THE JOURNAL OF Organic Chemistry®

VOLUME 40, NUMBER 22

OCTOBER 31, 1975

2-Halopyrroles. Synthesis and Chemistry[1a]

Geoffrey A. Cordell[1b]

Department of Chemistry, University of Manchester, Manchester, M13 9PL, England

Received May 12, 1975

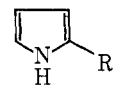
Following the confirmation that both 2-chloropyrrole (**1**) and 2-bromopyrrole (**2**) were unstable species, a number of 1-alkyl- and *C*-alkyl-2-halopyrroles were synthesized to investigate the range of instability. The 1-alkyl-2-halopyrroles synthesized were 2-chloro-1-methylpyrrole (**14**), 2-bromo-1-methylpyrrole (**15**), 1-benzyl-2-chloropyrrole (**47**), and 1-benzyl-2-bromopyrrole (**46**). The *C*-alkyl-2-halopyrroles synthesized were 5-chloro-2-methylpyrrole (**26**), 2-*tert*-butyl-5-chloropyrrole (**36**), 5-chloro-2,3,4-trimethylpyrrole (**29**), and 5-bromo-2,3,4-trimethylpyrrole (**20**). Also synthesized were the 1-methyl derivatives of **26** and **29**. Electrophilic substitution of 2-chloro- and 2-bromopyrroles (**1** and **2**) under the conditions for formylation and diazo coupling was examined. In the case of the latter reaction no crystalline compounds could be isolated, but diazo coupling of 2-chloro-1-methylpyrrole (**14**) gave rise to exclusive α substitution. Formylation of 2-chloropyrrole (**1**) gave the α-substituted derivative but 2-bromopyrrole (**2**) gave a product arising from the displacement of bromine, 5-chloropyrrole-2-carboxaldehyde (**28**), in addition to 5-bromopyrrole-2-carboxaldehyde (**41**).

Electrophilic substitution of simple pyrrole derivatives occurs regioselectively at the 2 position[2] and at a rate considerably faster than in the furan and thiophene series.[3] The simple electrophilic substitution reactions such as nitration,[4] sulfonation,[5] and formylation[6] therefore give rise to the 2-substituted product almost[2] to the exclusion of the 3-substituted derivative. In all cases these products are well-characterized compounds with clearly defined physical constants.[7] However, 2-chloropyrrole (**1**) and 2-bromopyrrole (**2**), the expected products of halogenation, are poorly characterized compounds. In addition, there is evidence that these compounds are quite unstable.

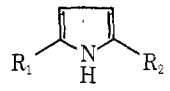
Mazzara and Borgo,[8] using sulfuryl chloride in ether as the chlorinating agent, were the first to report the synthesis of **1**. Attempted isolation indicated that both **1**[8] and 2,5-dichloropyrrole (**3**)[9] were probably labile. This observation was supported by the work of Hess and Wissing,[10] who heated the pyrrolyl Grignard (**4**) reagent[11] with chlorine in ether and obtained a highly unstable yellow oil. More recently, a Russian group[5] prepared 2-chloropyrrole (**1**) but no comment was made as to the stability of the product. Further evidence for the instability of 2-chloropyrrole (**1**) comes from the work of Hodge and Rickards.[12] Decarboxylation of 5-chloropyrrole-2-carboxylic acid (**5**) under reduced pressure afforded a yellow oil which rapidly decomposed to a black mass on exposure to air.

There are only two reported attempts to prepare 2-bromopyrrole (**2**). Bromination of the pyrrolyl Grignard (**4**) with bromine in ether afforded a highly unstable oil.[13] Attempts to decarboxylate 5-bromopyrrole-2-carboxylic acid (**6**)[14] also failed to give any **2**.

Neither 3-chloropyrrole (**7**) nor 3-bromopyrrole (**8**) is known. 3,4-Dichloropyrrole (**9**) has been prepared on three occasions and has consistently been described as a white, crystalline, stable solid.[15-17]

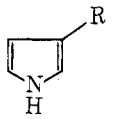


1, R = Cl
2, R = Br

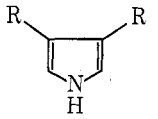


3, R_1, R_2 = Cl
5, R_1 = Cl; R_2 = CO_2H
6, R_1 = Br; R_2 = CO_2H
10, R_1, R_2 = Br
13, R_1, R_2 = CH_3
26, R_1 = Cl; R_2 = CH_3
28, R_1 = Cl; R_2 = CHO
39, R_1 = Cl; R_2 = SO_2OH
41, R_1 = Br; R_2 = CHO

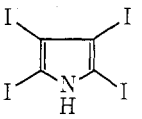
MgBr
4



7, R = Cl
8, R = Br



9, R = Cl
12, R = CH_3



11

The initial aim of this study was therefore to prepare 2-chloropyrrole (**1**) and 2-bromopyrrole (**2**) in a state suitable for thorough analysis.

Preparation of 2-Chloropyrrole (1), 2,5-Dichloropyrrole (3), 2-Bromopyrrole (2), and 2,5-Dibromopyrrole (10). 2-Chloropyrrole (**1**) was prepared from pyrrole by the two methods[8-10] described previously. A modification of the method due to Mazzara and Borgo[8] was the most effective (see Experimental Section).

NMR and GC[18] analysis of the crude product indicated the presence of a major component and two minor components, one of these being unreacted pyrrole.

The mixture was fractionally distilled with a series of high-boiling aliphatic tertiary amines to inhibit decomposi-

tion.[20] Two main fractions were obtained and NMR examination showed them to contain **1** and **3**.

The pure compounds were obtained in ether solution by precipitation of the quaternary ammonium salt with methyl iodide. The spectral properties of these compounds were consistent with the assigned structures.

A mixture containing 2-bromopyrrole (**2**) was produced by the method of Hess and Wissing[13] and purification effected by column chromatography. The spectral properties of the two compounds isolated were consistent with their formulation as 2-bromopyrrole (**2**) and 2,5-bromopyrrole (**10**).

Properties of 2-Halopyrroles. 2-Chloropyrrole (**1**), a colorless oil with a strong, characteristic odor, was stable in air for periods ranging from 10 sec to 55 min, presumably depending on trace impurities. Decomposition[21] spreads rapidly throughout the liquid, which becomes black, hydrogen chloride is vigorously evolved and the exothermic reaction is complete in 5–10 sec. The black mass remaining proved to be intractable and no spectroscopic data could be obtained. No melting point was observed below 700° and in the process of heating to this temperature, a white solid sublimed which analyzed well for ammonium chloride. Microanalytical data of the black mass were not reproducible, the product apparently adsorbing variable amounts of oxygen. The black mass produced by the spontaneous decomposition of 2-chloropyrrole (**1**) is reminiscent of the material obtained by the thermal decomposition of 2,3,4,5-tetraiodopyrrole (**11**).[22,23]

2-Chloropyrrole (**1**) distilled under high vacuum (10^{-4}–10^{-5} mmHg) as a colorless oil, but decomposition was initiated (5–7 min) on the glass surface.

2-Chloropyrrole (**1**) was recovered in 90–95% yield after treatment with sodium–liquid ammonia, sodium amide–liquid ammonia, or potassium amide–liquid ammonia. In the presence of ethanol, sodium–liquid ammonia effected quantitative removal of the halogen atom to afford pyrrole. Only under vigorous conditions (THF under reflux for 14 hr) was the halogen atom removed by lithium aluminum hydride. 2-Chloropyrrole (**1**) was stable in ether at 0° for several months, but in all other common solvents lifetimes were only 1–2 days. It was found to be very sensitive to acidic reagents such as dry HCl gas, hydroquinone, chloroform, or glacial acetic acid. Decomposition was also accelerated under basic conditions, such as potassium *tert*-butoxide in *tert*-butyl alcohol or alcoholic aqueous potassium hydroxide, or by benzoyl peroxide.

2-Bromopyrrole (**2**), a colorless liquid, decomposed upon removal of solvent within 60 sec. Attempted purification by fractional distillation in the presence of aliphatic tertiary amines failed, owing to thermal decomposition above 40°. The halogen atom was not removed by potassium amide in liquid ammonia, and dry hydrogen chloride gas greatly accelerated the decomposition process.

The dense, colorless liquid, 2,5-dichloropyrrole (**3**), was more stable (2–5 min induction time) than the white solid, 2,5-dibromopyrrole (**10**), which decomposed almost instantaneously upon removal of solvent.

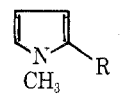
3,4-Dimethylpyrrole (**12**) is not readily autoxidized,[24] certainly not as readily as 2,5-dimethylpyrrole (**13**),[25] a situation parallel to that of the halopyrroles, where 3,4-dichloropyrrole (**9**) is a stable, white, crystalline solid[15–17] and 2,5-dichloropyrrole (**3**) is a very unstable, low-melting solid.

Having confirmed the literature reports[8,10,13] that 2-chloropyrrole (**1**) and 2-bromopyrrole (**2**) are indeed unstable, attention was turned to a study of the alkyl-substituted derivatives.

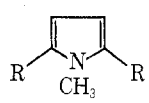
Studies on the autoxidation of pyrrole[26] and some 1-alkylpyrroles[25] have indicated that labile peroxides are formed in the initial stages of the reaction, and several of the initial products have been isolated and characterized. A *C*-alkylpyrrole such as 2,5-dimethylpyrrole (**13**) was found to consume oxygen at a considerably faster rate than did 1-methylpyrrole.

It was considered that the instability of 2-chloropyrrole (**1**) might be mitigated by the preparation of *N*-alkyl derivatives. Conversely, owing to electronic considerations, it was considered that C-alkylation would decrease the stability of a 2-halopyrrole. Subsequent work confirmed these ideas and gave preliminary information of the structure requirements for stability in the 2-halopyrrole series.

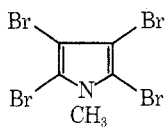
Preparation and Properties of 2-Chloro-1-methylpyrrole (14) and 2-Bromo-1-methylpyrrole (15). 2-



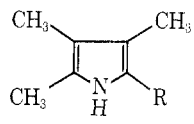
14, R = Cl
15, R = Br



16, R = Cl
18, R = Br



17



19, R = I
20, R = Br
21, R = H
29, R = Cl

Chloro-1-methylpyrrole (**14**) was prepared by chlorination of 1-methylpyrrole with 1 equiv of sulfuryl chloride in ether at 0°. GC of the ethereal extract after work-up indicated the presence of the 2-chloro and 2,5-dichloro products, **14** and **16**, as established by NMR analysis. The reaction product was found to be quite stable to heat and consequently it was fractionally distilled under reduced pressure without codistillant. It did not decompose to a black mass when in the pure state, but one sample did resinify after some weeks at 0° in a manner characteristic of pyrrole itself.[27] Dry hydrogen chloride gas also produced resinification rather than the decomposition reaction.

2-Chloro-1-methylpyrrole (**14**) was not attacked by lithium aluminum hydride or potassium amide in liquid ammonia; starting material was recovered in good yield. This is in contrast to the thiophene series,[28] where Cine substitution[29] occurs. The chlorine atom of **14** is effectively removed with sodium in liquid ammonia.

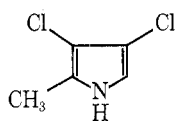
The synthesis of 2-bromo-1-methylpyrrole (**15**) proved to be more difficult and no pure sample was obtained. Bromination of 1-methylpyrrole, by the method of Anderson and Griffiths,[30] gave a complex mixture consisting mainly of the known compound 2,3,4,5-tetrabromo-1-methylpyrrole (**17**)[31] and unreacted 1-methylpyrrole. Similar results were obtained with pyridinium bromide perbromide,[14,32] cupric bromide,[14] and *N*-bromosuccinimide.[14]

The most successful method was to add bromine in carbon tetrachloride to a dilute solution of 1-methylpyrrole, with magnesium oxide as a slurry. Chromatography of the residue, after removal of the tetrabromo derivative by fractional crystallization, afforded a fraction which by NMR was shown to be predominantly (60%) 2-bromo-1-methylpyrrole (**15**), together with some 1-methylpyrrole and 2,5-dibromo-1-methylpyrrole (**18**, 35%).

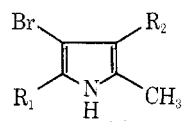
No *C*-alkyl-2-chloro- or 2-bromopyrroles are known and only one 2-iodo compound, 5-iodo-2,3,4-trimethylpyrrole (**19**), has been described.[33] This compound was fairly stable, decomposing readily in warm solution.

Johnson[34] and Kenner[35] and their respective coworkers attempted without success to prepare 5-bromo-2,3,4-trimethylpyrrole (**20**) by the bromination of 2,3,4-trimethylpyrrole (**21**). Even under mild conditions, however, no compound containing only one pyrrole nucleus could be isolated.

A number of dihalo-*C*-alkylpyrroles are known, and of these several are reported to be highly unstable. 3,4-Dichloro-2-methylpyrrole (**22**) became a "black solid" upon "brief exposure to atmospheric oxygen".[36] 4-Bromo-2-methylpyrrole (**23**) was apparently quite stable, but both 2,3-dibromo-5-methylpyrrole (**24**) and 2,4-dibromo-3,5-dimethylpyrrole (**25**) "reacted immediately upon isolation".[37]

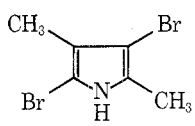


22

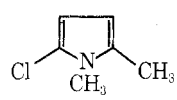


23, $R_1, R_2 = H$

24, $R_1 = Br; R_2 = H$



25



27

It is well known that carbonyl groups attached at the α or β positions of the pyrrole nucleus can be reduced by lithium aluminum hydride to hydrocarbon residues,[38,39] and Hinman and Theodoropoulos[40] have used this as a convenient method for the synthesis of many *C*-alkylpyrroles, mainly by the reduction of carbethoxy and formyl groups.

If "inverse" addition is employed, reduction stops at the hydroxymethyl stage, even under drastic conditions.[39,41]

When the ring nitrogen is substituted by an alkyl group, neither mode of addition affords complete reduction of a carbonyl at the α or β position.[40,42] Invariably, the reaction stops at the hydroxymethyl stage.

Since the halogen atom in 2-chloropyrrole (**1**) was not readily attacked by lithium aluminum hydride, reduction of carbonyl-containing 2-halopyrroles should be an efficient method to prepare *C*-methyl-2-halopyrroles. The carbonyl-containing precursors of these compounds should be fairly stable since they contain an electron-withdrawing group.[16,43-5]

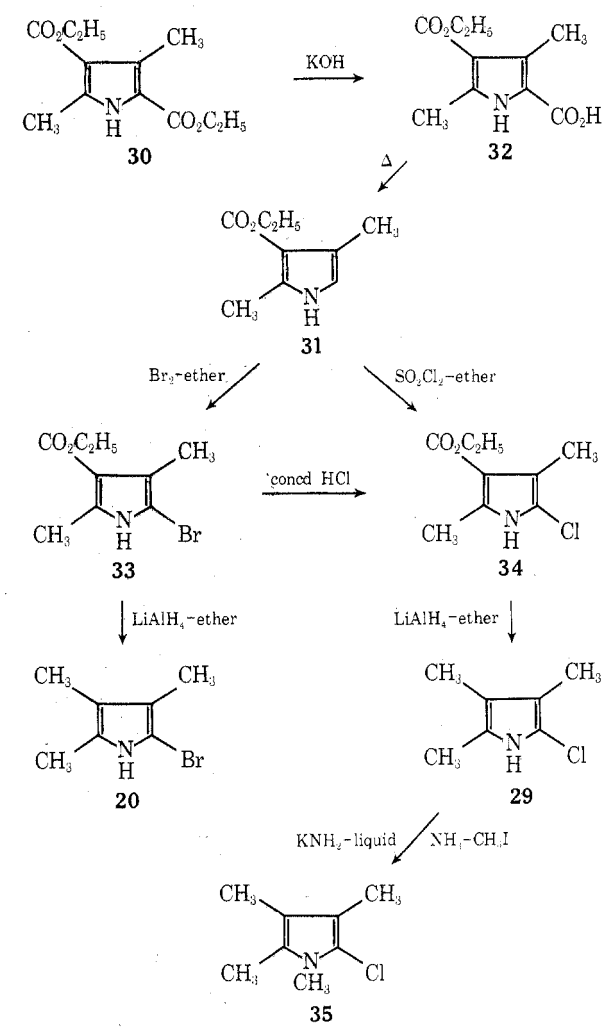
Preparation of 5-Chloro-2-methylpyrrole (26) and 5-Chloro-1,2-dimethylpyrrole (27). Treatment of 5-chloropyrrole-2-carboxaldehyde (**28**) (vide infra) with lithium aluminum hydride in ether under reflux for 14 hr gave a product which was shown by ir, NMR, and TLC to be 5-chloro-2-methylpyrrole (**26**). The product was quite unstable, resinifying in air after 10–12 min.

1-Methylation, using potassium amide and methyl iodide in liquid ammonia, of ethereal 5-chloro-2-methylpyrrole (**26**) followed by chromatography gave rise to extensive decomposition. One fraction was obtained which afforded a white solid melting slowly at room temperature, which was shown to be pure 5-chloro-1,2-dimethylpyrrole (**27**) by TLC and NMR analyses.

Preparation of 5-Chloro- and 5-Bromo-2,3,4-trimethylpyrrole (29 and 20). It was considered desirable to derive a synthetic scheme for the formation of 5-chloro- and 5-bromo-2,3,4-trimethylpyrrole (**29** and **20**) involving lithium aluminum hydride reduction as the terminal step. In this way, the possibility of pyrromethane formation would be essentially eliminated. Additionally, basic ethereal solutions would be involved which would reduce the possibility of decomposition in the reaction medium or during processing.

Knorr's pyrrole, 3,5-diethoxycarbonyl-2,4-dimethylpyrrole (**30**),[46] was used as starting material, and the sequence of reactions leading to the 5-halo-2,3,4-trimethylpyrroles is shown in Scheme I.

Scheme I



30 **32** **31** **33** **34** **20** **29** **35**

A key compound in this scheme is 3-ethoxycarbonyl-2,4-dimethylpyrrole (**31**), which can potentially be chlorinated or brominated. This compound was prepared from Knorr's pyrrole (**30**) in two steps, hydrolysis and decarboxylation.

Selective hydrolysis of the 5-ethoxycarbonyl group was achieved with alcoholic alkali,[46,47] to give the required 5-carboxylic acid (**32**) in good yield.

Decarboxylation and subsequent bromination has been accomplished in the pyrrole series by the use of bromine in acetic acid at 100°.[48] In the aromatic series this reaction may be carried out with the modified Hunsdiecker reaction.[49] This reaction failed when performed on **32**. Knorr describes the decarboxylation of **32** as taking place on melting although no indication of the yield was given.[46] Heating the acid until evolution of carbon dioxide ceased, followed by recrystallization of the resulting solid, afforded 3-ethoxycarbonyl-2,4-dimethylpyrrole (**31**) in very high yield.

Three methods have been used previously for the monobromination of **31**, bromine in ether,[50] bromine in methanol at −60°,[45] and dioxane dibromide.[51] On a small scale each of these methods gave only a low yield (20–30%) of the desired product. On a larger scale, the method of Corwin

and Viohl[45] gave an 84% yield of 5-bromo-3-ethoxycarbonyl-2,4-dimethylpyrrole (**33**).

Treibs and Kolm[33] treated **33** with concentrated hydrochloric acid in glacial acetic acid at room temperature, and obtained the corresponding 5-chloro compound **34**. Repetition of this reaction afforded **34** in high yield.

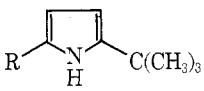
An alternative efficient synthesis of **34** involved the low-temperature chlorination of **31** with 1 equiv of sulfuryl chloride.

Initial attempts to prepare 5-bromo-2,3,4-trimethylpyrrole (**4**) by treatment of **33** with excess lithium aluminum hydride in tetrahydrofuran under reflux gave only 2,3,4-trimethylpyrrole (**21**). However, treatment of **33** with an excess of lithium aluminum hydride in ether under reflux for 1.5–2 hr had the desired effect of reducing the ethoxycarbonyl group without reductive removal of the bromine. NMR analysis indicated that together with 5-bromo-2,3,4-trimethylpyrrole (**20**), a trace of starting material was also present. The mixture was highly unstable and decomposed while the NMR was being run at 0°. Addition of a trace of deuterated pyridine greatly stabilized the solution and permitted the observation of an improved NMR spectrum.

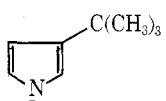
In a similar way, lithium aluminum hydride reduction of **34** in ether under reflux for 1.5 hr gave 5-chloro-2,3,4-trimethylpyrrole (**9**), as shown by ir and NMR analyses.

Preparation of 5-Chloro-1,2,3,4-tetramethylpyrrole (35). It was thought that since a 1-methyl group had a considerable stabilizing effect on 2-chloropyrrole (**1**), it might have a similar effect for its trimethyl homolog; this was found *not* to be the case. Methylation of **29** in the usual way afforded **35**, as shown by NMR. Decomposition to a bright red product was rapid, however. Attempts to prepare **35** by alternative routes failed.

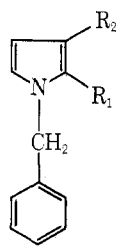
Preparation of 2-*tert*-Butyl-5-chloropyrrole (36). A bulky group at the 5 position to the 2 halogen, even if it has a comparatively large electron-releasing effect, should exhibit a slight stabilizing effect, if the mechanism of the decomposition of 2-chloropyrrole (**1**) involves attack at the opposite α position.



36, R = Cl
37, R = H



38



46, R_1 = Br; R_2 = H
47, R_1 = Cl; R_2 = H
48, R_1 = H; R_2 = Br

Stabilization, preventing polymerization, by the use of a *tert*-butyl group has previously been observed in the acetylenic series.[52] For example, $(CH_3)_3C(-C{\equiv}C-)_6C(CH_3)_3$ is a stable solid, whereas dodecahexyne, $H(-C{\equiv}C-)_6H$ is a very unstable substance.

2-*tert*-Butylpyrrole (**37**) was previously prepared by Skell and Bean,[53,54] but no electrophilic substitution reactions of this molecule were reported.

The compound was prepared by the alkylation of pyrrylmagnesium bromide with *tert*-butyl chloride,[53] and was separated from the 3 isomer (**38**), unchanged pyrrole, and polyalkyl pyrroles by distillation under reduced pressure, followed by preparative GC of the crude distillate. The pure compound is a white, crystalline solid, but aerial oxidation occurs quite rapidly.

Chlorination of 2-*tert*-butylpyrrole (**37**) with sulfuryl chloride afforded a pale yellow oil, which was shown by NMR and mass spectral analyses to be pure 2-*tert*-butyl-5-chloropyrrole (**36**). No evidence was obtained for the presence of any 4 isomer.

Resinification of **36** occurred in air after about 2 min; the characteristic decomposition reaction was not observed.

No mechanism can be proposed for the decomposition of 2-halopyrroles at this early stage of investigation, but several important conclusions can be drawn.

(a) Oxygen probably plays an important, if only initiating role, in the decomposition reaction; (b) the 2-chloro compounds are in general more stable than the corresponding 2-bromo compounds, possibly owing to the relative strengths of the C–Cl and C–Br bonds; (c) the 2,5-dihalo species are more unstable than the corresponding 2-halo species; (d) introduction of *C*-alkyl groups markedly decreases the stability of 2-halopyrroles whereas 1-methylation tends to increase the stability; (e) hydrogen chloride, one of the products of the decomposition of 2-chloropyrrole, also catalyzes the decomposition, so that the reaction is autocatalytic in nature; (f) ammonia is reported[55] to be one of the products of the ozonolysis of pyrrole, and ammonium chloride has been obtained from the decomposition product of 2-chloropyrrole.

Electrophilic substitution of pyrrole gives rise to predominant attack at the α position,[2] although in the case of an *N*-alkylpyrrole an increasing amount of the β isomer is also obtained.[30,56,57] When a pyrrole contains an electron-withdrawing group at the 2 position, further substitution gives rise to substantial amounts of the 4 isomer[14,16,58] in addition to the 5 isomer. It was of some interest, therefore, to evaluate the susceptibility of 2-chloropyrrole (**1**) and other 2-halopyrroles to further electrophilic attack.

The only previous report of an electrophilic substitution reaction on **1** was the sulfonation, using pyridine–sulfur trioxide, performed by Terent'ev and Yanovskaya[59] which afforded the barium salt of 5-chloropyrrole-2-sulfonic acid (**39**) in moderate yield.

Chlorination or bromination apparently gives rise to the di-α-substituted product, since these are the by-products from the halogenation of pyrrole itself.

Formylation and diazo coupling, both of which proceed readily with pyrrole[2] under conditions which would not be destructive to **1**, were examined for their regioselectivity.

Formylation of 2-chloropyrrole (**1**) with phosphorus oxychloride in dimethylformamide[60,61] gave a white, crystalline material, which was shown by ir, uv, NMR, and mass spectral analyses to be 5-chloropyrrole-2-carboxaldehyde (**28**). No evidence was obtained for the presence of any 4-substituted products.

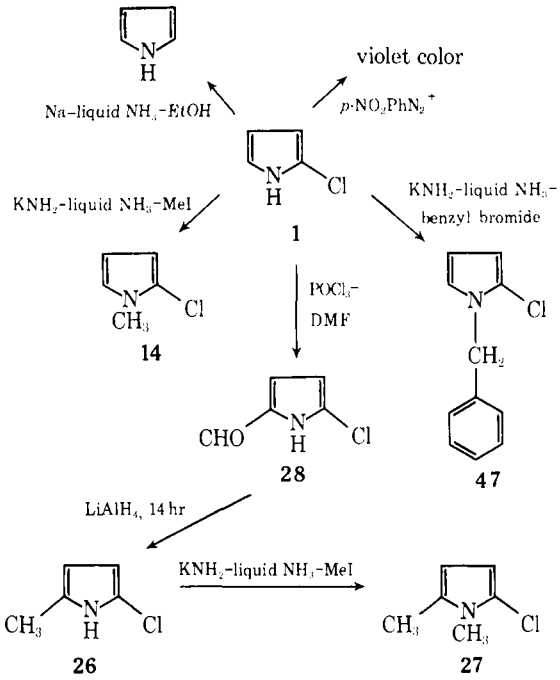
Similarly, treatment of 2-chloro-1-methylpyrrole (**14**) afforded a pale yellow oil, which was shown by ir, uv, NMR, and mass spectral analyses to be 5-chloro-1-methylpyrrole-2-carboxaldehyde (**40**).

Formylation of 2-bromopyrrole (**2**), however, led to a mixture of products. NMR, mass spectral, and GC analyses indicated that two formylated products, in the ratio 2.5:1, were formed. Comparison of retention times with those of authentic samples of 5-chloro- and 5-bromopyrrole-2-carboxaldehyde (**28** and **41**) demonstrated that these were indeed the compounds produced, the bromo compound predominating. An exactly analogous reaction has been observed in the thiophene series.[62,63]

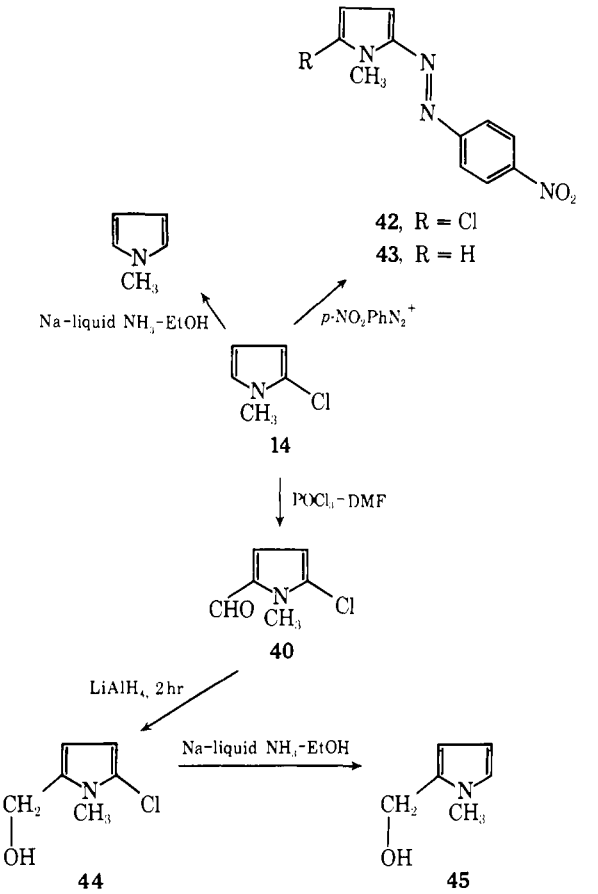
Another electrophilic substitution reaction, which, in the case of pyrrole, gives a fairly stable product is the azo-coupling reaction.[64,65]

Dropwise addition of diazotized 4-nitroaniline to a slightly alkaline solution of **1** in methanol at 5° gave an im-

Scheme II
Reactions of 2-Chloropyrrole (1)



Scheme III
Reactions of 2-Chloro-1-methylpyrrole (14)



mediate deep purple color (λ_{max} 345, 420, and 526 nm), which was stable for 2–3 hr. However, no crystalline derivative could be isolated from the reaction mixture. In a similar way, an alkaline solution of **2** in methanol at 5°, on addition of diazotized 4-nitroaniline solution, afforded an intense maroon color (λ_{max} 348 and 512 nm), but again no crystalline compound could be isolated.

In contrast to this was the reaction of the diazonium solution with a methanolic alkali solution of 2-chloro-1-methylpyrrole (**14**). An immediate red precipitate formed, which was shown by spectral analysis to be 2-chloro-1-methyl-5-(*4′-nitrophenylazo*)pyrrole (**42**). In a similar way the 2-(4′-nitrophenylazo) derivative of 1-methylpyrrole, **43**, was prepared.

Addition of excess methyl iodide to a mixture of **1** and potassium amide–liquid ammonia gave 2-chloro-1-methylpyrrole (**14**) as shown by ir, NMR, and TLC comparison with authentic material.

The action of lithium aluminum hydride in ether under reflux for 1 hr on 5-chloro-1-methylpyrrole-2-carboxaldehyde (**28**) afforded the unstable 5-chloro-2-hydroxymethyl-1-methylpyrrole (**44**). It was thought that the hydroxymethyl group could be reduced to a hydrocarbon residue by sodium in liquid ammonia in the presence of a proton source such as ethanol.[66] However, treatment of **44** with sodium in liquid ammonia in the presence of ethanol for 4 hr afforded 2-hydroxymethyl-1-methylpyrrole (**45**), as shown by ir, TLC, and NMR comparison with authentic material.

Hydrogenolysis of an aryl halide is known to occur, under these conditions, in the benzene[67] and pyrimidine[68] series. This reduction along with the previously described reductions of **1** and **14** constitute the first reports in the pyrrole series.

1-Benzyl-2-bromopyrrole (46) and 1-Benzyl-2-chloropyrrole (47). Anderson and Griffiths[30] demonstrated that a 1-benzyl group gives a greatly increased proportion of 3 substitution in bromination, nitration, and formylation compared with pyrrole and 1-methylpyrrole.

In view of the surprising regioselective formation of 1-benzyl-3-bromopyrrole (**48**), 1-benzyl-2-bromopyrrole (**46**) was synthesized to compare the NMR data with those obtained by Anderson for the 3 isomer. Addition of benzyl bromide to a mixture of **2** and potassium amide afforded a colorless oil which was shown by NMR and mass spectral analyses to be 1-benzyl-2-bromopyrrole (**46**).

The NMR data clearly indicate that bromination of 1-benzylpyrrole does indeed afford the 3 isomer.

The 1-benzyl derivative of **1** was prepared in an analogous manner, using benzyl bromide in potassium amide–liquid ammonia. 1-Benzyl-2-chloropyrrole (**47**) was stable at room temperature for periods up to 1 week.

Some of the reactions of 2-chloropyrrole (**1**) and 2-chloro-1-methylpyrrole (**14**) are summarized in Schemes II and III.

Details of the mass spectral fragmentation of the 2-halopyrroles synthesized in this study are discussed elsewhere.[69]

Experimental Section

Melting points were determined on covered slides using a Kofler heating stage, and are uncorrected. Infrared (ir) spectra were recorded on either a Perkin-Elmer 237 or 257 instrument. Cells of path 0.5 mm were used for solution spectra. Ultraviolet (uv) spectra were recorded on a Unicam SP 800 instrument.

Nuclear magnetic resonance (NMR) spectra were determined using either a Varian Associates A-60 or HA-100 instrument, an accurate shift from Me_4Si being obtained for at least one signal in each spectrum. Mass spectra were recorded on an A. E. I. MS-9 or MS-12 spectrometer at 70 eV. Thin layer chromatography (TLC) was performed with Silica F plates supplied by Anderman and Co. Ltd. Visualization was effected by a combination of uv lamp and spraying with a 4% solution of ceric sulfate in 1 *M* aqueous sulfuric acid. "Silica" used for column chromatography is silica M. F. C. supplied by Hopkin and Williams Ltd. Analytical gas chromatography (GC) was performed on a Perkin-Elmer F11 instrument using a 10% polyethylene glycol adipate on silanized Embacel 3-ft

glass column, with a nitrogen flow rate of 4 ml/min. Preparative gas chromatography was performed on a Perkin-Elmer F21 instrument using a 6-ft metal column, packed with the same material as for the analytical work. In all preparative work sodium-dried ether was used where appropriate, and solvents were redistilled prior to use. Ether solutions obtained in work-up were dried with potassium carbonate, filtered, and evaporated.

Preparation of Tertiary Amines. Ethyl di-*n*-butylamine, *n*-propyl di-*n*-butylamine, and tri-*n*-butylamine were prepared from di-*n*-butylamine and the appropriate alkyl iodide.

2-Chloropyrrole (1) and 2,5-Dichloropyrrole (3). A. To a mixture of 5 g (0.075 mol) of pyrrole in ether (200 ml) at 0° was added dropwise, a solution of 4.5 g (0.033 mol) of sulfuryl chloride in ether (50 ml). After 2–3 min of stirring, 100 ml of 10% potassium carbonate solution was added and the total mixture was rapidly steam distilled. The steam distillate was extracted with ether after the addition of ammonium chloride and the combined ether extracts processed. TLC on silica eluting with chloroform indicated the presence of three products, R_f 0.75, 0.63, and 0.52, the latter corresponding to pyrrole. GC examination of the chlorination mixture at 60° also confirmed the presence of three products with retention times (% of total) of 11.6 (7.6), 45.2 (86.0), and 60.8 min (6.2). Pyrrole was found to have a retention time of 11.8 min under these conditions.

An equimolar mixture of tri-*n*-propylamine and the synthetic tertiary amines (5 g) was added to the total ether extract from the chlorination reaction and the ether removed. The total residue was fractionally distilled under reduced pressure to afford two main fractions. Fraction 1, bp 52–56° (16 mm), was shown by ir and NMR to be 1 in tertiary amine: NMR (tertiary amine mixture) δ 5.50, 5.16, 5.07 (each 1 H); ir (film) ν_{max} 3450, 3390, 3130, 1140, 1190, 880 cm^{-1}. Fraction 2, bp 92–93° (16 mm), was shown by its ir and NMR spectra to be 3 in tertiary amine: NMR (tertiary amine mixture) δ 4.42 (s, 2, C_3 H, C_4 H); ir (film) ν_{max} 3440, 3360, 3140, 1032, 930 cm^{-1}.

The tertiary amines were removed by treatment of an ethereal solution of the appropriate fraction with excess methyl iodide at 0° for 2 days. Examination of the NMR spectrum after filtration showed that in both cases the impurities were of the order 1–2%. 2-Chloropyrrole (1): ^{1}H NMR (CCl_4) δ 5.96 (q, 1, J = 1.75, 3.6 Hz, C_3 H), 6.06 (q, 1, J = 3.05, 3.6 Hz, C_4 H), 6.46 (q, 1, J = 1.75, 3.05 Hz, C_5 H); ir (film) ν_{max} 3260, 1545, 1535, 1440, 1415, 1025, 920, 785, 760, 715 cm^{-1}. 2,5-Dichloropyrrole (3): ^{1}H NMR (CCl_4) δ 5.85 (s, C_3 H and C_4 H).

B. 2-Chloropyrrole (1) was also prepared by the method of Hess and Wissing.[10] The pale yellow, oily product was shown by TLC and ir analysis to be a mixture of pyrrole and 1 in the approximate ratio 10:1. Because of the easier preparation of a chlorination mixture, and higher content in that mixture using the modified method of Massara and Borgo,[8] this was the method of choice.

2-Bromopyrrole (2) and 2,5-Dibromopyrrole (10). Pyrrolylmagnesium bromide (4) was prepared as described previously. To this solution, 100 ml of ether was added, the mixture was cooled to −70°, and 2.64 g (0.016 mol) of redistilled bromine in 10 ml of ether was added. The mixture was stirred for 5 min and transferred to a separating funnel containing 150 ml of 10% potassium carbonate solution, 0.5 g of tertiary amine was added, and the ether layer was processed. TLC eluting with 4:1 petroleum ether–benzene indicated the presence of three products. Chromatography of approximately 300 mg of the bromination product on silica, eluting with 4:1:0.5 petroleum ether–benzene–chloroform, afforded two main fractions other than pyrrole (160 mg). Fraction 1 (~30 mg), a white solid melting slowly at room temperature, was identified as **10** by its ir and NMR spectra: NMR (CCl_4) δ 6.01 (d, 2, J = 2.5 Hz, C_3 H, C_4 H), 9.17 (br d, 1, NH); ir (CCl_4) ν_{max} 3460, 1420, 1410, 1030, 910 cm^{-1}. Fraction 2 (~80 mg), a colorless oil, was identified as **2** by its NMR spectrum: NMR (CCl_4) δ 6.58 (m, 1, C_5 H), 6.13 (m, 1, C_4 H), 6.05 (m, 1, C_3 H), NH not observed.

2-Chloro-1-methylpyrrole (14) and 2,5-Dichloro-1-methylpyrrole (16). To a solution of 5.0 g (0.06 mol) of 1-methylpyrrole in 20 ml of ether at 0° was added a mixture of 8.5 g (0.06 mol) of sulfuryl chloride in 20 ml of ether. After stirring below 10° for 10 min, 70 ml of 10% potassium carbonate solution was added and the mixture was steam distilled. The steam distillate was thoroughly extracted with ether. Processing afforded a pale yellow oil which was fractionally distilled under reduced pressure to afford two main fractions. Fraction 1 (5.34 g, 74%), bp 30–32° (10 mm), was shown to be **14:** NMR (CCl_4) δ 6.40 (q, 1, J = 2.5, 3.0 Hz, C_5 H), 5.92 and 5.90 (m, 2, C_3 H and C_4 H), 3.53 (s, 3, NCH_3); ir (film) ν_{max} 3125, 1295, 1110, 1085, 880 cm^{-1}.

Anal. Calcd for C_5H_6NCl: C, 52.2; H, 5.2; N, 12.2; Cl, 30.4. Found: C, 51.8; H, 5.2; N, 12.3; Cl, 31.7.

Fraction 2 (0.47 g, 5%), bp 40–42° (8 mm), was shown to be 2,5-dichloro-1-methylpyrrole (**16**): NMR (CCl_4) δ 5.96 (s, 2, C_3 H and C_4 H), 3.51 (s, 3, NCH_3).

Attempted Preparation of 2-Bromo-1-methylpyrrole (15). A. Following the method of Anderson and Griffiths,[30] to a solution of 5.01 g (0.06 mol) of 1-methylpyrrole in 20 ml of carbon tetrachloride at −10° was added slowly a solution of 5.5 g (0.034 mol) of bromine in 10 ml of carbon tetrachloride. After stirring for 20 min, the mixture was treated successively with 5% sodium carbonate solution, 5% sodium bisulfite solution, and water. The organic phase was separated and dried with magnesium sulfate. Filtration and removal of solvent afforded a crystalline solid which was recrystallized from alcohol–water to give 2.57 g (13.6%) of white needles, shown to be 2,3,4,5-tetrabromo-1-methylpyrrole (**17**): mp 153–154° (lit.[31] 154°); NMR (CCl_4) δ 3.69 (s, 3, NCH_3); ir (Nujol) ν_{max} 1495, 1315, 1082 cm^{-1}.

B. A solution of 2.7 g (0.017 mol) of bromine in 20 ml of carbon tetrachloride was added to a mixture of 1.2 g (0.015 mol) of 1-methylpyrrole in 150 ml of carbon tetrachloride at 0° containing magnesium oxide as a slurry. After 10 min, 50 ml of 10% potassium carbonate solution was added and the total mixture filtered. The organic phase was washed with 30 ml of 5% potassium bisulfite solution and 25 ml of water, and dried with magnesium sulfate. Removal of the solvent afforded a pale green solid, to which 75 mg of tertiary amine was added and the residue was repeatedly extracted with small quantities of hot petroleum ether. The solid remaining was identified as **17**, mp 153–154°, having spectral properties as before. TLC of the petroleum ether extract, eluting with 4:1 petroleum ether–benzene, indicated the presence of five products. The total residue was chromatographed over silica eluting with 2:1 petroleum ether–benzene to afford 128 mg (10%) of 1-methylpyrrole and two main fractions. Fraction 1 (136 mg) was shown by NMR analysis to be a mixture of the 2,5-dibromo, 2,3,5-tribromo-, and 2,3,4,5-tetrabromo-1-methylpyrroles in the ratio 2.5:4:5. 2,5-Dibromo-1-methylpyrrole (**18**): NMR ($CDCl_3$) δ 6.23 (s, 2, C_3 H and C_4 H), 3.60 (s, 3, NCH_3). 2,3,5-Tribromo-1-methylpyrrole: NMR ($CDCl_3$) δ 6.35 (s, 1, C_4 H), 3.64 (s, 3, NCH_3). Fraction 2, a colorless oil, was shown by NMR to be a mixture of mono- and dibromo derivatives in the ratio 3:2, and a small proportion of 1-methylpyrrole. 2-Bromo-1-methylpyrrole (**15**): NMR (CCl_4) δ 6.55 (q, 1, C_5 H), 6.11 (m, 1, C_4 H), 5.97 (m, 1, C_3 H), 3.63 (s, 3, NCH_3).

Birch Reduction of 1 and 14. Into a mixture of 103 mg (0.001 mol) of **1** in 2 ml of absolute ethanol, 25 ml of ammonia was distilled and 146 mg (0.006 mol) of sodium was added. The mixture was stirred for 4 hr and the ammonia allowed to evaporate. The residue was partitioned between ether and water, and the aqueous phase was thoroughly extracted with ether. Processing afforded 60 mg (90%) of a colorless oil which was shown by its spectral and chromatographic properties to be pyrrole.

Similarly, 116 mg (0.0009 mol) of **14** afforded, upon reduction, 58 mg (84%) of a colorless oil identified as 1-methylpyrrole.

5-Chloro-2-methylpyrrole (26). A solution of 123 mg (0.0011 mol) of **28** in 4 ml of ether was added carefully to 300 mg (0.008 mol) of lithium aluminum hydride in 20 ml of ether and the mixture refluxed for 14 hr. Sodium hydroxide solution (1*N*) was added to destroy the excess lithium aluminum hydride and the aqueous phase was thoroughly extracted with ether. TLC of the residue after processing on silica eluting with benzene indicated the presence of a major product, R_f 0.51. This product, a white, crystalline solid, was identified as **26:** NMR (CCl_4) δ 5.83 (d, 1, J = 3.7 Hz, C_4 H), 5.74 (d, 1, J = 3.7 Hz, C_3 H), 2.18 (s, 3, $-CH_3$); ir (CCl_4) ν_{max} 3470, 2920, 1472, 1410, 1115, 1030 cm^{-1}.

5-Chloro-1,2-dimethylpyrrole (27). An ether solution of **26** [prepared from 521 mg (0.0045 mol) of **28**] was added dropwise to potassium amide [from 756 mg (0.019 mol) of potassium and 50 mg of ferric nitrate] in 150 ml of redistilled liquid ammonia, and the mixture was stirred for 30 minutes. A solution of 1.4 g (0.01 mol) of methyl iodide in 5 ml of ether was added and the mixture was stirred for 5 hr. Excess potassium amide was decomposed by the addition of 10 ml of 1:1 methanol–benzene and the ammonia was allowed to evaporate overnight. Water was added and the aqueous phase was thoroughly extracted with ether. The residue after processing was chromatographed on silica eluting with 10:1 petroleum ether–benzene. Considerable decomposition occurred, but one fraction was shown to be 30 mg (5%) of **27:** NMR (CCl_4) δ 5.74 (d, 1, J = 4.0 Hz, C_4 H), 5.64 (d, 1, J = 4.0 Hz, C_3 H), 3.41 (s, 3, NCH_3), 2.17 (s, 3, $-CH_3$); ir (CCl_4) ν_{max} 2920, 1400, 1300, 1075 cm^{-1}.

3-Ethoxycarbonyl-2,4-dimethylpyrrole-5-carboxylic Acid (32). A solution of 4.97 g (0.021 mol) of **30** and 2.35 g (0.05 mol) of potassium hydroxide in 60 ml of 95% ethanol and 70 ml of water was distilled until 60 ml of distillate had collected. Cooling and acidification give a white solid which was filtered and recrystallized from 95% ethanol to yield 3.25 g (74%) of **32:** mp 203–204° dec (lit.[46] 204°); NMR (pyridine-*d*) δ 4.39 (q, 2, J = 7.5 Hz, $-CO_2CH_2CH_3$), 3.15 (s, 3, C_2 CH_3), 2.76 (s, 3, C_4 CH_3), 1.34 (t, 3, J = 7.5 Hz, $-CO_2CH_2CH_3$); uv (EtOH) λ_{max} 254 nm (log ϵ 4.10), 269 (4.21); ir (Nujol) ν_{max} 3300, 2660, 1690, 1667 cm^{-1}.

3-Ethoxycarbonyl-2,4-dimethylpyrrole (31). Heating 2.75 g (0.013 mol) of **32** to melting, and until carbon dioxide evolution had ceased, gave a pale pink liquid which crystallized on cooling. Recrystallization from petroleum ether gave 1.86 g (86%) of **31** as white needles: mp 78° (lit.[7] 79°); NMR (CCl_4) δ 6.18 (broad s, 1, C_5 H), 4.21 (q, 2, J = 7.5 Hz, $-CO_2CH_2CH_3$), 2.42 (s, 3, C_2 CH_3), 2.15 (s, 3, C_4 CH_3), 1.33 (t, 3, J = 7.5 Hz, $-CO_2CH_2CH_3$); uv (EtOH) λ_{max} 230 nm (log ϵ 3.91), 258 (3.67); ir (Nujol) ν_{max} 3305, 1665, 1160 cm^{-1}.

5-Bromo-3-ethoxycarbonyl-2,4-dimethylpyrrole (33). Following the method of Corwin and Viohl, **33** was prepared from **31** in 25% yield as pale yellow needles: mp 112–114° dec (lit.[45] 110°); NMR ($CDCl_3$) δ 4.26 (q, 2, J = 7.5 Hz, $-CO_2CH_2CH_3$), 2.45 (s, 3, C_2 CH_3), 2.17 (s, 3, C_4 CH_3), 1.33 (t, 3, J = 7.5 Hz, $-CO_2CH_2CH_3$); uv (EtOH) λ_{max} 224 nm (log ϵ 3.97), 262 (3.76); ir (Nujol) ν_{max} 3270, 1665, 1315, 770 cm^{-1}.

Repetition of the reaction but starting with 13.5 g of **31** gave a greatly improved (84%) yield of **33.**

5-Chloro-3-ethoxycarbonyl-2,4-dimethylpyrrole (34). A. To a solution of 48 mg (0.0003 mol) of **31** in 2 ml of ether at −70° was added 38 mg (0.0003 mol) of sulfuryl chloride in 2 ml of ether. After 5 min, 5 ml of 10% potassium carbonate solution was added and the aqueous phase was thoroughly extracted with ether. Processing afforded a residue which was chromatographed on silica eluting with chloroform to give 4.2 mg of **31,** identical with an authentic sample. The major product was recrystallized from aqueous alcohol to give 53 mg (91%) of **34** as pale yellow needles: mp 140–142° (lit.[45] 140–141°); NMR ($CDCl_3$) δ 4.27 (q, 2, J = 7.5 Hz, $-CO_2CH_2CH_3$), 2.46 (s, 3, C_2 CH_3), 2.18 (s, 3, C_4 CH_3), 1.35 (t, 3, J = 7.5 Hz, $-CO_2CH_2CH_3$); uv (EtOH) λ_{max} 221 nm (log ϵ 3.92), 264 (3.65); ir (Nujol) ν_{max} 3255, 1670, 1225, 1050 cm^{-1}.

B. Following the method outlined by Treibs and Kolm,[33] 246 mg (0.001 mol) of **33** was suspended in 4 ml of glacial acetic acid, and 0.5 ml of concentrated hydrochloric acid was added. After 10 min at room temperature, 10 ml of water was added. The precipitate was filtered and recrystallized from aqueous ethanol to give 163 mg (81%) of **34** as pale yellow needles, physical and spectral properties as above.

5-Bromo-2,3,4-trimethylpyrrole (20). A solution of 55 mg (0.00022 mol) of **33** in 5 ml of ether was added to a mixture of 100 mg (0.0026 mol) of lithium aluminum hydride in 5 ml of ether and the mixture was refluxed for 2 hr. Processing in the usual way gave an ether solution, which upon evaporation afforded white needles decomposing within 30 sec. Addition of 20 mg of pyridine-d_5 and repeated evaporation from carbon tetrachloride afforded a solution which was shown to contain **20** by NMR at 0°: NMR (CCl_4) δ 2.16 (s, 3, C_2 CH_3), 1.83 (s, 6, C_3 CH_3 and C_4 CH_3); uv (EtOH) λ_{max} 230 nm.

5-Chloro-2,3,4-trimethylpyrrole (29). A solution of 66 mg (0.00033 mol) of **34** in 5 ml of ether was added to a mixture of 100 mg (0.0026 mol) of lithium aluminum hydride in 5 ml of ether and the mixture was refluxed for 2 hr. Processing in the usual way gave an ether solution, which upon evaporation afforded white needles decomposing within 7–8 min. Repeated evaporation from carbon tetrachloride afforded a solution which was shown by NMR to contain only **29:** NMR (CCl_4) δ 2.18 (s, 3, C_2 CH_3), 1.89 (s, 6, C_3 CH_3 and C_4 CH_3); ir (CCl_4) ν_{max} 3480, 1605, 1440, 1295, 1120 cm^{-1}.

5-Chloro-1,2,3,4-tetramethylpyrrole (35). 5-Chloro-2,3,4-trimethylpyrrole (**29**) in ether [prepared from 303 mg (0.0015 mol) of **34**] was added to potassium amide [from 604 mg (0.015 mol) of potassium and 50 mg of ferric nitrate] in 125 ml of redistilled liquid ammonia. After stirring for 30 min, 1.14 g (0.008) of methyl iodide was added and the mixture stirred for 4 hr. At the end of this time 10 ml of 1:1 methanol–benzene was added to destroy the excess potassium amide and the ammonia allowed to evaporate overnight. To this mixture was added 20 ml of saturated ammonium chloride solution and the aqueous phase was thoroughly extracted with ether. TLC indicated the presence of both the NH and NCH_3 compounds in the approximate ratio 1:1.

The N-methylation procedure was repeated on this mixture and the reaction mixture extracted with hexane prior to decomposition of potassium amide to afford pure **35** as a highly unstable, pale yellow solid: NMR (CCl_4) δ 3.32 (s, 3, NCH_3), 2.02 (s, 3, C_2 CH_3), 1.81 and 1.79 (s, 3 each, C_3 CH_3 and C_4 CH_3); uv (EtOH) λ_{max} 231 nm; ir (CCl_4) ν_{max} 1460, 1370, 1290, 1035 cm^{-1}.

2-*tert*-Butylpyrrole (37). The method used was essentially that of Skell and Bean.[53] Analytical GC at 120° showed a complex mixture consisting of pyrrole (35%), retention time 1.25 min, 2-*tert*-butylpyrrole (30%), retention time 2.75 min, 3-*tert*-butylpyrrole (22%), retention time 3.6 min, and polyalkylated pyrroles (5%), retention time 5 min. The total reaction mixture was distilled and the fraction boiling below 120° discarded, and the residue was distilled under reduced pressure (20 mm). The colorless distillate was subjected to preparative GC to afford 17.3 g (28%) of **37** and 11.1 g (18%) of **38.** 2-*tert*-Butylpyrrole (**37**): mp 43–44°; NMR (CCl_4) δ 6.45 (dd, 1, J = 1.5 and 2.75 Hz, C_5 H), 5.91 (dd, 1, J = 2.75 and 3.5 Hz, C_4 H), 5.76 (dd, 1, J = 1.5 and 3.5 Hz, C_3 H), 1.27 [s, 9, $-C(CH_3)_3$]; ir (film) ν_{max} 3380, 3090, 1600, 1560, 1525, 1282, 1260, 1015 cm^{-1}.

2-*tert*-Butyl-5-chloropyrrole (36). A solution of 292 mg (0.0022 mol) of sulfuryl chloride in 2 ml of ether was added to 231 mg (0.0019 mol) of **37** in 8 ml of ether at 0°. After 5 min, 10 ml of 10% potassium carbonate solution was added and the aqueous phase was thoroughly extracted with ether.

The reaction product was chromatographed on silica eluting with 3.5:1 petroleum ether–benzene to afford 255 mg (90%) of **36** as a pale yellow oil: NMR (CCl_4) δ 5.78 (d, 1, J = 3.6 Hz, C_3 H), 2.27 [s, 9, $-C(CH_3)_3$]; ir (CCl_4) ν_{max} 3485, 3280, 3100, 1570, 1280 cm^{-1}.

5-Chloropyrrole-2-carboxaldehyde (28). A solution of 102 mg (0.001 mol) of **1** in 1 ml of ether was added to 160 mg of redistilled phosphorus oxychloride in 4 ml of dimethylformamide and the mixture shaken at room temperature for 30 min. The mixture was cooled in ice and 3 ml of water added. The ether layer was separated and discarded and the aqueous layer treated with 1 ml of 40% sodium hydroxide solution at room temperature for 30 min. The aqueous solution was acidified to pH 3 and thoroughly extracted with ether. Recrystallization of the yellow-white residue from hexane gave 91 mg (78%) of **28** as white needles: mp 110–111° (lit.[12,16] 110–111°); NMR (CCl_4) δ 10.43 (broad s, 1, NH), 9.41 (s, 1, CHO), 6.89 (d, 1, J = 3.9 Hz, C_4 H); uv (EtOH) λ_{max} 240 nm (log ϵ 3.68), 293 (4.285); ir (CCl_4) ν_{max} 3440, 3210, 3080, 2720, 1660, 1290 cm^{-1}.

Formylation of 2-Bromopyrrole (2). A solution of approximately 15 mg of **2** in 1 ml of ether was added to 16 mg of phosphorus oxychloride in 2 ml of dimethylformamide and the mixture allowed to stand at room temperature for 3 hr. Processing as described above afforded an ether solution which by TLC apparently contained a single material. Several techniques, however, indicated that a mixture had been obtained. GC analysis at 150° indicated two components with retention times of 6.8 and 12 min, in the ratio 2.5:1. 5-Chloropyrrole-2-carboxaldehyde (**28**) has retention time 6.9 min and 5-bromopyrrole-2-carboxaldehyde (**41**) has retention time 11.8 min under these conditions. The mass spectrum showed M^+ at *m/e* 175 and 173 for the 5-bromo compound **41** and M^+, *m/e* 131 and 129, for the 5-chloro compound **28.** The NMR spectrum in CCl_4 after addition of D_2O indicated two pairs of doublets, each J = 4.0 Hz, at δ 6.87 and 6.16 ppm for **28,** and δ 6.75 and 6.26 ppm for **41.**

5-Chloro-1-methylpyrrole-2-carboxaldehyde (40). A solution of 588 mg (0.0044 mol) of **14** in 3 ml of ether was added to 880 mg of phosphorus oxychloride in 8 ml of dimethylformamide and the mixture allowed to stand overnight at room temperature under nitrogen. Processing as described above afforded a residue which was chromatographed on silica, eluting with 1:1 chloroform–ethyl acetate to give 646 mg (89%) of **40** as a colorless oil: NMR (CCl_4) δ 9.38 (s, 1, CHO), 6.80 (d, 1, J = 4.0 Hz, C_4 H), 3.95 (s, 3, NCH_3); uv (EtOH) λ_{max} 250 nm (log ϵ 3.82), 286 (4.30); ir (CCl_4) ν_{max} 2950, 2710, 1675, 1428, 1310, 1025 cm^{-1}.

Anal. Calcd for C_6H_6ClNO: C, 50.2; H, 4.2; N, 9.7. Found: C, 50.0; H, 3.9; N, 9.7.

2-Chloro-1-methyl-5-(4′-nitrophenylazo)pyrrole (42). A solution of 4-nitroaniline in dilute hydrochloric acid was diazotized with 10 ml of 10% sodium nitrite solution at 5°. An aliquot of this solution was added to 110 mg (0.00095 mol) of **14** in 5 ml of methanolic alkali. After standing for 10 min, the red precipitate was filtered and recrystallized from glacial acetic acid to afford 84 mg (34%) of **42** as fine red needles: mp 137–138°; NMR (acetone-*d*) δ 8.34 and 7.97 (m, 2 each, aromatic H), 6.82 (d, 1, J = 3.8 Hz, C_4 H), 6.39 (d, 1, J = 3.8 Hz, C_3 H), 3.99 (s, 3, NCH_3); uv (EtOH) λ_{max} 434

nm (log ε 4.47); ir (Nujol) ν_{max} 3200, 1600, 1580, 1490, 1310, 1270, 1110, 1040 cm^{-1}.

Anal. Calcd for $C_{11}H_9ClN_4O_2$: C, 50.1; H, 3.4; N, 21.1; Cl, 13.4. Found: C, 49.8; H, 3.4; N, 20.9; Cl, 13.6.

Red needles of **43** were prepared similarly: mp 133–134°; NMR (acetone-*d*) δ 8.33 and 7.94 (m, 2 each, aromatic H), 7.32 (dd, 1, *J* = 1.65 and 2.65 Hz, C_5 H), 6.78 (dd, 1, *J* = 1.65 and 4.35 Hz, C_3 H), 6.36 (dd, 1, *J* = 2.65 and 4.35 Hz, C_4 H), 4.01 (s, 3, NCH_3); uv (EtOH) λ_{max} 414 nm (log ε 4.43); ir (Nujol) ν_{max} 3120, 1510, 1320, 1200, 1095 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}N_4O_2$: C, 57.0; H, 4.3; N, 24.8. Found: C, 56.4; H, 4.6; N, 25.1.

2-Chloro-1-methylpyrrole (14). A solution of 106 mg (0.001 mol) of **1** in 5 ml of ether was added to potassium amide [from 212 mg (0.0055 mol) of potassium and 75 mg of ferric nitrate] in 75 ml of redistilled liquid ammonia. After 25 min, a solution of 2.3 g (0.016 mol) of methyl iodide in 3 ml of ether was added and the mixture stirred for 4 hr. Processing in the usual way afforded an ether solution which was chromatographed on silica, eluting with chloroform, to afford 75 mg (63%) of **14** as a colorless oil, having identical spectral properties with the material obtained from the chlorination of 1-methylpyrrole.

1-Benzyl-2-bromopyrrole (46). A solution of approximately 50 mg (0.00033 mol) of **2** in 2 ml of ether was added to potassium amide [from 30 mg (0.00077 mol) of potassium and 50 mg of ferric nitrate] in 25 ml of redistilled liquid ammonia. After 30 min, a solution of 85 mg (0.0005 mol) of benzyl bromide in 2 ml of ether was added and the mixture stirred for 2 hr. Processing in the usual way afforded a mixture of two products, one of which was identified, by TLC, as unreacted **2**. The total residue was chromatographed on silica eluting with 5:1 petroleum ether–benzene to afford unreacted **2** and 31.2 mg (39%) of a colorless oil identified as **46:** NMR (CCl_4) δ 7.3–6.9 (m, 5, aromatic H), 6.60 (m, 1, C_5 H), 6.09 and 6.07 (m, 1 each, C_3 H and C_4 H), 5.07 (s, 2, $-CH_2Ar$); ir (CCl_4) ν_{max} 3040, 2920, 1600, 1495, 1292 cm^{-1}.

1-Benzyl-2-chloropyrrole (47). A solution of 243 mg (0.0024 mol) of **1** in 4 ml of ether was added to potassium amide [from 156 mg (0.0037 mol) of potassium and 72 mg of ferric nitrate] in 40 ml of redistilled liquid ammonia. After 30 min, a solution of 504 mg (0.003 mol) of benzyl bromide in 2 ml of ether was added and the mixture stirred for 4 hr. Processing in the usual way afforded a mixture of three products, one of which was identified, by TLC, as unreacted **1**. The total residue was chromatographed on silica eluting with 5:1 petroleum ether–benzene to afford two fractions other than 86 mg (35%) of **1**. Fraction 1 was 165 mg (61%) of a white solid identified as *trans*-stilbene: mp 122–123° (lit.[7] 124°); NMR (CCl_4) δ 6.96 (s, 2, olefinic H), 7.5–7.1 (m, 10, aromatic H); uv (EtOH) λ_{max} 295 nm, 307, sh 320; mass spectrum *m/e* 180 (M^+, 10%), 77 (100). Fraction 2 was 14 mg (3%) of **47**, a white, crystalline solid: mp 123–124°; NMR δ 7.35–6.90 (m, 5, aromatic H), 6.48 (m, 1, C_5 H), 6.02 and 5.98 (m, 1 each, C_3 H and C_4 H), 5.04 (s, 2, $-CH_2Ar$); ir (film) ν_{max} 3100, 3060, 2920, 1605, 1520, 1290, 1065 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}ClN$: C, 69.1; H, 5.2; N, 7.3. Found: C, 68.5; H, 5.3; N, 6.9.

5-Chloro-2-hydroxymethyl-1-methylpyrrole (44). A solution of 94.3 mg (0.00065 mol) of **40** in 5 ml of ether was added to 120 mg (0.0032 mol) of lithium aluminum hydride in 8 ml of ether and the mixture refluxed for 1 hr. Processing in the usual way afforded an ether solution which was evaporated several times from carbon tetrachloride. The final carbon tetrachloride solution was shown to contain only **44:** NMR (CCl_4) δ 5.92 (m, 2, C_3 H and C_4 H), 4.46 (d, 2, *J* = 7 Hz, CH_2OH), 3.67 (s, 3, NCH_3).

Birch Reduction of 44. A solution of **44** [prepared from 190.5 mg (0.001 mol) of **40**] in 5 ml of ether, was added to 0.9 g (0.39 mol) of sodium in 100 ml of redistilled liquid ammonia and 2 ml of ethanol. The mixture was stirred for 2 hr and the ammonia allowed to evaporate. Processing in the usual way afforded 136 mg (92%) of **45** as a pale yellow oil: NMR (CCl_4) δ 6.43 (m, 1, C_5 H), 5.85 (m, 2, C_3 H and C_4 H), 4.41 (s, 2, CH_2OH), 3.63 (s, 3, NCH_3); ir (film) ν_{max} 3360, 2930, 1500, 1305, 995 cm^{-1}.

Acknowledgments. The author would like to thank Dr. G. F. Smith, University of Manchester, for his invaluable advice and encouragement and the Science Research Council for a scholarship.

Registry No.—**1**, 56454-22-9; **2**, 38480-28-3; **3**, 56454-23-0; **4**, 56454-24-1; **10**, 56454-25-2; **14**, 56454-26-3; **15**, 56454-27-4; **16**, 56454-28-5; **17**, 56454-29-6; **18**, 56454-30-9; **20**, 56454-31-0; **26**, 56454-32-1; **27**, 56454-33-2; **28**, 1757-28-4; **29**, 56453-91-9; **30**, 2436-79-5; **31**, 2199-51-1; **32**, 5442-91-1; **33**, 56453-92-0; **34**, 56453-93-1; **35**, 56453-94-2; **36**, 56453-95-3; **37**, 5398-58-3; **40**, 56453-96-4; **42**, 56453-97-5; **43**, 56453-98-6; **44**, 56453-99-7; **45**, 52160-51-7; **46**, 56454-00-3; **47**, 56454-01-4; 1-methylpyrrole, 96-54-8; sulfuryl chloride, 7791-25-5; bromine, 7726-95-6; 4-nitroaniline, 100-01-6; *trans*-stilbene, 103-30-0; pyrrole, 109-97-7.

References and Notes

(1) (a) This work was submitted in fulfillment of the requirements of the degree of Master of Science, University of Manchester, Manchester, England. (b) College of Pharmacy, University of Illinois at the Medical Center, Chicago, Ill. 60612.
(2) A. H. Corwin in "Heterocyclic Compounds", Vol. I, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1950; T. S. Stevens in "Chemistry of Carbon Compounds", Vol. 4a, E. H. Rodd, Ed., Elsevier, Amsterdam, 1957, p 34; R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds", 2nd ed, Wiley-Interscience, New York, N.Y., 1967; A. R. Katritsky and J. M. Lagowski, "The Principles of Heterocyclic Chemistry", Chapman and Hall, London, 1967; M. H. Palmer, "The Structure and Reactions of Heterocyclic Compounds", Edward Arnold, London, 1967; A. Albert, "Heterocyclic Chemistry", 2nd ed, Athlone Press, London, 1968; L. A. Paquette, "Modern Heterocyclic Chemistry", W. A. Benjamin, New York, N.Y., 1968; J. A. Joule and G. F. Smith, "Heterocyclic Compounds", Van Nostrand-Reinhold, Princeton, N.J., 1972.
(3) P. Linda and G. Marino, *J. Chem. Soc. B*, 392 (1968). G. Marino, *Pr. Nauk. Inst. Chem. Technol. Nafty Wegla Politech. Wroclaw.*, 89 (1973); *Chem. Abstr.*, **79**, 77564a (1973).
(4) K. J. Morgan and D. P. Morrey, *Tetrahedron*, **22**, 57 (1966).
(5) A. P. Terent'ev and L. A. Yanovskaya, *J. Gen. Chem. USSR (Engl. Transl.)*, **19**, 538 (1949).
(6) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).
(7) I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds", 4th ed, Eyre and Spottiswoode, London, 1965, and Supplements.
(8) G. Mazzara and A. Borgo, *Gazz. Chim. Ital.*, **35**, 20 (1905).
(9) G. Mazzara and A. Borgo, *Gazz. Chim. Ital.*, **35**, 477 (1905).
(10) K. Hess and F. Wissing, *Chem. Ber.*, **47**, 1416 (1914).
(11) B. Oddo, *Gazz. Chim. Ital.*, **39**, 649 (1909); B. Oddo, *Chem. Ber.*, **43**, 1020 (1910).
(12) P. Hodge, Ph.D. Thesis, Manchester University, Manchester, England, 1963.
(13) K. Hess and F. Wissing, *Chem. Ber.*, **48**, 1884 (1915).
(14) H. J. Anderson and S.-F. Lee, *Can. J. Chem.*, **43**, 409 (1965).
(15) H. Fischer and K. Gangl, *Hoppe-Seyler's Z. Physiol. Chem.*, **267**, 188 (1941).
(16) P. Hodge and R. W. Rickards, *J. Chem. Soc.*, 459 (1965).
(17) R. J. Motekaitis, D. H. Heinert, and A. E. Martell, *J. Org. Chem.*, **35**, 2504 (1970).
(18) A previous attempt[19] to use preparative GC to obtain pure 2-chloropyrrole (**1**) failed.
(19) K. J. Morgan, Lancaster University, private communication, 1968.
(20) The use of aliphatic tertiary amines also permitted direct examination of the δ 7.0–5.5-ppm region in the NMR spectrum of the distillates.
(21) "Decomposition" in this and subsequent instances was a violent, exothermic reaction with gas evolution and total charring.
(22) R. Cuisa, *Gazz. Chim. Ital.*, **52**, 130 (1922); **55**, 385 (1925).
(23) J. H. Wardlaw, D. E. Weiss, R. McNeill, and R. Suldak, *Aust. J. Chem.*, **16**, 1056 (1963).
(24) H. Fischer and H. Hofelmann, *Justus Liebigs Ann. Chem.*, **538**, 216 (1938).
(25) E. B. Smith and H. B. Jensen, *J. Org. Chem.*, **32**, 3330 (1967).
(26) L. Chierici and G. P. Gardini, *Tetrahedron*, **22**, 53 (1966).
(27) G. F. Smith, *Adv. Heterocycl. Chem.*, **2**, 287 (1963).
(28) M. G. Reinecke and H. W. Adickes, *J. Am. Chem. Soc.*, **90**, 511 (1968).
(29) H. Smith, "Organic Reactions in Liquid Ammonia", Wiley, New York, N.Y., 1963.
(30) H. J. Anderson and S. J. Griffiths, *Can. J. Chem.*, **45**, 2227 (1967).
(31) G. De Varda, *Chem. Ber.*, **21**, 2871 (1888).
(32) C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **70**, 417 (1948).
(33) A. Treibs and H. G. Kolm, *Justus Liebigs Ann. Chem.*, **614**, 176 (1958).
(34) H. Booth, A. W. Johnson, and F. Johnson, *J. Chem. Soc.*, 98 (1962).
(35) J. Ellis, A. H. Jackson, A. C. Jain, and G. W. Kenner, *J. Chem. Soc.*, 1935 (1964).
(36) R. J. Motekaitis, D. H. Heinert, and A. E. Martell, *J. Org. Chem.*, **35**, 2504 (1970).
(37) P. E. Sonnet, *J. Heterocycl. Chem.*, **9**, 1395 (1972).
(38) A. Treibs and H. Scherer, *Justus Liebigs Ann. Chem.*, **577**, 139 (1952); **589**, 180 (1954).
(39) W. Herz and C. Courtney, *J. Am. Chem. Soc.*, **76**, 576 (1954).
(40) R. L. Hinman and S. Theodoropoulos, *J. Org. Chem.*, **28**, 3052 (1963).
(41) R. M. Silverstein, E. E. Ryskiewicz, and S. W. Chaikin, *J. Am. Chem. Soc.*, **76**, 4485 (1954).
(42) F. P. Doyle, M. D. Mehta, and G. S. Sach, *J. Chem. Soc.*, 4458 (1958).
(43) H. J. Anderson and S.-F. Lee, *Can. J. Chem.*, **43**, 409 (1965).
(44) H. J. Anderson and C. W. Huang, *Can. J. Chem.*, **45**, 897 (1967).
(45) A. H. Corwin and P. Viohl, *J. Am. Chem. Soc.*, **66**, 1143 (1944); A. H. Corwin and G. G. Kleinspehn, *ibid.*, **75**, 2089 (1953).
(46) L. Knorr, *Justus Liebigs Ann. Chem.*, **236**, 290 (1886).
(47) H. Kuster, *Hoppe-Seyler's Z. Physiol. Chem.*, **121**, 138 (1922).
(48) A. H. Corwin, W. A. Bailey, and P. Viohl, *J. Am. Chem. Soc.*, **64**, 1267 (1942).
(49) S. J. Cristol and W. C. Firth, Jr., *J. Org. Chem.*, **26**, 280 (1961).

(50) H. Fischer and R. Baumler, *Justus Liebigs Ann. Chem.*, **468**, 58 (1929).
(51) A. P. Terent'ev, *J. Gen. Chem. USSR (Engl. Transl.)*, **24**, 1265 (1954).
(52) F. Bohlmann, *Chem. Ber.*, **86**, 657 (1953).
(53) P. S. Skell and G. P. Bean, *J. Am. Chem. Soc.*, **84**, 4655 (1962).
(54) G. P. Bean, *J. Org. Chem.*, **32**, 228 (1967).
(55) J. P. Wibaut and A. R. Gulse, *Proc. K. Ned. Akad. Wet., Ser. B*, **54**, 330 (1951); *Chem. Abstr.*, **47**, 6934*h* (1952).
(56) P. Fournari and J. Tirouflet, *Bull. Soc. Chim. Fr.*, 488 (1963).
(57) H. J. Anderson and S. J. Griffiths, *Can. J. Chem.*, **45**, 2227 (1967).
(58) C. Jaureguiberry, M.-C. Fournie-Zaluski, J.-P. Chevallier, and B. Roques, *C. R. Acad. Sci., Ser. C*, **273**, 276 (1971).
(59) A. P. Terent'ev and L. A. Yanovskaya, *J. Gen. Chem. USSR (Engl. Transl.)*, **21**, 281 (1951).
(60) R. M. Silverstein, E. E. Ryskiewicz, and S. W. Chaikin, *J. Am. Chem. Soc.*, **76**, 4485 (1954).
(61) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).
(62) W. J. King and F. F. Nord, *J. Org. Chem.*, **13**, 638 (1948).
(63) A. W. Weston and R. J. Michaels, *J. Am. Chem. Soc.*, **72**, 1422 (1950).
(64) O. Fischer and E. Hepp, *Chem. Ber.*, **19**, 2251 (1886).
(65) H. Fischer and E. Bartholomaus, *Hoppe-Seyler's Z. Physiol. Chem.*, **76**, 478 (1912); **87**, 257 (1913).
(66) A. J. Birch, *J. Chem. Soc.*, 809 (1945).
(67) G. F. White, *J. Am. Chem. Soc.*, **45**, 779 (1923).
(68) L. P. Fuller, E. Lieber, and Q. B. L. Smith, *J. Am. Chem. Soc.*, **59**, 1150 (1937).
(69) G. A. Cordell, manuscript in preparation.

Thianaphthen-2-one Chemistry. I. Synthesis of 6*H*-Benzothieno[3,2-*c*][1]benzopyran-6-ones (11-Thiacoumestans)

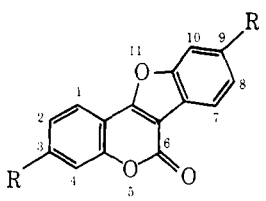
Richard A. Conley and Ned D. Heindel*

Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania 18015

Received March 27, 1975

The condensation of thianaphthen-2-one and salicylaldehyde gave 6a,11a-dihydro-6*H*-benzothieno[3,2-*c*][1]benzopyran-6-one (dihydro-11-thiacoumestan). Several analogs were prepared. Oxidation of the dihydro compounds with DDQ (2,3-dichloro-5,6-dicyano-1,4-quinone) gave 6*H*-benzothieno[3,2-*c*][1]benzopyran-6-ones (11-thiacoumestans), a new heterocyclic ring system, and the sulfur analog of the naturally occurring 6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (coumestan) ring system. The reaction of thianaphthen-2-one with 5-nitrosalicylaldehyde and pyridoxal in alcohol gave the corresponding 2-aryl-2,3-dihydrothianaphthene-3-carboxylates.

Derivatives of the 6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one ring system[1] (commonly called coumestan) have been found in many natural products. 3,9-Dihydroxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (coumestrol) was isolated from ladino clover and showed marked estrogenic activity.[2,3] The laboratory syntheses of the coumestans have involved multistep reactions.[1,3-5]



R = H, coumestan
R = OH, coumestrol

This paper reports a convenient two-step synthesis of the corresponding sulfur analogs, 6*H*-benzothieno[3,2-*c*][1]benzopyran-6-ones (11-thiacoumestans).[6] The first step involves a unique condensation–rearrangement of thianaphthen-2-one (1) and salicylaldehyde to form 6a,11a-dihydro-6*H*-benzothieno[3,2-*c*][1]benzopyran-6-one (dihydro-11-thiacoumestan, **2a**). Oxidation of the rearrangement product with 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) gives 6*H*-benzothieno[3,2-*c*][1]benzopyran-6-one (Scheme I).

A plausible mechanism for the condensation–rearrangements of thianaphthen-2-one and salicylaldehyde is shown in Scheme I.[7] This suggested pathway has precedent in the mechanism suggested for the Perkin coumarin synthesis.[8] The intermolecular Michael addition of thiophenols to the C-4 position of coumarins is, of course, well known,[9] and an intramolecular addition, proposed herein, is equally likely. Although numerous intramolecular rearrangements of α-salicylidene lactones,[10-14] α-salicylidene oxazolones,[15] and α-salicylidenelactams[16,17] to coumarin derivatives have been reported, this is the first report of such a rearrangement followed by a Michael addition.[18]

In addition to the parent compound, several substituted dihydrothiacoumestans were prepared (Table I). The dihydro compounds were readily identified by their NMR and ir spectra. The NMR spectra displayed the methinyl protons as characteristic downfield doublets with $J = 7$ Hz (cis methinyls, decoupling collapsing the doublets to singlets). The ir spectra of the dihydrothiacoumestans were characterized by strong carbonyl absorptions at approximately 1755 cm^{-1}.

The 6*H*-benzothieno[3,2-*c*][1]benzopyran-6-one (**4a**) could be obtained by four different synthetic procedures: (1) direct combination of thianaphthen-2-one and salicylaldehyde in refluxing ethanol with triethylamine as a catalyst (10% yield); (2) heating dihydrothiacoumestan with triethylamine (15% yield); (3) sulfur dehydrogenation of dihydrothiacoumestan (73% yield); and (4) DDQ (2,3-dichloro-5,6-dicyano-1,4-quinone) oxidation of dihydrothiacoumestan (75% yield). High yields and simplicity of operation made the DDQ oxidation of the dihydro forms the method of choice for preparation of all thiacoumestans (see Table II).

Wide variations in the relative reactivities observed during the DDQ oxidation of dihydrothiacoumestans to thiacoumestans can be explained by reference to the hydride-abstraction mechanism proposed for DDQ.[19] The dihydrothiacoumestans (**2a–d**) with electron-donating groups were oxidized in good yields by 6–12 hr of reflux. However, the chloro compound **2e** required 59 hr and the naphtho compound **3** required 117 hr for equivalent conversion. Removal by the DDQ of the hydride adjacent to the sulfur would yield a carbonium ion resonance stabilized by both the benzene ring and the sulfur. The more effective stabilization of the benzylic carbonium ion by the electron-donating groups in **2a–d** is reflected in their more rapid oxidation