyl 5-bromo-2-pyrrole-
carboxylate and 5-bromo-2-pyrrolecarboxaldehyde could not
be replaced by the methoxy group at the refluxing temp-
erature of methanol. It is possible that a more vigorous
reaction condition should be tried.

Tables of nuclear magnetic resonance
chemical shifts and coupling constants.

Tables of product percentages from
brominations of pyrrole derivatives.

Table I

Nuclear magnetic resonance spectra of pyrrole and its derivatives

Chemical shifts (p. p. m.)

COMPOUND	m.p. °C	-COOCH₃	-CHO	δ_2	δ_3	δ_4	δ_5
Pyrrole				6.56	6.15	6.15	6.56
Methyl 2-pyrrolecarboxylate	72 - 73	3.83			6.83	6.17	6.91
Methyl 5-deutero-2-pyrrolecarboxylate		3.85			6.84	6.19	
Methyl 4,5-dideutero-2-pyrrolecarboxylate		3.84			6.82		
Methyl 4-bromo-2-pyrrolecarboxylate	98 - 99	3.87			6.79		6.90
Methyl 5-bromo-2-pyrrolecarboxylate	102 - 103	3.92			6.81	6.17	
Methyl 4,5-dibromo-2-pyrrolecarboxylate	158 - 159	3.92			6.88		
Methyl 4-cyano-2-pyrrolecarboxylate (b)	169 - 170	3.93			7.15		7.43
Methyl 5-cyano-2-pyrrolecarboxylate (b)	165 - 166	3.97			6.85	6.85	
Methyl 4-formyl-2-pyrrolecarboxylate (c)	121 - 122	4.00	9.71		7.51		7.86
Methyl 5-formyl-2-pyrrolecarboxylate	92 - 93	3.94	9.69		6.86	6.86	
Methyl 2,4-pyrroledicarboxylate	126 - 127	3.82,3.89			7.27		7.57
Methyl 2,5-pyrroledicarboxylate	128.5-129.5	3.92,3.92			6.82	6.82	
2-pyrrolecarboxaldehyde	44 - 45		9.48		6.94	6.27	7.19
5-deutero-2-pyrrolecarboxaldehyde			9.49		6.95	6.30	
4,5-dideutero-2-pyrrolecarboxaldehyde			9.48		6.95		
4-bromo-2-pyrrolecarboxaldehyde	123 -124		9.47		6.98		7.19
5-bromo-2-pyrrolecarboxaldehyde	93 - 94		9.39		6.90	6.30	
4,5-dibromo-2-pyrrolecarboxaldehyde	155 -156		9.35		6.96		
4-cyano-2-pyrrolecarboxaldehyde (c)	170 -171		9.53		7.59		7.86

(a) Spectra were recorded at 60 mc/sec in carbon tetrachloride, using tetramethylsilane as internal reference.   (b) Spectra were recorded in deuterochloroform.

(c) Spectra were recorded in trifluoroacetic acid.

TABLE I (PART II)
Nuclear magnetic resonance spectra of pyrrole and its derivatives

	J_{13}	J_{14}	J_{15}	Coupling constant (c.p.s.) J_{34}	J_{35}	J_{45}	$J_{CHO/5}$
Pyrrole							
Methyl 2-pyrrolecarboxylate				3.84	1.46	2.56	
Methyl 5-deutero-2-pyrrolecarboxylate				3.85			
Methyl 4,5-dideutero-2-pyrrolecarboxylate							
Methyl 4-bromo-2-pyrrolecarboxylate	2.86		3.04		1.42		
Methyl 5-bromo-2-pyrrolecarboxylate				3.85			
Methyl 4,5-dibromo-2-pyrrolecarboxylate	2.80						
Methyl 4-cyano-2-pyrrolecarboxylate (b)	2.50		3.20		1.70		
Methyl 5-cyano-2-pyrrolecarboxylate (b)							
Methyl 4-formyl-2-pyrrolecarboxylate (c)					1.60		
Methyl 5-formyl-2-pyrrolecarboxylate							
Methyl 2,4-pyrroledicarboxylate					1.60		
Methyl 2,5-pyrroledicarboxylate							
2-pyrrolecarboxaldehyde				3.92	1.40	2.44	
5-deutero-2-pyrrolecarboxaldehyde				3.90			
4,5-dideutero-2-pyrrolecarboxaldehyde							
4-bromo-2-pyrrolecarboxaldehyde					1.50		1.10
5-bromo-2-pyrrolecarboxaldehyde				3.90			
4,5-dibromo-2-pyrrolecarboxaldehyde							
4-cyano-2-pyrrolecarboxaldehyde (c)					1.40		1.10

(a) Spectra were recorded at 60 mc/sec in carbon tetrachloride, using tetramethylsilane as internal reference.

(b) Spectra were recorded in deuterochloroform. (c) Spectra were recorded in trifluoroacetic acid.

TABLE II

Chemical shifts (p. p. m.) of substituted pyrrole, relative

to the shifts of the α - and β - hydrogens in pyrrole

Substituent	Character	δ_3	δ_4	δ_5
2-COOCH$_3$	electron-withdrawing	-0.68	-0.02	-0.35
2-CHO	electron-withdrawing	-0.79	-0.12	-0.63

(- represents change to lower field).

Table III

Iodine-Catalyzed bromination of Methyl 2-pyrrole Carboxylate (a).

Time (min.)	Temperature ^{o}C.	Mole ratio ester:bromine	Conversion (mole %)	Product distribution (mole %)		
				4-bromo ester	5-bromo ester	4,5-dibromo ester
20	28	1:0.8	31.50	26.60	3.88	1.02
10	28	1:1	69.66	58.45	9.49	1.72
90	0	1:1	74.90	68.43	6.47	-
90	70	1:1	84.24	46.47	31.40	6.37
30	28	1:1	84.90	74.06	7.59	3.25
60	28	1:1	96.94	83.07	11.92	1.95
90	28	1:1	97.54	82.78	12.46	2.30
20	70	1:1¼	100.00	49.01	38.11	12.87
90	70	1:1¼	100.00	46.34	34.98	18.66
120	28	1:1¼	100.00	15.60	2.32	82.08
120	28	1:2	100.00	2.01	-	97.99

(a)   Reactant : methyl 2-pyrrolecarboxylate (0.004 mole)

iodine (1 mg.)

Bromine

Solvent : Carbon tetrachloride (40 ml).

TABLE IV

Iodine-catalyzed bromination of 2-pyrrolecarboxaldehyde (a)

Time (min)	Temperature °C	mole ratio aldehyde:bromine	conversion (mole %)	product distribution (mole %)		
				4-bromoaldehyde	5-bromoaldehyde	4,5-dibromoaldehyde
90	0	1:1	62.81	60.73	2.08	–
90	28	1:1	74.77	62.30	11.03	1.44
90	70	1:1	66.10	26.01	24.04	16.05
120	28	1:2	100.00	5.19	0.39	94.42

(a)   Reactant: 2-pyrrolecarboxaldehyde (0.004 mole)

iodine (1 mg).

bromine

Solvent: carbon tetrachloride (40 ml).

TABLE V

Bromination of Methyl 2-pyrrolecarboxylate (a)

Brominating reagent	temperature $^\circ$C	time (min)	solvent	catalyst	conversion (mole %)
hypobromous acid (prepared from mercuric oxide and bromine)	28	30			3.73
hypobromous acid (prepared from mercuric oxide and bromine)	28	30		HClO$_4$	6.10
copper bromide and lithium bromide	150	120	DMF		6.35
sodium hypobromite	60	180	NaOH (6N)		22.19
para-nitro-N-bromoacetanilide	28	2880	CCl$_4$	CF$_3$COOH	28.01
para-Nitro-N-bromoacetanilide	28	2880	CCl$_4$	CH$_3$COOH	29.22
hypobromous acid (prepared from silver perchlorate perchloric acid and bromine)	28	30	CCl$_4$		35.40
bromine	60	30	HOAc and NaOAC		36.36
N-bromosuccinimide	70	90	CCl$_4$	benzoyl peroxide	40.72
pyridinium bromide perbromide	28	60	pyridine		55.67
bromine	28	120	CCl$_4$	AlCl$_3$	65.09
dibromodioxane	60	30	dioxane		68.04
bromine	70	60	CCl$_4$	Fe	69.63
dibromodioxane	28	5	CCl$_4$		82.17
bromine	28	90	CCl$_4$	I$_2$	97.54

(a) Reactant = methyl 2-pyrrolecarboxylate (0.004 mole) brominating reagent (0.004 mole) Solvent = 40 ml.

Table V a.   Bromination of methyl 2-pyrrolecarboxylate (a)

BROMINATING REAGENT	product distribution (mole %)		
	4-Br-2-ester	5-Br-2-ester	4,5-dibr-2-ester
hypobromous acid (prepared from mercuric oxide and bromine)	2.74	0.12	0.87
hypobromous acid (prepared from mercuric oxide and bromine)	4.67	0.36	1.07
copper bromide and lithium bromide	3.32	3.03	0
sodium hypobromite	20.53	1.66	0
para-nitro-N-bromoacetanilide	12.53	6.06	9.42
para-nitro-N-bromoacetanilide	14.00	13.72	1.50
hypobromous acid (prepared from silver perchlorate perchloric acid and bromine)	14.94	5.21	15.25
bromine	12.34	3.30	20.72
N-bromosuccinimide	15.29	14.20	11.23
pyridinium bromide perbromide	49.09	1.78	4.80
bromine	29.07	29.71	5.68
dibromodioxane	38.06	16.41	13.57
bromine	47.48	16.70	5.45
dibromodioxane	52.05	4.08	26.04
bromine	82.78	12.46	2.30

(a)   Reactant =   methyl 2-pyrrolecarboxylate (0.004 mole)

         =   brominating reagent (0.004 mole)

Solvent =   40 ml.

TABLE VI

Bromination of 2-pyrrolecarboxaldehyde (a)

Brominating reagent	temperature $^{\circ}$C	Time (min)	solvent	catalyst	conversion (mole %)	product distribution (mole %)		
						4-Br-2-CHO	5-Br-2-CHO	4,5-Br-2-CHO
Hypobromous acid	28	60			0.56	0.56	0	0
" "	28	60		perch-loric acid	1.81	1.53	0.28	0
sodium hypobromite	60	180	NaOH (6N)		10.48	9.56	0.92	0
pyridinium bromide perbromide	28	60	pyridine		25.24	17.35	6.39	1.50
N-bromosuccinimide peroxide	70	90	CCl_4		34.00	18.00	15.33	0.67
Bromine	28	90	CCl_4	I_2	74.77	62.30	11.03	1.44

(a) Reactant = 2-pyrrolecarboxaldehyde (0.004 mole)   Solvent = 40 ml.
brominating reagent (0.004 mole)

TABLE VII

Completely catalytic hydrogenation or deuteration of brominated pyrrole derivatives

at atmospheric pressure of hydrogen or deuterium (a)

Compound	Catalyst		Solvent		Amount of compound (mg.)	Time req'd (at 3 atm. 60°C) minute	Time req'd. (at 1 atm. room temp.) minute
	Name	Amount (mg.)	Name	Amount (ml).			
Methyl 5-bromo-2-pyrrolecarboxylate	Pd/C (5% Pd)	20	CH₃COOH/ NaOAc	25	50	10	15
Methyl 4-bromo-2-pyrrolecarboxylate	Pd/C (5% Pd)	20	CH₃COOH/ NaOAc	25	50	20	30
Methyl 4,5-dibromo-2-pyrrolecarboxylate	Pd/C (5% pd)	20	CH₃COOH/ NaOAc	25	50	45	60
5-bromo-2-pyrrolecarboxaldehyde	Pd/C (5% Pd)	20	CH₃COOH/ NaOAc	25	50	25	30
4-bromo-2-pyrrolecarboxaldehyde	Pd/C (5 % Pd)	20	CH₃ COOH/ NaOAc	25	50	40	55
4,5-dibromo-2-pyrrolecarboxaldehyde	Pd/C (5 %Pd)	20	CH₃COOH/ HaOAc	25	50	120	180

(a) CH₃COOD used as solvent for deuterations.

TABLE VII

Completely catalytic hydrogenation or deuteration of brominated pyrrole derivatives

at atmospheric pressure of hydrogen or deuterium (a)

Compound	Catalyst		Solvent		Amount of compound (mg.)	Time req'd (at 3 atm. 60°C) minute	Time req'd. (at 1 atm. room temp.) minute
	Name	Amount (mg.)	Name	Amount (ml).			
Methyl 5-bromo-2-pyrrolecarboxylate	Pd/C (5% Pd)	20	$CH_3COOH/$ NaOAc	25	50	10	15
Methyl 4-bromo-2-pyrrolecarboxylate	Pd/C (5% Pd)	20	$CH_3COOH/$ NaOAc	25	50	20	30
Methyl 4,5-dibromo-2-pyrrolecarboxylate	Pd/C (5% pd)	20	$CH_3COOH/$ NaOAc	25	50	45	60
5-bromo-2-pyrrolecarboxaldehyde	Pd/C (5% Pd)	20	$CH_3COOH/$ NaOAc	25	50	25	30
4-bromo-2-pyrrolecarboxaldehyde	Pd/C (5 % Pd)	20	CH_3 COOH/ NaOAc	25	50	40	55
4,5-dibromo-2-pyrrolecarboxaldehyde	Pd/C (5 %Pd)	20	$CH_3COOH/$ HaOAc	25	50	120	180

(a) CH_3COOD used as solvent for deuterations.

TABLE VIII

Reaction of bromo-pyrrole derivatives and
cuprous cyanide in dimethylsulfoxide

COMPOUND	Starting material amount (mole)	Cuprous cyanide (mole)	Time (hours)	Temperature (^{o}C)	Melting Point (^{o}C)	Yield %
4-CN-2-COOCH$_3$	0.01	0.015	5	180	169 - 170	21
5-CN-2-COOCH$_3$	0.01	0.015	5	180	165 - 166	18
4-CN-2-CHO	0.01	0.015	5	180	170 - 171	15
5-CN-2-CHO	0.01	0.015	5	180	-	Trace

EXPERIMENTAL

General:

Elemental analyses were determined by Alfred Bern-
hardt, Mülheim (Ruhr), Germany.

Melting points were observed by using a Fisher-
Johns melting point block and are uncorrected.

Infrared spectra were recorded for the 500-3500
cm^{-1} region by a Unicam SP100 spectrophotometer and for
the 800-4000 cm^{-1} region by a Perkin-Elmer 237B spectro-
photometer using the potassium chloride disc technique
(2 mg of sample in 198 mg KCl).

Ultraviolet spectra were recorded in 95% ethanol
with a Beckman DK-2A recording spectrophotometer.

Using a Varian A-60 spectrophotometer, nuclear mag-
netic resonance spectra were determined at 60 mc/s in
carbon tetrachloride, deuterochloroform, or trifluoro-
acetic acid. The chemical shifts are in p.p.m. from
tetramethylsilane as internal reference and are recorded
on the δ scale.

Neutral alumina (200   mesh; Woelm #1) was used
for adsorption chromatography for the preliminary separ-
ation of reaction mixtures.

Gas-liquid partition chromatographic analyses were
made using a Beckman GC-2A gas chromatograph, equipped
with a 13½-in column (number 70008) packed with Apiezon L
on firebrick and operated at 220°C. (for bromo-pyrrole
esters) or 190°C (for bromo-pyrrole aldehydes) with hel-

ium as the carrier gas (inlet pressure 20 psig.). Retention times (column temperature: 220°C; inlet pressure: 20 psig.) established for pyrrole esters were:

Methyl 2-pyrrolecarboxylate:	0.9 minutes.
Methyl 5-bromo-2-pyrrolecarboxylate	2.1 "
Methyl 4-bromo-2-pyrrolecarboxylate	3.5 "
Methyl 4,5-dibromo-2-pyrrolecarboxylate	6.5 "

Retention times (column temperature: 190°C; inlet pressure: 20 psig.) established for pyrrole aldehydes were:

2-pyrrolecarboxaldehyde	1.3 "
5-bromo-2-pyrrolecarboxaldehyde	3.3 "
4-bromo-2-pyrrolecarboxaldehyde	4.7 "
4,5-dibromo-2-pyrrolecarboxaldehyde	12.5 "

All Grignard reactions were carried out under an atmosphere of nitrogen.

Section 1:

Bromination of methyl 2-pyrrolecarboxylate and 2-pyrrolecarboxaldehyde.

The reaction vessel for the bromination of pyrrole derivatives was a 100 ml. three-neck round bottom flask equipped with a sealed stirrer, dropping funnel and reflux condenser.

(1) With hypobromous acid prepared from mercuric oxide and bromine.

    (a) Preparation of hypobromous acid.

        Mercuric chloride (0.146 mole) was dissolved in H_2O (2000 ml); sodium hydroxide solution (0.5 mole in 500 ml H_2O) was added slowly until the brown color was removed (the brown precipitate changing to a yellow coloured precipitate). Macerated filter paper was dropped into the solution obtained above, and then the mercuric oxide mixed with macerated paper was filtered off by suction. The mixture of the mercuric oxide (which was mixed with macerated paper), H_2O (1500 ml), and bromine (0.139 mole) was shaken for 3-4 minutes, filtered again by suction using macerated filter paper. The clear yellow solution was hypobromous acid. It was found to be 0.0789N by titration with standardized sodium thiosulfate solution.

    (b) Bromination.

        A mixture of starting material (0.004 mole) and hypobromous acid (0.004 mole) was stirred for 30 minutes at room temperature. The reaction mixture was

extracted with ether and the combined extract was
dried over anhydrous sodium sulphate. The solvent was
removed by distillation and the residue analyzed by
gas chromatography.

A further attempt was made in which perchloric acid
(0.1 mole) was added to the starting solution, and the
reaction mixture was also analyzed by gas chromato-
graphy (see Tables V and VI).

(2) With hypobromous acid prepared from silver perchlorate,
perchloric acid and bromine.

Methyl 2-pyrrolecarboxylate (0.004 mole) and bromine
(0.004 mole) were dissolved in perchloric acid (0.035 mole)
silver perchlorate solution (0.012 mole in 1 ml H_2O) was
then added and the mixture was stirred for 30 minutes at
room temperature. The reaction mixture was extracted with
ether, the extract was dried over anhydrous sodium sul-
phate. The solvent was removed by distillation and the
residue analyzed by gas chromatography (see Table V).

(3) With cupric bromide and lithium bromide.

A mixture of cupric bromide (0.004 mole), lithium
bromide (0.0005 mole) and dimethylformamide (25 ml) was
heated to 80°C, methyl-2-pyrrolecarboxylate (0.004 mole)
in dimethylformamide (15 ml) was added, and the whole mix-
ture was stirred for two hours at 150°C. The dark reaction
mixture was extracted with ether, and the extract was dried
over anhydrous sodium sulfate. The solvent was removed by
distillation and the residue analyzed by gas chromatography
(see Table V).

(4) With sodium hypobromite.

A mixture of starting material (0.004 mole) and sodium hypobromite solution (0.004 mole bromine in 40 ml 6$\underline{N}$ sodium hydroxide) was stirred for 3 hours at 60°C. The reaction mixture was neutralized with dilute hydrochloric acid and then extracted with ether. The extract was dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue analyzed by gas chromatography (see Table V and VI).

(5) With p-nitro-N-bromoacetanilide.

This acid catalyzed reaction was carried out in the dark; the reaction vessel was wrapped with foil to avoid the occurrence of free radical attack through the exposure of the reaction mixture to light. A mixture of methyl 2-pyrrolecarboxylate (0.004 mole), p-nitro-N-bromoacetanilide (0.004 mole), carbon tetrachloride (40 ml), and trifluoroacetic acid or glacial acetic acid (2 ml) was stirred for 2 days at room temperature. The reaction mixture was neutralized with dilute sodium hydroxide and the corresponding anilide was filtered off. The aqueous layer was extracted with ether and the extract was dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue analyzed by gas chromatography (see Table V).

(6) With bromine in acetic acid.

Bromine (0.004 mole) in glacial acetic acid (10 ml) was added dropwise with stirring to the methyl 2-pyrrolecarboxylate (0.004 mole) in glacial acetic acid (30 ml) containing sodium acetate (0.09 mole). The mixture was

stirred for 30 minutes at 60°C. Most of the solvent was removed under reduced pressure, and the product was then neutralized with dilute sodium hydroxide solution. The aqueous layer was extracted with ether, the extract was dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue analyzed by gas chromatography (see Table V).

(7) With N-bromosuccinimide and benzoyl peroxide.

A mixture of starting material (0.004 mole), N-bromosuccinimide (0.004 mole), benzoyl peroxide (0.0004 mole) and carbon tetrachloride (40 mole) was stirred for 1.5 hours at 70°C. The solvent was removed by distillation and the residue analyzed by gas chromatography. (See Table V and VI).

(8) With pyridinium bromide perbromide.

The reaction was carried out by an adaptation of the method of preparation of 3-bromoindole by Piers et al (43). To a solution of starting material (0.004 mole) in pyridine (20 ml), pyridinium bromide perbromide (0.004 mole) in pyridium (20 ml.) was slowly added (61). The mixture was stirred for an hour at room temperature. The reaction mixture was extracted with ether and the extract was washed with cold dilute aqueous hydrochloric acid to remove the pyridine. The residual ether solution of the crude product was then washed first with cold dilute aqueous sodium hydroxide, then with water. The dried ether solution was freed from ether and analyzed by gas chromatography (see Table V and VI).

(9)   With dibromodioxane in carbon tetrachloride or dioxane.

To freshly distilled dioxane (5 g) placed in an ice bath was added rapidly, with cooling, bromine (9.9 g). An orange precipitate was formed and dried on a porous plate. Dibromodioxane was obtained in a yield of 90% (mp. $60^{\circ}C$).

A mixture of methyl 2-pyrrolecarboxylate (0.004 mole), dibromodioxane (0.004 mole) and carbon tetrachloride (40 ml) was stirred for 5 minutes at room temperature. The reaction mixture was concentrated by distillation and analyzed by gas chromatography.

The use of dioxane as a solvent was also attempted (see Table V).

(10) With bromine in carbon tetrachloride.

(a)   With aluminum chloride as catalyst.

Bromine (0.004 mole) in carbon tetrachloride (10 ml) was added dropwise with stirring to the methyl-2-pyrrole-carboxylate (0.004 mole) in carbon tetrachloride (30 ml) containing anhydrous aluminum chloride (0.008 mole). The mixture was stirred for 2 hours at room temperature, and was then neutralized with 20% sodium carbonate solution. The layers were separated and the aqueous layer was extracted with ether. Organic solutions were combined and dried over anhydrous sodium sulfate. The residue left after removing solvent under reduced pressure was a mixture, and it was analyzed by gas chromatography. (See Table V).

(b) With ion powder as catalyst.

This reaction was carried out at 70°C for one hour by using procedure (a).

(c) With iodine as catalyst.

This reaction was carried out under a variety of reaction conditions (see Table III) by using procedure (a). The removal of iodine was carried out by extracting with 5 % $Na_2S_2O_3$ aqueous solution.

(11) The isolation of brominated products.

The crude reaction mixtures were separated for isolation and identification by adsorption chromatography on neutral alumina. Sublimation and the fractional crystallization from petroleum pentane (b.p. 37-50°C) were necessary to obtain the pure components.

Methyl 4-bromo-2-pyrrolecarboxylate m.p. 98-99°C. Cal. for $C_6H_7NO_2Br$: C, 35.32; H, 2.96; N, 6.87; Br, 39.17. Found C, 35.52; H, 2.93; N, 7.01; Br, 39.21.

Methyl 5-bromo-2-pyrrolecarboxylate m.p. 102-103°C. Calc. for $C_6H_7NO_2Br$: C, 35.32; H, 2.96; N, 6.87; Br, 39.17. Found: C, 35.15; H, 3.07; N, 6.55; Br, 39.31.

Methyl 4,5-dibromo-2-pyrrolecarboxylate m.p. 158-159°C. Calc. for $C_6H_6NO_2Br_2$: C, 25.47; H, 1.78; N, 4.95; Br, 56.49. Found: C, 25.30; H, 1.65; N, 4.86; Br, 56.71.

4-Bromo-2-pyrrolecarboxaldehyde m.p. 123-124°C. Calc. for C_5H_4NOBr: C, 34.48; H, 2.29; N, 8.04; Br, 45.97. Found: C, 34.68; H, 2.39; N, 7.87; Br, 46.04.

5-Bromo-2-pyrrolecarboxaldehyde m.p. 93-94°C. Calc. for C_5H_4NOBr: C, 34.48; H, 2.29; N, 8.04; Found: C, 34.67; H, 2.51; N, 7.80.

4,5-dibromo-2-pyrrolecarboxaldehyde m. p. 155-156°C.

Calc. for $C_5H_3NOBr_2$: C, 23.71; H, 1.18; N, 5.53.

Found: C, 23.66; H, 1.43; N, 5.71

Section II.

Some attempted reactions of mono- and di- brominated methyl 2-pyrrolecarboxylate.

(1) Carbonation of the Grignard reagent.

In a 100 ml three-neck round bottom flask, equipped with a sealed stirrer, a dropping funnel, and a reflux condenser, was placed magnesium (0.015 mole) in dried ether (25 ml). Ethyl bromide (4 ml) diluted in ether (5 ml) was added dropwise with stirring through the dropping funnel and then the methyl monobromo-2-pyrrolecarboxylate (0.004 mole) diluted in ether (15 ml) was also added slowly. The mixture was stirred for 1 hour at room temperature. "Dry Ice" was dropped through the reflux condenser and the mixture was stirred for another 30 minutes. The reaction mixture was hydrolyzed with 10% ammonium chloride solution (15 ml). The aqueous layer was separated, and extracted with ether. The combined organic extract was dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue analyzed by gas chromatography. The result was a failure.

The same reaction was also attempted using tetra-hydrofuran as a solvent instead of ether. Results showed this reaction did not occur successfully, the isolation of the expected acid from the reaction mixture which contained a large amount of starting material was a failure.

(2) Preparation of acids.

The corresponding acids of the brominated products were obtained by refluxing the esters (0.008 mole) in 20% aqueous potassium hydroxide solution (20 ml) and methanol (20 ml) for 2 hours. The methanol was distilled out and the unreacted ester was extracted in ether. The aqueous layer was acidified with dilute hydrochloric acid and was then extracted with ether. The extract was dried over anhydrous sodium sulfate. The solvent was removed by distillation and the crude acid was recrystallized from pentane or sublimed under vacuum. Melting points are as follows: 4-bromo-2-pyrrolecarboxylic acid: 155° - 165°C; 5-bromo-2-pyrrole-carboxylic acid decomposed by standing in air; 4,5-dibromo-2-pyrrolecarboxylic acid, $165-175^{\circ}$C. Further attempts at purification were not successful.

(3) Decarboxylation.

(a) With quinoline and copper powder.

A mixture of crude 4-bromo-2-pyrrolecarboxylic acid (0.005 mole), copper powder (0.002 mole) and freshly distilled quinoline (15 ml) was heated by oil bath (150°C) and distilled under vacuum pressure (10 mm Hg). The product mixed with quinoline was collected and extracted with ether, the extract was then washed with 1% sulphuric acid to remove quinoline and dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue analyzed by gas chromatography [30-in. column (number 70007), column temperature: 190°C, inlet pressure 30 p.s.i.g.] The result showed four components existed in the reaction mixture. One of

them had the same retention time compared with one
component which was found in the reaction mixture of
brominated pyrrole itself. It was probably 3-bromo-
pyrrole. The isolation of the expected 3-bromo-
pyrrole from the reaction mixture was a failure.

(b) With copper powder:

Crude 4-bromo-2-pyrrolecarboxylic acid (0.005
mole) ground with copper powder (0.002 mole) was sub-
jected to dry distillation under high temperature
(160°C) and vacuum pressure (10 mm Hg). No 3-bromo-
pyrrole was collected.

(c) With soda lime.

Crude 4-bromo-2-pyrrolecarboxylic acid (0.005
mole) ground with soda lime (0.002 mole) was pyro-
lyzed by using procedure (b). No 3-bromopyrrole
was collected.

4. Attempted methoxylation.

Monobrominated methyl 2-pyrrolecarboxylate (0.004
mole) and pulverized cupric oxide (0.001 mole) were added
to a solution of sodium methoxide [from 1.0 g. Na in ab-
solute methanol (40ml)]. The mixture was stirred and gen-
tly refluxed for 30 hours. The cooled suspension was fil-
tered, two volumes of cold water poured in and was then
extracted with ether. The organic layer was washed with
water and dried over anhydrous sodium sulfate. The solvent
was removed by distillation and the residue analyzed by
gas chromatography. The results showed this reaction did
not occur.

Section III:

(1) Conversion of brominated 2-pyrrolecarboxaldehydes to the corresponding brominated methyl 2-pyrrolecarboxylates.

The brominated 2-pyrrolecarboxaldehyde (0.0002 mole) in ethanol (2 ml) was added to a suspension of silver oxide (18% [silver nitrate (50 mg) in water (5 ml) was added slowly, with stirring, to 1N sodium hydroxide (10 ml)]. The mixture was shaken mechanically for one hour at room temperature and was then filtered. The filtrate was acidified, and then extracted with ether. The extract was dried with anhydrous sodium sulfate and excess etheral diazomethane (19) was dropped into the ether solution. Mono- and dibrominated methyl 2-pyrrolecarboxylates were obtained. In each case the identity was proven by gas chromatographic analysis and mixed melting point with the substances prepared by bromination of methyl 2-pyrrolecarboxylate.

(2) Conversion of methyl 4-formyl-2-pyrrolecarboxylate and methyl 5-formyl-2-pyrrolecarboxylate to corresponding methyl 2,4-pyrroledicarboxylate and methyl 2,5-pyrroledicarboxylate.

This reaction was carried out following the oxidation and esterification procedure of (1). Methyl 2,5-pyrrole-dicarboxylate m. p. 128.5 - 129.5°C (ref. 15 gives m. p. 129-130°C). U. V. λ max 274 $m\mu$ (ref.15 gives 277 $m\mu$), methyl 2,4-pyrroledicarboxylate, m. p. 126-127° (ref. 15 gives 126-127°C). U. V. λ max 264 $m\mu$ (ref. 15 gives 267 $m\mu$). Infrared and n. m. r. spectral properties are given in Tables I and IX.

Section IV

Reduction of brominated pyrrole derivatives.

(1) With zinc dust and acetic acid.

A mixture of methyl 4,5-dibromo-2-pyrrolecarboxylate (0.004 mole) and glacial acetic acid (30 ml) was heated to reflux temperature, and then zinc dust (0.001 mole) was added. The solution was refluxed for 3 hours and then neutralized with sodium hydroxide solution. The aqueous layer was extracted with ether and the extract was dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue analyzed by gas chromatography. It was found that 8% of the starting material had been reduced giving methyl 2-pyrrolecarboxylate: trace, methyl 4-bromo-2-pyrrolecarboxylate: 5.91%, methyl 5-bromo-2-pyrrolecarboxylate 2.10%.

(2) By the Grignard technique.

A small scale Grignard reaction was carried out by using tetrahydrofuran (25 ml), ethyl bromide (4ml) and magnesium (0.015 mole). Methyl 4,5-dibromo-2-pyrrole-carboxylate (0.004 mole) dissolved in tetrahydrofuran (15 ml) was added slowly, with stirring into the Grignard reagent. The mixture was refluxed for one hour, and then hydrolyzed with 10% ammonium chloride solution (15 ml). Layers were separated, the aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue analyzed by gas chromatography. It was found that 45% has been reduced giving methyl 2-pyr-rolecarboxylate: trace, methyl 4-bromo-2-pyrrolecarboxylate 24.60%; methyl 5-bromo-2-pyrrolecarboxylate: 20.40%.

(3)   Catalytic hydrogenation.

(a) At 3 atmospheres and 60° C.

A solution of the brominated derivative (50 mg) in glacial acetic acid(25 ml) containing anhydrous sodium acetate (10 mg) and palladium-charcoal (5% Pd. 20 mg) was placed in a heavy-wall glass bottle mounted in a shaking device and attached to a hydrogen cylinder fitted with a pressure gauge. Once the apparatus (52) had been calibrated, the mixture was agitated vigorously under the 3 atmospheres of hydrogen at 60°C for the required time. The reaction mixture was filtered by suction to remove the palladium/charcoal using a sintered glass filter, most of the solvent was removed under reduced pressure, and the solution was then neutralized with dilute sodium hydroxide solution. The aqueous solution was extracted with ether, and the extract was dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue analyzed by gas chromatography. Results showed pure methyl 2-pyrrolecarboxylate and 2-pyrrolecarboxaldehyde were obtained from the corresponding brominated pyrrole derivatives. The required times for complete reduction are listed in Table VII.

(b) At atmospheric pressure and room temperature.

A series of reduction experiments were carried out in order to study the best reaction conditions. The apparatus for hydrogenation described by Linstead. Elvidge and Whalley (53) was adopted, but using a magnetic stirrer. The treatment of the reaction mix-

ture after completing reduction followed procedure

(a). Gas chromatographic analysis showed a completely successful reduction and the results are listed in Table VII.

(a) Catalytic deuteration.

The apparatus for hydrogenation at atmospheric pressure was adopted except that a high boiling point petroleum mixture (80-100°C) was used for the reservoir instead of using water. A mixture of acetic acid-d (25 ml) which was prepared from acetic anhydride and deuterium oxide, anhydrous sodium acetate (10 mg) and palladium/charcoal (5% Pd.20 mg) was stirred under one atmosphere of deuterium (Matheson. purity: 99.5% (atom) min.) for 30 minutes and the bromo-pyrrole derivative (50 mg) was then added. The reactions were carried out for required time according to Table XII. After completion of the reaction the mixture was treated by using the general procedure described in (3) (a). Gas chromatographic analysis and n. m. r. spectra showed that bromo-pyrrole derivatives were completely deuterated in the desired positions.

Section V:

Preparation of the cyano-pyrrole derivatives.

(1) From corresponding bromo-pyrrole derivatives.

A series of reactions of monobromo-pyrrole derivatives with cuprous cyanide in dimethylsulfoxide was carried out. The general technique was as follows. A mixture of bromo-pyrrole derivatives (0.01 mole), cuprous cyanide (0.015 mole) and dimethylsulfoxide (50 ml) was refluxed for 5 hours. Most of the dimethylsulfoxide (40 ml) was removed from the reaction mixture by vacuum distillation. The dark residue was washed with 20 % ammonium

chloride solution (30 ml) and was then extracted with ether. The extract was washed with water to remove dimethylsulfoxide and dried over anhydrous sodium sulfate. The solvent was removed by distillation and the nitrile was obtained by fractional recrystallization from pentane and sublimation under vacuum.

Methyl 5-cyano-2-pyrrolecarboxylate m. p. 165-166°C. Calc. for $C_7H_6O_2N_2$: C, 56.00; H, 4.00; N, 18.66. Found: C, 55.82; H, 4.11; N, 18.57.

Methyl 4-cyano-2-pyrrolecarboxylate m. p. 169-170°C. Calc. for $C_7H_6O_2N_2$: C, 56.00; H, 4.00; N, 18.66. Found: C, 55.96; H, 4.19; N, 18.71.

(2) From the dehydration of the oximes of the corresponding aldehydes.

(a) Formylation of methyl 2-pyrrolecarboxylate.

This reaction was carried out following the procedure described by Silverstein (3). The reaction mixture was vacuum distilled (120°C, 5 mm. Hg), 90% pure methyl 5-formyl-2-pyrrolecarboxylate (m. p. 92-93°C) was obtained and the methyl 4-formyl-2-pyrrolecarboxylate (m. p. 121-122°C) was left in the residue. Their structures were proven by n. m. r. spectra, and by conversion to known methyl 2,5-pyrroledicarboxylate and methyl 2,4-pyrroledicarboxylate. Spectral properties are given in Table I and IX. Methyl 4-formyl-2-pyrrolecarboxylate, Calc. for $C_7H_7O_3N$; C, 54.90; H, 4.57; N, 9.15; Found: C, 54.97; H, 4.71 N, 9.21. Methyl 5-formyl-2-pyrrolecarboxylate,

Calc. for $C_7H_7O_3N$: C, 54. 90; H, 4.57; N, 9.15;
Found: C, 54.97; H, 4.72; N, 9.32.

(b) Conversion of methyl 4-formyl-2-pyrrolecarbo-
xylate and methyl 5-formyl-2-pyrrolecarboxylate to
corresponding oximes.

This reaction was carried out following the pro-
cedure described by Anderson (17). After recrystal-
lization from benzene, the melting point of corres-
ponding 5-oxime melted of 123-124°C. Calc. for
$C_7H_8O_3N_2$: C, 50.00; H, 4.76; N, 16.66. Found:
C, 50.17; H, 4.92; N, 16.57. Whereas the 4-oxime
melted at 204-205°C.

(c) Dehydration of the oximes.

This reaction was carried out following the pro-
cedure described by Anderson (17). Methyl 5-cyano-2-
pyrrolecarboxylate and methyl 4-cyano-2-pyrrolecarboxy-
late were obtaned. Their infrared spectra were iden-
tical with those of specimens which had been obtained
from corresponding brominated 2-pyrrolecarboxylates
(see Section V, 1) and the mixed melting points were
undepressed.

TABLE IX. Spectral properties of pyrrole derivatives

Compound	I. R. Spectrum		U. V. Spectrum			
	$C=O(cm^{-1})$	N-H(cm^{-1}) (bonded)	λmax ($m\mu$)		log. ε	
pyrrole						
methyl 2-pyrrolecarboxylate	1680	3275	265.5	233.5	4.212	3.724
methyl 5-deutero-2-pyrrolecarboxylate	1675	3275				
methyl 4,5-dideutero-2-pyrrolecarboxylate	1674	3275				
methyl 4-bromo-2-pyrrolecarboxylate	1705	3246	274.0	236.0	4.087	3.786
methyl 5-bromo-2-pyrrolecarboxylate	1721	3242	277.0	242.0	4.309	3.552
methyl 4,5-dibromo-2-pyrrolecarboxylate	1721	3225	278.0	235.0	4.219	3.752
methyl 4-cyano-2-pyrrolecarboxylate	1693	3280	259.0	207.0	4.102	4.316
methyl 5-cyano-2-pyrrolecarboxylate	1700	3267	266.0	206.0	4.839	4.029
methyl 4-formyl-2-pyrrolecarboxylate	1670,1700	3280	277,0	228.0	4.109	4.342
methyl 5-formyl-2-pyrrolecarboxylate	1675,1730	3285	295.0	221.0	4.345	4.095
methyl 2,5-pyrroledicarboxylate	1713,1730	3280	274.5	215.0	4.386	4.119
methyl 2,4-pyrroledicarboxylate	1718,1690	3280	264.0	212.5	4.137	4.408
4-bromo-2-pyrrolecarboxylic acid	1672	3355				
4,5-dibromo-2-pyrrolecarboxylic acid	1662	3382				
2-pyrrolecarboxaldehyde	1650	3260	289.5	253.0	4.452	3.703
5-deutero-2-pyrrolecarboxaldehyde	1660	3260				
4,5-dideutero-2-pyrrolecarboxaldehyde	1650	3260				
4-bromo-2-pyrrolecarboxaldehyde	1665	3230	297.0	254.0	4.174	3.903
5-bromo-2-pyrrolecarboxaldehyde	1650	3200	297.0	248.0	4.413	3.612
4,5-dibromo-2-pyrrolecarboxaldehyde	1650	3190	304.0	252.0	4.267	3.765
4-cyano-2-pyrrolecarboxaldehyde	1660	3240	279.0	214.0	4.074	4.198

Table X

Comparison of Major I. R. bands for parent compounds and deuterated pyrrole esters

Compound	Methyl 2-pyrrole-carboxylate	Methyl 5-deutero-2-pyrrolecarboxylate	Methyl 4,5-dideutero-2-pyrrolecarboxylate	Methyl 5-bromo-2-pyrrolecarboxylate	Methyl 4,5-dibromo-2-pyrrolecarboxylate
C-O stretching vibrations (cm^{-1})	1135 1175 1210	1130 1170 1205	1130 1160 1200	1126 1216 1234	1100 1219 1248
Ring vibrations (cm^{-1})	1325 1412 1450 1565	1313 1380 1449 1549	1312 1370 1445 1537	1333 1400 1455 1562	1333 1410 1451 1560
C=O stretching vibrations (cm^{-1})	1680	1675	1674	1721	1721
Aromatic C-H stretching (cm^{-1})	2945	2950	2950	2950	2945
N-H stretching (cm^{-1})	3275	3275	3275	3242	3225

Table XI.

Comparison of major I. R. bands for parent compounds and deuterated pyrrole aldehyde

Compound	2-pyrrolecarbox-aldehyde	5-deutero-2-pyrrolecarboxaldehyde	4,5-dideutero-2-pyrrolecarboxaldehyde	5-bromo-2-pyrrolecarboxaldehyde	4,5-dibromo-2-pyrrolecarboxaldehyde
Ring vibrations (cm^{-1})	1310	1300	1340	1310	1310
	1351	1345	1370	1340	1340
	1410	1400	1395	1405	1387
	1549	1538	1533	1525	1545
C-H stretching and deformation vibrations of CHO (cm^{-1})	2820	2830	2820	2840	2830
	880	875	890	925	985
C=O stretching vibration (cm^{-1})	1650	1660	1650	1650	1650
Aromatic C-H stretching (cm^{-1})	2970	2960	2960	2970	2960
N-H stretching (cm^{-1})	3260	3260	3260	3200	3190

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