Pyrrole chemistry. VI. Syntheses and electrophilic substitution reactions of some 3-substituted pyrroles

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The Friedel–Crafts acetylation of methyl 2-pyrrolecarboxylate, 2-pyrrolecarboxaldehyde, and 2-pyrrolecarbonitrile was investigated and found to give 4-substitution mainly or exclusively. The 4-acetyl-2-substituted products were converted into the 4-acetyl-2-acid, and then into 3-acetylpyrrole (methyl 3-pyrryl ketone). The Friedel–Crafts isopropylation and the bromination of both methyl 3-pyrrolecarboxylate and 3-acetylpyrrole were found to produce almost exclusively 5-substituted products.

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INTRODUCTION

Some preparations and electrophilic substitution reactions of pyrroles with electron-withdrawing groups in the 3-position were undertaken as a continuation of studies on simple pyrrole derivatives. The starting materials used were 3-acetylpyrrole (methyl 3-pyrryl ketone) and methyl 3-pyrrolecarboxylate.

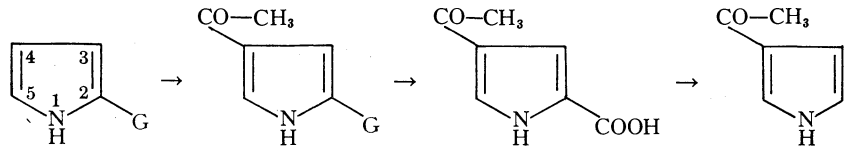
A good method for the preparation of the 3-ester by ring closure is known (1). However, the preparation (by the reaction of pyrrylmagnesium bromide with methyl chloroformate) of large amounts of the 2-ester for Friedel–Crafts studies led to the availability of a quantity of methyl 1,3-pyrroledicarboxylate (2) as a by-product, together with the 1,2-diester (3), traces of the 1-ester, and small amounts of both 2-pyrryl 2′-pyrryl ketone and 2-pyrryl 1′-pyrryl ketone. This last compound has so far been identified only by its elemental analysis and nuclear magnetic resonance (n.m.r.) spectrum. Methyl 1,3-pyrroledicarboxylate was easily decarbomethoxylated to the 3-ester.

The reaction of pyrrylmagnesium bromide and acetic anhydride produced both 2-acetylpyrrole and the desired 3-acetylpyrrole (4), but the yield of the 3-ketone was low and the separation tedious. Experience with the Friedel–Crafts alkylation reaction (5) and other electrophilic substitutions (6) suggested that Lewis acid catalyzed acetylation of pyrroles with an electron-withdrawing group in the 2-position should give mostly 4-substitution. Subsequent elimination of the group in the 2-position by conversion into an acid and decarboxylation would then give 3-acetylpyrrole (see Reaction Scheme 1).

Loader (7) found that the perchloric acid catalyzed acetylation of the 2-ester gave an excellent yield of almost equal amounts of the 4- and 5-acetyl-2-esters, and Tirouflet and Fournari (8) observed similar results for the nitration of the 2-acid and 2-ketone. Both are very unselective reactions, and we felt that the Friedel–Crafts acetylation should give predominantly the 4-isomer in a much more selective attack.

Preparation of 3-Acetylpyrrole

There seem to have been few recent attempts to carry out Friedel–Crafts acylations of pyrroles which possess an electron-withdrawing group only at the 2-position, other than the BF_3-catalyzed acetylation of 1-methyl-2-nitropyrrole (9), which gave



REACTION SCHEME 1. G = CHO, $COOCH_3$, or CN.

only the 4-acetyl derivative. The uncatalyzed acetylation of 2-benzoylpyrrole (10) has been reported, but not proved, to give the 5-isomer. The early literature, as summarized by Gore (11), shows a number of examples where pyrrole and *N*-alkylpyrroles were claimed to be 2,5-diacylated. The forced acetylation of thiophene and of 2-acetylthiophene (12) has been reported to give 2,5-diacetylthiophene in a small yield.

The results closely paralleled previous experience with Friedel–Crafts isopropylation (5), except for the absence of concurrent or subsequent rearrangement. The acetylation of methyl 2-pyrrolecarboxylate with acetic anhydride gave roughly 10 parts of the 4-acetyl to 1 of the 5-acetyl derivative, with an overall conversion of about 80%. However, acetylation of 2-pyrrolecarboxaldehyde and of 2-pyrrolecarbonitrile was found to give exclusively 4-substitution. The yield from the 2-nitrile was good, but that from the 2-aldehyde was much less satisfactory because of extensive decomposition, although a wide variety of conditions was tried. Milder conditions with aluminium chloride in nitromethane proved best for the aldehyde.

For each substrate, the molar ratio of catalyst needed for the best yield was found to be about 3.2:1. Since 1 mole of the Lewis acid is almost certainly complexed by the carbonyl or nitrile group, this means that about 2 moles are needed for the acetylation. This is in agreement with the results of Saboor (13) for the acid anhydride acylation of simpler substrates. The attempted acetylation of 2-pyrrolecarboxaldehyde and of 2-pyrrolecarbonitrile with phosphorus oxychloride and dimethylacetamide (14) failed.[1]

Each of the 4-acetyl-2-substituted pyrroles was converted by hydrolysis or oxidation into 4-acetyl-2-pyrrolecarboxylic acid. The yields from the ester and aldehyde were good, but that from the nitrile was only fair. However, none of the various methods that were tried gave satisfactory yields in the decarboxylation step, the best giving about 20% 3-acetylpyrrole. Both thermal decomposition with a variety of catalysts and displacement of the carboxyl group with iodine (15) were equally unsatisfactory. Although Rinkes (16) found that the decarboxylation of the isomeric 3-acetyl-2-acid gave very poor yields, Khan *et al.* (17) greatly improved the result with modified conditions. An earlier paper in this series (6) reported unsuccessful attempts to decarboxylate the 4-bromo-2-acids. It would appear that, when no electron-donating group is attached to the ring, the yields in these decarboxylations are quite variable.

Electrophilic Substitution of the 3-Ketone and the 3-Ester

There are many examples of electrophilic substitution reactions of thiophenes (18) and furans (19) possessing an electron-withdrawing group only in the 3-position. In the pyrrole series, the only previous examples where no alkyl group was present on the ring have been the nitration of methyl 3-pyrrolecarboxylate (16) and the acetylation (9) and nitration (20) of 1-methyl-3-nitropyrrole. The only product isolated from all the reactions was the 5-substituted isomer. These results are consistent with the customary electronic view.

Nevertheless, it was felt that further examples of electrophilic substitution reactions of this type of pyrrole derivative should be carried out and the products examined by gas–liquid partition chromatography for the presence of other isomers. The reactions chosen were bromination and Friedel–Crafts isopropylation. Both of these reactions have been applied to the 2-ester (2, 6) and found to produce mixtures of isomeric 4- and 5-substitution products whose composition could be varied somewhat with the conditions. Also, an excess of either reagent led easily to disubstitution in the two reactive positions of the 2-ester.

When either the 3-ester or the 3-ketone was brominated or isopropylated, no monosubstituted isomer other than the 5-isomer

[1]An earlier paper (6) erroneously reported that Vilsmeier formylation of methyl 2-pyrrolecarboxylate gave mostly the 4-formyl-2-ester. In fact, the 5-isomer predominates (see H. J. Anderson and S.-F. Lee, Can. J. Chem., 45, 99 (1967)).

was formed in more than trace amounts (too small to be isolated or identified). Also, no disubstitution product could be isolated, although under forcing conditions tribromination of the ester was observed and small amounts of other products appeared in gas chromatography. The preferred reagent for monobromination was dioxane dibromide. The use of bromine in carbon tetrachloride or dimethylformamide gave mainly tribromination. The product yields for the brominations and isopropylations were 50–60%, which is substantially lower than the overall conversions obtained in the same reactions with the corresponding 2-substituted pyrroles.

The structures of the products from the bromination and isopropylation of the 3-ketone and 3-ester were established by the n.m.r. coupling constants of the remaining aromatic protons (see Table I). These values were confirmed for the 3-ketone by spin decoupling the aromatic protons. The catalytic replacement of bromine by deuterium provided additional support for the position of substitution through the n.m.r. chemical shifts and coupling constants of the remaining aromatic protons in the 5-deuterio compounds obtained in this way. The values of $J_{2,4}$ were all slightly larger than those reported by Gronowitz (21), but below the range for $J_{2,5}$.

The n.m.r. spectra of the compounds prepared for this study showed all the coupling constants within the usual ranges for pyrrole derivatives (21), except as mentioned above, and all the chemical shifts consistent with those of compounds of similar types as well as with those of compounds identified in earlier papers in this series. The compounds with electron-withdrawing groups in the 3-position were all much less soluble than their 2-isomers. Morgan and Morrey (22) have reported the greater water solubility of 2- than 3-nitropyrrole. Consequently, the n.m.r. spectra were determined in chloroform-*d*. Where comparison with a carbon tetrachloride spectrum was possible, it was evident that chloroform-*d* caused a greater deshielding effect on some protons than on others. Where two electron-withdrawing groups were in the 2- and 4-positions in the ring, there appeared to be a significant concentration dependence of the chemical shifts as well. The chemical shifts in Table I and in the text are for dilute solutions and are consistent among themselves. The coupling constants were obtained in more concentrated solutions.

In the n.m.r. spectra of the 5-isopropyl-3-ester (methyl 2-isopropyl-4-pyrrolecarboxylate) and the 5-isopropyl-3-ketone (methyl 2-isopropyl-4-pyrryl ketone), the signal for the 4-proton was a quartet in the presence of deuterium oxide. The 4-proton was coupled with the =CH— of the isopropyl group as well as with the 2-proton of the ring. Coupling between side-chain methyls and ring protons has been observed in pyrrole derivatives before (21). The =CH— to aromatic coupling constants observed were of the same magnitude (about 0.9 c.p.s.) as those reported by Gronowitz. A reexamination of some isopropyl derivatives of 2-carbonyl pyrroles

TABLE I

Nuclear magnetic resonance spectra*

Compound	Aromatic			$J_{2,5}$	$J_{2,4}$	$J_{4,5}$	$J_{1,2}$	$J_{1,4}$
	2-Proton	4-Proton	5-Proton					
3-Ester†	7.52	6.78	6.78	2.10	1.60	2.89	—	—
5-Bromo-3-ester	7.33	6.55	—	—	1.72	—	2.90	2.58
5-Isopropyl-3-ester	7.33	6.36	—	—	1.64	—	—	—
3-Ketone‡	7.41	6.68	6.77	1.90	1.60	2.98	—	—
5-Bromo-3-ketone	7.34	6.59	—	—	1.80	—	3.12	2.56
5-Isopropyl-3-ketone	7.30	6.34	—	—	1.68	—	—	—

*In $CDCl_3$ and recorded on the δ scale.
†Coupling constant in dioxane.
‡Coupling constant values confirmed by spin decoupling.

reported earlier (2, 5) showed similar, though slightly smaller (about 0.6 to 0.8 c.p.s.), couplings where they could be resolved. In each spectrum they appeared to be coupled only from 4-isopropyl to 5-H or from 5-isopropyl to 4-H.

EXPERIMENTAL

General

Melting points were measured on a Fisher–Johns melting point block, and are uncorrected.

Infrared spectra were recorded on a Perkin–Elmer 237B spectrophotometer by the potassium chloride disk (2 mg sample in 200 mg of KCl) and (or) solution (chloroform, 0.5 mm NaCl cell) techniques.

Ultraviolet spectra were determined in 95% ethanol with a Perkin–Elmer 202 recording spectrophotometer.

The n.m.r. spectra were determined on a Varian A-60 spectrometer at 60 Mc.p.s. The chemical shifts are in parts per million from tetramethylsilane as internal reference in chloroform-*d*, unless specified otherwise, and are recorded on the δ scale.

Elemental analyses were determined by Alfred Bernhardt, Mülheim (Ruhr), Germany.

The reaction mixtures were analyzed by means of gas–liquid partition chromatography with a Beckman GC-2A chromatograph, equipped with a 13½ in. column (No. 70008) packed with Apiezon L on firebrick and operated at 220° with helium as the carrier gas.

Reaction of Pyrrylmagnesium Bromide with Methyl Chloroformate

To a stirred, cold solution of ethylmagnesium bromide (1.9 mole) in 600 ml of ether was added dropwise pyrrole (2 mole) in 200 ml of ether. The reaction mixture was then refluxed for 20 min. After the solution was cooled, ether (100 ml) was added, followed by methyl chloroformate (1 mole) in 150 ml of ether (dropwise). The reaction mixture was again refluxed for 30 min, then cooled, and carefully hydrolyzed with 10% ammonium chloride solution. The aqueous layer was separated and extracted with ether. The combined ether layers were dried, the ether was removed by flash evaporation, and the product was vacuum distilled. The boiling points of the fractions collected were: 80–120° at 13 mm, 120–127° at 13 mm, 127–135° at 13 mm, 135–142° at 13 mm, 142–154° at 13 mm, 137–145° at 3 mm, 159–172° at 3 mm, 147–150° at 0.4–0.5 mm, and 150–180° at 0.4–0.5 mm. The residue was then extracted fractionally with benzene, ethanol, and dioxane. The products in each fraction were separated by adsorption chromatography on neutral alumina with appropriate solvents as eluents, until a 95% pure sample was obtained (as shown by gas chromatography). Each sample was then recrystallized from a suitable solvent so that a melting point within a 2 degree range could be obtained.

The products and average yields were: pyrrole, 13 g; methyl 1-pyrrolecarboxylate, 0.3 g; methyl 2-pyrrolecarboxylate, 28 g; methyl 3-pyrrolecarboxylate, trace (not isolated); methyl 1,2-pyrroledicarboxylate, 10.1 g; and methyl 1,3-pyrrolecarboxylate, 8.53 g. Also isolated was 2-pyrryl 1′-pyrryl ketone, 0.53 g, m.p. 58.5–60°, prisms after crystallization from petroleum ether, infrared carbonyl at 1 660 cm^{-1} ($CHCl_3$). Nuclear magnetic resonance: H_3',H_4',H_4, 6.33; H_3, 6.95; H_5, 7.12; and H_2',H_5', 7.50.

Anal. Calcd. for $C_9H_8N_2O$: C, 67.49; H, 5.34; N, 17.49. Found: C, 67.24; H, 5.26; N, 17.40.

Another product was 2-pyrryl 2′-pyrryl ketone, 1.7 g, m.p. 160–161°, prisms after crystallization from ethanol–benzene (lit. m.p. 160–161° (23)). The ultraviolet spectrum and infrared carbonyl agreed with those in the literature (23). Nuclear magnetic resonance: H_3, 7.18; H_4, 6.33; and H_5, 7.08 ($J_{3,5}$ 1.36, $J_{3,4}$ 3.83, and $J_{4,5}$ 2.61 c.p.s.).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.49; H, 5.34; N, 17.49. Found: C, 67.52; H, 5.26; N, 17.43.

Methyl 3-Pyrrolecarboxylate

Methyl 1,3-pyrroledicarboxylate (4 g, 0.022 mole), obtained as a by-product in the preparation of the 2-ester above, was dissolved in a minimum of methanol, cold 10% aqueous potassium hydroxide (12 ml) was added, and the mixture was shaken mechanically for 6 h and cooled. The solid was filtered off, washed with water, and dried. A further small amount was recovered through ether extraction of the mother liquor. Recrystallization gave 2.29 g (84%) of methyl 3-pyrrolecarboxylate, m.p. 86–87° (lit. m.p. 88° (16)).

Methyl 4- and 5-Acetyl-2-pyrrolecarboxylate

In a 1 l, three-necked, round-bottomed flask equipped with a sealed stirrer, dropping funnel, and double-surface condenser (with drying tube) were placed anhydrous aluminium chloride (120 g, 0.9 mole) and carbon disulfide (250 ml). The mixture was cooled, and methyl 2-pyrrolecarboxylate (35.5 g, 0.284 mole) in carbon disulfide (150 ml) was added carefully, with stirring. The flask was then immersed in an oil bath kept at 50°. Acetic anhydride (30.6 g, 0.3 mole) in carbon disulfide (100 ml) was added drop by drop, and stirring continued for a further 15 h. The reaction was quenched by pouring the solution into a dilute hydrochloric acid and ice mixture. After the lumpy reaction complex was completely decomposed, the solid was filtered off, washed thoroughly with water, and dried. It was then dissolved in chloroform and passed through a neutral alumina column, the separation being followed by gas chromatography. Removal of the solvent by flash evaporation gave a single, nearly pure product and a very small amount of the other isomer. Recrystallization from benzene gave pure methyl 4-acetyl-2-pyrrolecarboxylate as needles, (33.2 g, 70%), m.p. 110–111° (lit. m.p. 109–110° (7)). Nuclear magnetic resonance: H_3, 7.25; and H_5, 7.53 ($J_{3,5}$ 1.60 c.p.s.).

Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.43. Found: C, 57.29; H, 5.62; N, 8.31.

The aqueous layer from the acetylation reaction was separated, saturated with sodium chloride, and

extracted with ether. The combined organic layers were washed with sodium acetate (saturated aqueous solution) and dried over anhydrous magnesium sulfate. The solvent was removed and the products were separated by adsorption chromatography on neutral alumina. A further 1.6 g (3.4%) of methyl 4-acetyl-2-pyrrolecarboxylate was obtained, along with 5-acetyl-2-pyrrolecarboxylate. The latter, on recrystallization from benzene – petroleum ether, was obtained as prisms, 3.6 g (7.6%), m.p. 109–110° (lit. m.p. 110–111.5° (7)). Nuclear magnetic resonance: H_3, 6.95; and H_5, 6.95.

4-Acetyl-2-pyrrolecarbonitrile

This compound was prepared in a 71% yield by the acetylation procedure used for the 2-ester. Prisms were obtained after crystallization from ethanol–water, m.p. 216–217° (decomp.). Nuclear magnetic resonance: H_3, 7.37; and H_5, 7.92 ($J_{3,5}$ 1.45 c.p.s.) (methyl sulfoxide-d_6).

Anal. Calcd. for $C_7H_6N_2O$: C, 62.67; H, 4.51; N, 20.88. Found: C, 62.80; H, 4.68; N, 21.17.

4-Acetyl-2-pyrrolecarboxaldehyde

A slow stream of nitrogen was conducted into a flask containing anhydrous aluminium chloride (8.04 g, 0.06 mole) and nitromethane (20 ml). The flask was cooled in an ice–salt mixture, and 2-pyrrolecarboxaldehyde (1.9 g, 0.02 mole) in nitromethane (15 ml) was added, with stirring. Acetic anhydride (2.56 g, 0.025 mole) in nitromethane (15 ml) was then added gradually at a rate such that the temperature could be kept below 0°. The mixture was stirred for an additional 3 h. The stream of nitrogen was then discontinued and the temperature allowed to rise to 3–4° for 60 h. The reaction was quenched by pouring the solution into a dilute hydrochloric acid and ice mixture. The aqueous layer was separated and extracted with ether. The combined organic layers were washed with saturated sodium acetate solution and dried. Removal of the solvent gave 4-acetyl-2-pyrrolecarboxaldehyde, which, on recrystallization from benzene–cyclohexane, yielded 0.6 g (22%) of prisms, m.p. 136–137°. Nuclear magnetic resonance: H_3, 7.49; and H_5, 7.82.

Anal. Calcd. for $C_7H_7N_2O$: C, 61.30; H, 5.14; N, 10.21. Found: C, 61.98; H, 5.21; N, 10.40.

4-Acetyl-2-pyrrolecarboxylic Acid

This compound was obtained (*a*) in a 75% yield by hydrolysis of methyl 4-acetyl-2-pyrrolecarboxylate in 15% aqueous potassium hydroxide; (*b*) in a 35% yield by hydrolysis of 4-acetyl-2-pyrrolecarbonitrile in 40% aqueous potassium hydroxide; and (*c*) in a 38% yield by oxidation of 4-acetyl-2-pyrrolecarboxaldehyde with silver oxide (24). It had m.p. 221.5–223° (decomp.).

Anal. Calcd. for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.15. Found: C, 55.22; H, 4.69; N, 9.15.

3-Acetylpyrrole

(*i*) This compound was prepared, separated from 2-acetylpyrrole, and purified by the method of Castro *et al.* (4).

(*ii*) Attempts were made to decarboxylate 4-acetyl-2-pyrrolecarboxylic acid by heating the acid in quinoline with copper powder, copper bronze, or copper chromite. These methods all led to no reaction or to complete decomposition, as did heating the acid itself or in ethylene glycol.

The acid (10 g, 0.065 mole) and 50 g of sand were thoroughly mixed and heated at 220–230° for 30 min. The mixture was cooled and extracted with ether, and the extract was dried. After evaporation, the product was recrystallized from benzene – petroleum ether to give 20% of the desired ketone. A mixture melting point with a sample prepared by method *i* showed no depression, and the infrared spectra were identical.

3-Acetylpyrrole was obtained as prisms, m.p. 114–115° (lit. m.p. 115–116° (16)). The ultraviolet, infrared, and n.m.r. (Table I) spectra were in agreement with those in the literature (17, 25).

General Procedure for Brominations

The mixture of methyl 3-pyrrolecarboxylate or 3-acetylpyrrole (0.016 mole) and anhydrous sodium acetate (2.46 g) in dioxane (150 ml) was stirred at room temperature, and dioxane dibromide solution (prepared from 0.015 mole of bromine and 100 ml of dioxane) was added at a rate such that the bromine color did not persist. After the mixture was stirred for a further 4 h, the dioxane was removed by flash evaporation at room temperature. The residue was poured into a mixture of 5% sodium carbonate (40 ml) and ice. It was then extracted with ether, the ether layer was washed with saturated sodium chloride solution and dried, and the solvent was removed by evaporation. The residue was analyzed by gas chromatography and separated by adsorption chromatography on neutral alumina. In this way was obtained methyl 5-bromo-3-pyrrolecarboxylate (methyl 2-bromo-4-pyrrolecarboxylate) as prisms after crystallization from cyclohexane–chloroform, 1.58 g (51.7%), m.p. 106–108° (decomp.). See Table I for the n.m.r. spectrum.

Anal. Calcd. for $C_6H_6BrNO_2$: C, 35.32; H, 2.96; N, 6.87; Br, 39.17. Found: C, 35.51; H, 3.08; N, 6.67; Br, 39.16.

Also produced was methyl 5-bromo-3-pyrryl ketone (2-bromo-4-acetylpyrrole), 1.77 g (62.8%), m.p. 151–152.5°, prisms after crystallization from chloroform–cyclohexane. See Table I for the n.m.r. spectrum.

Anal. Calcd. for C_6H_6BrNO: C, 38.33; H, 3.22; N, 7.45; Br, 42.50. Found: C, 38.25, H, 3.33; N, 7.32; Br, 42.61.

Bromination of the 3-Ester in Carbon Tetrachloride

A mixture of methyl 3-pyrrolecarboxylate (0.040 mole) and anhydrous sodium acetate (4.1 g) in 100 ml of carbon tetrachloride was cooled in an ice–salt bath. Bromine (0.04 mole) in 50 ml of carbon tetrachloride was then added drop by drop, with stirring. Stirring was continued for a further 3 h, when the reaction mixture was poured into a mixture of 10 ml of 10% sodium hydroxide solution and ice. The aqueous layer was separated and extracted with ether. The combined organic layers were washed with saturated sodium chloride solution and dried. The residue obtained by evaporation of the solvent

was separated by adsorption chromatography on neutral alumina. The product isolated was methyl 2,4,5-tribromo-3-pyrrolecarboxylate, which, on recrystallization from benzene–cyclohexane, gave a yield of 1.9 g (41%) of prisms, m.p. 207–208.5° (decomp.).

Anal. Calcd. for $C_6H_4Br_3NO_2$: C, 19.92; H, 1.11; N, 3.87; Br, 66.26. Found: C, 20.14; H, 1.11; N, 3.70; Br. 66.21

Other minor products decomposed before separation. No further attempt was made to isolate them.

General Procedure for Isopropylations

To the cold mixture of methyl 3-pyrrolecarboxylate or 3-acetylpyrrole (0.04 mole) in 50 ml of carbon disulfide and anhydrous aluminium chloride (0.08 mole) in 50 ml of carbon disulfide was added isopropyl chloride or isopropyl bromide (0.037 mole) in 50 ml of carbon disulfide, with stirring. Stirring was continued for a further 30 min, when the reaction mixture was immersed in an oil bath kept at 50° and stirred for 20 h. The reaction was quenched by pouring the solution into an ice–water mixture. The aqueous layer was separated, saturated with sodium chloride, and extracted with ether. The combined organic layers were washed with saturated sodium chloride solution and dried. Evaporation of the solvent gave the crude product, which was then dissolved in benzene and passed through a neutral alumina column. The solvent was removed and the solid recrystallized twice from cyclohexane. In this way was obtained methyl 5-isopropyl-3-pyrrolecarboxylate (methyl 2-isopropyl-4-pyrrolecarboxylate) as prisms, 3.64 g (59%), m.p. 74–74.5°. See Table I for the n.m.r. spectrum.

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.60; H, 7.73; N, 8.28.

Also produced were prisms of methyl 5-isopropyl-3-pyrryl ketone (2-isopropyl-4-acetylpyrrole), 3.48 g (62.2%), m.p. 68.5–69.5°. See Table I for the n.m.r. spectrum.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.41; H, 8.49; N, 9.23.

Catalytic Deuteration of Bromopyrroles

The 5-bromo-3-ester or 5-bromo-3-ketone was deuterated in acetic acid-*d* according to the earlier procedure (6), except that Adams platinum oxide replaced palladium on charcoal. Gas chromatography indicated complete replacement of the bromine. The products isolated were methyl 5-deuterio-3-pyrrolecarboxylate (n.m.r.: H_2, 7.38; and H_4, 6.58 ($J_{2,4}$ 1.6 c.p.s.)) and 5-deuterio-3-acetylpyrrole (n.m.r.: H_2, 7.42; and H_4, 6.66 ($J_{2,4}$ 1.6 c.p.s.)).

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REFERENCES

1. H. Rapoport and C. D. Willson. J. Org. Chem. **26**, 1102 (1961).
2. H. J. Anderson and L. C. Hopkins. Can. J. Chem. **42**, 1279 (1964).
3. F. K. Signaigo and H. Adkins. J. Am. Chem. Soc. **58**, 1122 (1936). P. Hodge and R. W. Rickards. J. Chem. Soc. 2543 (1963).
4. A. J. Castro, J. R. Lowell, Jr., and J. P. Marsh, Jr. J. Heterocyclic Chem. **1**, 207 (1964).
5. H. J. Anderson and L. C. Hopkins. Can. J. Chem. **44**, 1831 (1966).
6. H. J. Anderson and S.-F. Lee. Can. J. Chem. **43**, 409 (1965).
7. C. E. Loader. M.Sc. Thesis, Memorial University of Newfoundland, St. John's, Newfoundland. 1965.
8. J. Tirouflet and P. Fournari. Bull. Soc. Chim. France, 1651 (1963).
9. H. J. Anderson. Can. J. Chem. **35**, 21 (1957).
10. I. J. Rinkes. Rec. Trav. Chim. **60**, 650 (1941).
11. P. H. Gore. *In* Friedel–Crafts and related reactions. Vol. III. *Edited by* G. A. Olah. Interscience Publishers, Inc., New York. 1964. pp. 92 and 308.
12. H. D. Hartough and A. I. Kosak. J. Am. Chem. Soc. **69**, 1012 (1947).
13. M. A. Saboor. J. Chem. Soc. 922 (1945).
14. W. C. Anthony. J. Org. Chem. **25**, 2049 (1960).
15. G. P. Arsenault and S. F. MacDonald. Can. J. Chem. **39**, 2043 (1961).
16. I. J. Rinkes. Rec. Trav. Chim. **57**, 423 (1938).
17. M. K. A. Khan, K. J. Morgan, and D. P. Morrey. Tetrahedron, **22**, 2095 (1966).
18. S. Gronowitz. *In* Advances in heterocyclic chemistry. Vol. 1. *Edited by* A. R. Katritzky. Academic Press, Inc., New York. 1963. p. 55.
19. R. C. Elderfield and T. N. Dodd, Jr. *In* Heterocyclic compounds. Vol. 1. *Edited by* R. C. Elderfield. John Wiley & Sons, Inc., New York. 1950. p. 154.
20. E. N. Safonova, V. M. Belikov, and S. S. Novikov. Chem. Abstr. **54**, 1486 (1960).
21. S. Gronowitz, A.-B. Hörnfeldt, B. Gestblom, and R. A. Hoffman. Arkiv Kemi, **18**, 133 (1961).
22. K. J. Morgan and D. P. Morrey. Tetrahedron, **22**, 57 (1966).
23. H. Rapoport and C. D. Willson. J. Am. Chem. Soc. **84**, 630 (1962).
24. E. Compaigne and W. M. LeSuer. *In* Organic syntheses. Collective Vol. IV. *Edited by* N. Rabjohn. John Wiley & Sons, Inc., New York. 1963. p. 919.
25. G. P. Bean. J. Heterocyclic Chem. **2**, 473 (1965).