Tetrahedron, 1966, Vol. 22, pp. 2095 to 2105. Pergamon Press Ltd. Printed in Northern Ireland

CARBONYL DERIVATIVES OF HETEROCYCLIC COMPOUNDS—III*

THE PREPARATION OF 3-ACYLPYRROLES

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(*Received* 8 *December* 1965)

Abstract—Synthetic routes to 3-acylpyrroles by methods involving ring closure, transformation of substituents and further substitution of mono-substituted pyrroles have been investigated. The condensation of aminoacetaldehyde with acylpyruvates appears to provide a general route to the 3-ketones. The related condensation of N-carbethoxy-glycine ester and acrylonitrile gave poor yields of 3-*cyanopyrrole* but attempts to obtain the 3-acetyl derivative by the use of methyl vinyl ketone showed the occurrence of an alternative reaction path and gave no useful product. Attempts to convert 3-cyano- and 3-carboxy-pyrroles into acyl derivatives by the action of nucleophilic reagents were not successful. *Pyrrole-3-aldehyde* was obtained by decarboxylation of the minor formylation product of ethyl pyrrole-2-carboxylate.

THE ease with which pyrrole can be acylated in the 2-position has enabled the chemical and physical properties of the 2-pyrrolyl ketones to be examined in detail.[1] Largely due to their relative inaccessibility few studies have been reported of the corresponding 3-acyl derivatives (I). In order to obtain materials for a study of their chemical and spectroscopic characteristics some possible synthetic routes to 3-acylpyrroles have been examined.

None of the simple reactions of pyrrole leads to preferential substitution in the 3-position.[2] The direct acylation of pyrrole or pyrrolylmagnesium bromide has been reported[3] to yield exclusively 2-acylpyrrole but more recently small yields of 3-acylpyrroles have been obtained from the action of the Grignard reagent on aliphatic acyl chlorides.[4] In an attempt to approach the synthesis of 3-acylpyrroles by less direct routes, three general synthetic schemes which have apparent advantages were chosen for study *viz* the ring closure of suitable intermediates; the transformation of a group already sited at the 3-position; and substitution of a mono-substituted pyrrole followed by removal of the initial substituent.

(a) *Ring closure methods.* A number of routes has already been developed for the synthesis of pyrrole-3-carboxylic acid involving the formation of C_3—C_4 or C_5—N—C_2 bonds in the pyrrole ring. The possibility of modifying these to yield the 3-acyl derivatives was explored.

In the first successful synthesis[5] of the acid, ethyl oxaloacetate was condensed with

* Part II: *Tetrahedron* **21**, 2197 (1965).

[1] M. K. A. Khan and K. J. Morgan, *J. Chem. Soc.* 2579 (1964).

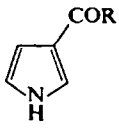
[2] S. Gronowitz, A-B Hörnfeldt, B. Gestblom and R. A. Hoffman, *Arkiv för Kemi* **18**, 151 (1961); K. J. Morgan and D. P. Morrey, *Tetrahedron* **22**, 57 (1966).

[3] P. S. Skell and G. P. Bean, *J. Amer. Chem. Soc.* **84**, 4655 (1962).

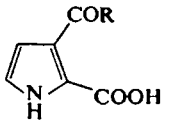
[4] A. J. Castro, J. R. Lowell and J. P. Marsh, *J. Heterocyclic Chem.* **1**, 207 (1964).

[5] I. J. Rinkes, *Rec. Trav. Chim.* **56**, 1224 (1937).

aminoacetaldehyde giving ethyl pyrrole-2,3-dicarboxylate which on hydrolysis and decarboxylation left pyrrole-3-carboxylic acid. By replacing ethyl oxaloacetate with ethyl oxaloacetone as the reactive carbonyl compound Rinkes[6] obtained 3-acetylpyrrole on decarboxylation of the corresponding acid (II). By modifying the experimental conditions it has been possible to increase the yield of 3-acetylpyrrole obtained by this method (16% from ethyl oxaloacetone) and extension of the synthesis to the preparation of 3-benzoylpyrrole was achieved by the use of ethyl benzoylpyruvate as starting material. This method appears to be capable of providing a general route to 3-pyrrolyl ketones, but evident limitations are the relatively small overall yields and its inability to give 3-formylpyrrole.



I



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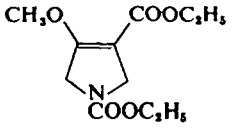

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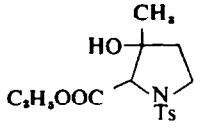


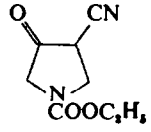
IV

A more convenient route[7] to pyrrole-3-carboxylic acid using the same C_3—C_4 ring closure lies in the condensation using sodium ethoxide of N-ethoxycarbonylglycine ethyl ester and ethyl acrylate. Conversion of the resultant pyrrolidone[8] to its O-methyl ether (III) followed by hydrolytic elimination of water and carbon dioxide gives pyrrole-3-carboxylic acid. It seemed possible that the use of methyl vinyl ketone in place of ethyl acrylate might lead similarly to 3-acetypyrrole. However, it has been established[9] that the addition of N-methoxysulphonylglycine ethyl ester to methyl vinyl ketone proceeds by a different reaction mechanism and yields the hydroxy pyrrolidine (IV). In this case, the product of Michael addition of the amino group across the double bond appears to cyclize preferentially through the more reactive ketonic carbonyl group rather than the carboxyl group. Altering the basic catalyst from sodium t-butoxide in t-butanol to sodium ethoxide in benzene appeared to offer the possibility of retarding ketonization of the initially formed enol sufficiently to allow the effectively irreversible attack at the carboxyl group. When these conditions were applied to the reaction of N-ethoxycarbonylglycine ethyl ester and methyl vinyl ketone the product, in accord with expectation, showed a positive ferric chloride reaction and an IR spectrum in agreement with that expected for the pyrrolidone. However, after treatment with diazomethane and fractionation the only volatile product was N-ethoxycarbonylglycine ethyl ester. The failure to detect any methylated material suggests that the major part of the reaction proceeds by the same mechanism as the t-butoxide catalysed reaction using N-methoxysulphonylglycine ethyl ester. It is possible that under the conditions used for fractionation of the adduct this

[6] I. J. Rinkes, *Rec. Trav. Chim.* **57**, 423 (1938).
[7] H. Rapoport and C. D. Willson, *J. Org. Chem.* **26**, 1102 (1961).
[8] R. Kuhn and G. Osswald, *Chem. Ber.* **89**, 1423 (1956).
[9] W. G. Terry, A. H. Jackson, G. W. Kenner and G. Kornis, *J. Chem. Soc.* 4389 (1965).

addition is reversible and N-ethoxycarbonylglycine ethyl ester distills from polymerized methyl vinyl ketone.

In an attempt to circumvent the change in mechanism accompanying the use of methyl vinyl ketone the reaction between acrylonitrile and N-ethoxycarbonylglycine ethyl ester was investigated. The initially formed cyanopyrrolidone (V) was a viscous liquid which polymerized on heating but after methylation with diazomethane the resultant methoxycyanopyrroline (VI) could be distilled satisfactorily. When the hydrolytic conditions used for the corresponding carboxylic ester were employed, the nitrile group was completely hydrolysed and the only homogeneous product was pyrrole-3-carboxylic acid.[10] By using TLC to monitor the reaction, it was found possible to reduce both the concentration of alkali and the reaction time and under the optimum conditions, a small yield of a nitrile—subsequently identified as 3-cyanopyrrole—was obtained.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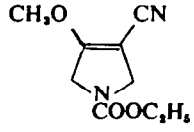
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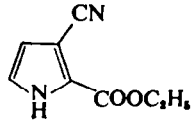
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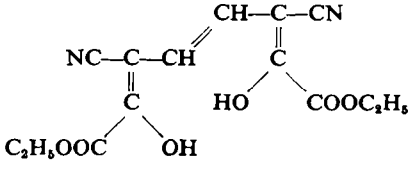
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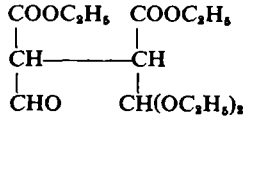
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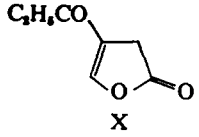

X

The preparation of ethyl 3-cyanopyrrole-2-carboxylate (VII) from the C_2—N—C_5 cyclisation of the cyano ester (VIII) with ammonia has been reported by Huisgen and Laschtuvka[11] and suggests an alternative route to 3-cyanopyrrole. Cautious hydrolysis of the ester grouping and decarboxylation of the resultant carboxylic acid gave 3-cyanopyrrole in reasonable yield. Subsequent attempts to convert the nitrile to the corresponding aldehyde by Stephen's method[12] (stannous chloride) or by the action of Raney nickel and sodium hypophosphite[13] were not successful: 3-cyanopyrrole was recovered in good yield from each reaction. Similarly the action of methyl Grignard reagent left the nitrile unchanged. Equally unaffected by these reagents were 1-methyl-3-cyanopyrrole, ethyl 3-cyanopyrrole-2-carboxylate and the methoxy-cyanopyrroline (VI). The failure of these standard methods to convert the nitrile to the appropriate carbonyl derivative can be ascribed to the pronounced donor character of the pyrrole

[10] cf J. Blake, C. D. Willson and H. Rapoport, *J. Amer. Chem. Soc.* **86**, 5293 (1964).
[11] R. Huisgen and E. Laschtuvka, *Chem. Ber.* **93**, 65 (1960).
[12] cf J. W. Williams, *Organic Syntheses* (Edited by E. C. Horning) Coll. Vol. III; p. 626. Wiley, New York (1955).
[13] B. Staskun and O. G. Backberg, *J. Chem. Soc.* 3961 (1962).

and methoxypyrroline systems present in these compounds. A similar lack of reactivity was evinced by the corresponding carboxyl derivatives (see below).

The Paal-Knorr condensation of a 1,4-diketone with ammonia has been applied to the synthesis of pyrrole-3-carboxylic acid. Kornfeld and Jones[14] cyclized the monoacetal of 2,3-diethoxycarbonylsuccindialdehyde (IX) with ammonia to obtain pyrrole-3,4-dicarboxylic acid which was subsequently decarboxylated giving pyrrole-3-carboxylic acid. By the use of ethyl β-benzoylpropionate as starting material it seemed possible that this synthesis might provide a route to 3-benzoylpyrrole. However, the formylation of ethyl β-benzoylpropionate with ethyl formate gave a crystalline product whose analysis indicated that lactonization had occurred. Since the relative positions of all the carbon atoms except one are fixed, the number of possible structures for this lactone is limited and this number is further reduced by consideration of its spectra. Because of its low solubility in the usual solvents the NMR spectrum was measured for a solution in deuteroacetonitrile and showed absorption at δ-values 2·77, corresponding to a methylene group, and at 6·68 corresponding to a vinyl ether (=CH—O—). There is no indication either of an aldehydic proton or of a methylene group directly bonded to oxygen so that the structure can be written as that of the $\beta\gamma$-unsaturated γ-lactone (X). In confirmation the IR spectrum, also measured in acetonitrile, contained bands at 1763 and 1673 cm^{-1} ascribable to the ester and ketonic carbonyl groups respectively. In other solvents, the carbonyl bands appeared at lower frequencies: 1748, 1660 cm^{-1} ($CHBr_3$), 1740, 1666 (CCl_4), 1732, 1633 ($CHCl_3$) and it is possible that these unusual solvent shifts indicate the occurrence of tautomerism in the lactone. In view of these observations, no further attempt was made to prepare 3-benzoylpyrrole by this route.

(b) *Transformations of 3-substituted pyrroles.* The availability of pyrrole-3-carboxylic acid and the existence of standard methods for converting carboxyl derivatives to ketones and aldehydes suggested that the preparation of 3-acylpyrroles might be achieved in this way.

It is well established that 2-carbonyl derivatives of pyrrole show only a low susceptibility to nucleophilic attack. Pyrrole-2-aldehyde is stable to sodium hydroxide and to sodium cyanide and gives condensation reactions only under forcing conditions.[15] Since carboxylic derivatives are in general less susceptible than ketones and aldehydes to nucleophilic attack, it was anticipated that such nucleophilic reactions as are necessary to convert carboxylic to ketonic functions might proceed only with difficulty on the pyrrole carboxylic acid. Further it seemed possible that the better electron release manifested at the 2-position of a pyrrole ring[16] might lead to greater deactivation in the 2-carboxyl derivatives than the 3-carboxyl derivatives. To this end model experiments were conducted first using the more readily accessible pyrrole-2-carboxylic acid.

The acid was readily converted to the corresponding acid chloride[17] and treatment of this with cadmium methyl gave a small yield of 2-acetylpyrrole. The preparation[18]

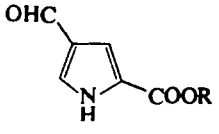
[14] E. C. Kornfeld and R. G. Jones, *J. Org. Chem.* **19**, 1671 (1954).
[15] H. Fischer and H. Orth, *Die Chemie des Pyrrols*, Vol. 1; p. 150. Akademische Verlagsgesellschaft, Leipzig (1934).
[16] R. D. Brown and M. L. Heffernan, *Austr. J. Chem.* **12**, 319 (1959).
[17] H. Gilman and R. M. Pickens, *J. Amer. Chem. Soc.* **47**, 245 (1925).
[18] J. Harley-Mason and E. H. Parri, *J. Chem. Soc.* 2565 (1963).

of indole-2-aldehyde by first reduction of the corresponding ester to the alcohol using LAH and then oxidation with manganese dioxide appeared to provide a possible route to the corresponding pyrroles. The alcohol initially obtained from methyl pyrrole-2-carboxylate decomposed too rapidly to allow any useful oxidation even when the oxidation was carried out *in situ*. Attempts to methylate lithium pyrrole-2-carboxylate with lithium methyl led only to recovery of the 2-carboxylic acid.

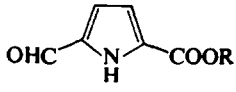
Pyrrole-3-carboxylic acid is most conveniently prepared by the hydrolysis of the methoxypyrroline (III) obtained from the cyclization of N-ethoxycarbonylglycine ethyl ester and ethyl acrylate;[7] it was converted to its methyl ester by diazomethane. Attempts to prepare the corresponding acid chloride from both the acid and the ester were unsuccessful: the first product isolated even under mild conditions was a resinous solid and even attempts to trap the chloride by the addition of dimethylamine gave no significant amount of amide. The hydrazide was obtained in good yield by the action of hydrazine on the ester. Conversion of this to its benzene sulphonyl derivative and treatment with sodium carbonate according to the method of Stephens and Mcfadyen[19] gave a vigorous evolution of nitrogen but the product contained only a small amount of a carbonyl compound. The product of reduction of methyl pyrrole-3-carboxylate with LAH proved to be resinous and was not oxidized by manganese dioxide to the aldehyde. Lithium pyrrole-3-carboxylate was not attacked by lithium methyl; equally unaffected by lithium methyl was the 1-methyl analogue.

The preparation of 3-cyanopyrrole allowed the investigation of the action of similar nucleophiles on this compound (see above) in all cases the nitrile was recovered in good yield.

(c) *Formylation of alkyl pyrrole-2-carboxylates.* The properties of the pyrrole ring cause electrophilic substituents to be directed largely to the 2-position. In many mono-substituted pyrroles these directing properties are modified so that significant quantities of both alpha and beta substituted derivatives can be obtained. Of particular interest in this respect, are the properties of the esters of pyrrole-2-carboxylic acid. It has been reported that[20,21] formylation of these compounds leads to a separable mixture of the isomeric 4-formyl- (XI) and 5-formyl-pyrrole-2-carboxylates (XII). Since it has already been established that the hydrolysis and decarboxylation of similar esters affords 3-acylpyrroles, it seemed possible that 3-formylpyrrole would be available by this route.



XI



XII

The most promising reaction for this purpose appeared to be the formylation of methyl pyrrole-2-carboxylate. It has been reported[21] that in this case the principal product is the 4-formyl derivative (XI, R=CH_3) whereas for the corresponding

[19] J. S. Mcfadyen and T. S. Stevens, *J. Chem. Soc.* 584 (1936).
[20] W. A. M. Davies, A. R. Pinder and I. G. Morris, *Tetrahedron* **18**, 405 (1962).
[21] H. J. Anderson and S-F. Lee, *Canad. J. Chem.* **43**, 409 (1965).

ethyl ester the 5-formyl derivative (XII, R=C_2H_5) constitutes the major product.[20] Formylation of methyl pyrrole-2-carboxylate by the Vilsmeier reaction[22] gave in good yield a product whose properties corresponded to those quoted for methyl 4-formylpyrrole-2-carboxylate, (cf Ref. 21). Hydrolysis of the ester and decarboxylation of the acid went smoothly but the product was pyrrole-2-aldehyde. The possibility of rearrangement or of skeletal modification of the aldehydo acid during the hydrolysis stage was excluded by remethylation of the acid to a methyl ester identical with the starting material. Consequently it appeared probable that this formylation product had been wrongly identified and was in fact the isomeric 5-formyl derivative (XII, R = CH_3). Confirmation of this was provided in two ways. Hydrolysis of ethyl 5-formylpyrrole-2-carboxylate (XII, R = C_2H_5)—whose structure has been established unambiguously[20]—gave an acid identical in all respects with that obtained previously. The action of diazomethane converted this to a methyl ester identical with the formylation product from methyl pyrrole-2-carboxylate. Comparison of the NMR spectra of the esters provided additional confirmation. The signals derived from the ring protons of the methyl and ethyl formyl esters are closely similar and in each case appear as a doublet at a δ-value of 6·93 (J_{13}, J_{14} = 2·45 c/s); these values are in good agreement with those expected for β-protons.[2] The appearance of the absorption as a doublet arises from the similarity of the environment of the two protons and is in complete accord with the structure of the esters as 2,5 disubstituted pyrroles. The identification of the major formylation product from methyl pyrrole-2-carboxylate as the 5-formyl derivative clearly resolves the anomaly apparent in the previously reported difference between the methyl and ethyl esters in the site of preferential substitution.[19,20]

The minor product from the formylation of ethyl pyrrole-2-carboxylate has been identified as ethyl 4-formylpyrrole-2-carboxylate[20] (XI, R = C_2H_5). The NMR spectrum of this compound differs markedly from that of the 2,5-isomer and its form supports the assignment of this structure. The ring protons give absorption at δ 7·34 (H_5) and 7·63 (H_3) (2 quartets). Spin decoupling of the imino proton simplifies the bands to two doublets and allows the coupling constants to be estimated as J_{35}, 1·5, J_{13} 2·6, J_{15}, 3·4 c/s. These values are in satisfactory agreement with those found for other pyrroles.[2] Hydrolysis of the ester and decarboxylation of the acid went smoothly to give an aldehyde which from its mode of preparation can be assigned the structure of 3-formylpyrrole (I, R = H).

In confirmation of this structure, the IR spectrum contains bands at 3479 (NH) and 1683 (CO) cm^{-1} (CCl_4 solution). The NMR spectrum shows bands at δ 9·9 (CHO) and at 6·69 (H_5), 6·86 (H_4) and 7·47 (H_2); these values for the chemical shifts are in good agreement with those of the ring protons of 3-acetylpyrrole.[2] In contrast the spectrum differs markedly from that of pyrrole-2-aldehyde in which the absorption due to the aldehydic proton is split by coupling with H_5 ($J_{CHO,5}$ 1·4 c/s) and the ring protons give bands at 6·35 (H_4), 7·02 (H_3) and 7·20 (H_5). By replacing the imino proton by deuterium and spin decoupling, the H_5 and CHO protons a complete analysis of this spectrum was possible giving J_{13}, 2·6; J_{14}, 2·6; J_{15}, 3·0; J_{34}, 4·3; J_{35}, 1·5; J_{45}, 2·65 c/s.

[22] R. M. Silverstein, E. E. Ryskiewicz and C. Willard, *Organic Syntheses* (Edited by N. Rabjohn) Coll. Vol. IV; p. 831. Wiley, New York (1963).

EXPERIMENTAL

3-Acetylpyrrole-2-carboxylic acid[6]

A mixture of aminoacetaldehyde (from aminoacetal, 15 g) and ethyl 2,4-dioxovalerate (14·9 g) was digested at 35° for 12 hr with an excess of 20% NaOHaq. After acidification of the resultant solution with dilute (1:1) H_2SO_4 the precipitated solid was collected, washed with water and extracted into chloroform (5 × 50 ml). Evaporation of the chloroform left 3-acetylpyrrole-2-carboxylic acid (3·6 g, 21%) m.p. 188° (from aq. EtOH).

3-Acetylpyrrole

Acid (2·5 g) in quinoline (10 ml) was heated at 160–190° for 70 min with copper chromite catalyst[22] (1 g) giving a steady evolution of CO_2. Ether was added to the cooled mixture and the filtered solution poured over dilute (1:1; HCl:ice); the combined aqueous layers were extracted by ether (4 × 75 ml) and subsequently continuously with ether for 18 hr. Evaporation of the combined ethereal extracts left 3-acetypyrrole (1·1 g, 71%) m.p. 112–113° (from benzene), sublimes 120°/0·9 mm; *3-Acetoximinopyrrole* m.p. 132–133° (from water) was prepared from ketone (0·7 g) in a mixture of water (9 ml) and EtOH (1·5 ml). (Found: C, 57·8; H, 6·3. $C_6H_8N_2O$ requires: C, 58·0; H, 6·5%.)

3-Benzoylpyrrole-2-carboxylic acid

Aminoacetaldehyde (from aminoacetal 14 g) ethyl 2,4-dioxo-4-phenylbutyrate (22 g) and an excess of 20% NaOHaq were digested at 35° for 12 hr. After acidification the mixture was extracted into chloroform (4 × 50 ml). The chloroform solution was re-extracted with 20% Na_2CO_3aq (4 × 200 ml) and on acidification there was precipitated *acid* (1 g, 4·7%) m.p. 199° (from EtOHaq), (Found: C, 66·8; H, 4·5. $C_{12}H_9NO_3$ requires: C, 67·0; H, 4·2%.) Continuous extraction of the aqueous phase with chloroform gave no additional quantity of acid.

3-Benzoylpyrrole

Acid (1 g) in quinoline (5 ml) containing copper chromite catalyst[22] (0·5 g) was heated at 160° for 1 hr. After the addition of ether the solution was filtered onto dilute (1:1) HCl (20 ml). Evaporation of the ethereal layer left *3-benzoylpyrrole*, (0·6 g, 77%), m.p. 96–97° (from EtOHaq). (Found: C, 77·0; H, 5·0. $C_{11}H_9NO$ requires: C, 77·2; H, 5·3%.)

Condensation of N-ethoxycarbonylglycine ethyl ester and methyl vinyl ketone

N-ethoxycarbonylglycine ethyl ester[9] (43 g) was added with stirring to powdered Na (5·6 g) in benzene (500 ml). After 2 hr methyl vinyl ketone (18·2 g) was added slowly to the stirred mixture. When the brisk reaction had subsided the stirring was continued for a further 2 hr. Water was added to dissolve the Na salts and the aqueous solution was washed with ether (150 ml). The aqueous phase was poured over ice and H_2SO_4 (10 ml) and the liberated oil was extracted into chloroform (4 × 50 ml). Removal of the chloroform left a viscous oil (40 g); a sample of the oil had b.p. 135°/0·4 mm.

Treatment of the crude product (20 g) with diazomethane (from nitrosomethylurea, 15 g) gave an oil (17·9 g); fractional distillation of part (2 g) of this gave N-ethoxycarbonylglycine ethyl ester (0·8 g) b.p. 140–145°/0·3 mm and left a non-volatile resinous residue.

A mixture of N-ethoxycarbonylglycine ethyl ester (17·3 g) and methyl vinyl ketone (7·2 g) in ether (50 ml) to which was added a solution of K (3·9 g) in t-butanol (150 ml) was allowed to stand for 2 days. The solution was filtered and evaporated leaving an oil (8·5 g) identical with that obtained using Na in benzene.

3-Cyano-1-ethoxycarbonyl-4-methoxy-Δ^3-pyrroline

Acrylonitrile (6·5 g) was added to a suspension of sodio N-ethoxycarbonylglycine ethyl ester prepared from ester (21·5 g) and Na (2·8 g) in benzene (250 ml). The mixture was boiled under reflux for 1 hr and the Na salt was then dissolved in water (200 ml). The aqueous solution was washed with ether (50 ml) and added to ice (50 g) and H_2SO_4 (5 ml). The product was extracted into chloroform (5 × 50 ml) and evaporation left crude 3-cyano-1-ethoxycarbonylpyrrolid-4-one (21 g) b.p. 145°/0·2

[22] M. Kinsey, K. Folkers and H. Adkins, *J. Amer. Chem. Soc.* **44**, 1138 (1922).

mm. Methylation of the pyrrolidone (12 g) with diazomethane (from nitrosomethylurea, 15 g) gave the *pyrroline* (12·6 g) b.p. 150°/0·1 mm. (Found: C, 54·6; H, 6·4. $C_9H_{13}N_3O_3$ requires: C, 55·1; H, 6·2%.)

3-*Cyanopyrrole*

(a) The previously prepared pyrroline (10 g) was boiled under reflux with $Ba(OH)_2 8H_2O$ (17·5 g, 2½ equiv.) in water (90 ml). After 30 min TLC showed the presence of a new compound and the persistence of a small amount of starting material. The mixture was cooled and extracted with ether (5 × 50 ml) giving an oil (0·5 g) b.p. 195°/2 mm, whose IR spectrum was identical with that of 3-cyanopyrrole. Hydrolysis of a small amount of the oil with NaOHaq gave pyrrole-3-carboxylic acid m.p. 160°.

When the time of reflux was reduced to 15 min, the oil (0·8 g) was contaminated by a small amount of ester; after 4 hr reflux, pyrrole-3-carboxylic acid (1·6 g), m.p. 160° was obtained.

(b) A saturated solution of ammonia in EtOH (14 ml) was added during 2 hr to a suspension of diethyl 2,5-dicyano-1,6-dihydroxyhexatriene dicarboxylate[11] (6 g) in AcOEt (60 ml). After the mixture had been boiled under reflux for 6 hr the solvents were removed and the residue (4·7 g) was chromatographed on a silica gel column. Elution with benzene (500 ml) gave ethyl 3-cyanopyrrole-2-carboxylate (1·2 g), m.p. 92° (from benzene–light petroleum).

The ester (1·5 g) in EtOH (5 ml) was warmed for 30 min with KOH (0·56 g) in water (1 ml). The precipitated K salt was treated with HCl (1 ml) in water (5 ml) giving *3-cyanopyrrole-2-carboxylic acid* (0·8 g), m.p. 218°. (Found: C, 52·9; H, 2·8. $C_6H_4N_2O_2$ requires: C, 52·9; H, 3·0%.)

The acid (900 mg) was decarboxylated in the usual way with quinoline (6 ml) and copper chromite catalyst[33] (600 mg) giving *3-cyanopyrrole* (400 mg) m.p. 55–56 from benzene–light petroleum. (Found: C, 65·0; H, 4·6. $C_5H_4N_2$ requires: C, 65·2; H, 4·4%.)

3-Cyano-1-methylpyrrole. By replacing the solution of ammonia in the previous preparation by a solution of methylamine, ethyl 3-cyano-1-methylpyrrole-2-carboxylate,[11] m.p. 93–94° was obtained. Hydrolysis of the ester (2·7 g) in EtOH (5 ml) by warming with a solution of KOH (0·56 g) in water (1 ml) gave, after acidification by HCl, *3-cyano-1-methylpyrrole-2-carboxylic acid* (2·4 g), m.p. 235° (dec). (Found: C, 55·9; H, 4·2. $C_7H_6N_2O_2$ requires: C, 56·0; H, 4·0%.)

Decarboxylation of the acid (1·5 g) in the usual way gave *3-cyano-1-methylpyrrole* (1 g) b.p. 135°/1 mm. (Found: C, 68·6; H, 6·1. $C_6H_6N_2$ requires: C, 67·9; H, 5·7%.)

Formylation of ethyl 3-oxo-3-phenylbutyrate

A mixture of ethyl formate (14·8 g) and ethyl 3-oxo-3-phenylbutyrate (41 g) was added slowly to a suspension of Na wire (4·6 g) in ether. The resultant Na salt was cautiously treated with water and the aqueous layer separated. Acidification of the aqueous layer and extraction into ether (3 × 100 ml) gave a solid substance which after recrystallization from benzene yielded 4-benzoyl-2,3-dihydro-2-oxofuran, m.p. 174°. (Found: C, 69·9; H, 4·1; O, 24·9, $C_{11}H_8O_3$ requires: C, 70·2; H, 4·2; O, 25·5%.)

Attempted reactions with cyano compounds

(i) Attempted preparation of ethyl 3-formylpyrrole-2-carboxylate. To a solution of stannous chloride (2·8 g) in ether (50 ml) saturated with dry HCl[12] was added ethyl 3-cyanopyrrole-2-carboxylate (1·5 g) in ether (25 ml). The mixture was stirred for 4 hr and the resultant oil was then separated, warmed with water and the aqueous solution extracted into ether. Evaporation of the ether gave cyano ester (1·2 g).

Similar treatment of 3-cyanopyrrole, 3-cyano-1-methylpyrrole and ethyl 3-cyano-4-methoxy-Δ^3-pyrroline-1-carboxylate led only to recovery of starting material. Under the same conditions benzonitrile (1 g) gave benzaldehyde (0·9 g, 88%).

(ii) Attempted preparation of 3-formylpyrrole. A solution of 3-cyanopyrrole (0·5 g) in a mixture of water (4 ml), AcOH (4 ml) and pyridine (8 ml) was treated with Raney Ni (0·15 g) and sodium hypophosphite (1 g)[13]. After 2 hr the mixture was filtered and extracted into ether. Evaporation of the ether gave 3-cyanopyrrole (0·45 g).

Similar treatment of ethyl 3-cyanopyrrole-2-carboxylate and ethyl 3-cyano-4-methoxy-Δ^3 pyrroline-1-carboxylate led only to recovery of starting material.

(iii) Attempted preparation of ethyl 3-acetyl-4-methoxy-Δ^3-pyrroline-1-carboxylate. The cyano pyrroline (9·5 g) in dry ether (20 ml) was treated with methyl Grignard reagent from Mg (1·2 g) and MeI (7·1 ml). Ice and 1:1 H_2SO_4 were added to decompose the adduct and the product extracted into ether. Evaporation of the ether gave cyanopyrroline (8·5 g).

Repetition using Grignard reagent (2 equiv) and boiling the mixture under reflux for 10 hr gave unchanged starting material. Use of tetrahydrofuran in place of ether and boiling for 12 hr effected no useful reaction and starting material (66%) was recovered.

Starting material was similarly recovered when 3-cyanopyrrole and ethyl 3-cyanopyrrole-2-carboxylate were used.

Pyrrole-2-carbonyl chloride[17]

Acid (4 g) was added in small portions to a cold solution of $SOCl_2$ (8·6 g) in chloroform (30 ml). The solvent was removed *in vacuo* after 2 hr and the residue dissolved in dry ether (40 ml). After the addition of light petroleum (40 ml) the solution was filtered and evaporated leaving acid chloride (4 g). For characterization part of the chloride was converted to *pyrrole-2-carboxydimethylamide*, m.p. 101° (from benzene–light petroleum) by the action of dimethylamine in ether. (Found: N, 20·4. $C_7H_{10}N_2O$ requires: N, 20·3%.)

The use of pyrrole-3-carboxylic acid led under similar conditions to a dark-coloured resin. Pyrrole-3-carboxylic acid (0·25 g) was added slowly to a cold solution of $SOCl_2$ (1 ml) in CH_2Cl_2 (10 ml). After 2 hr excess $SOCl_2$ was removed in a stream of N_2 and the residue was added to a cooled solution of dimethylamine (2 g) in ether (20 ml). The solution was filtered and evaporated leaving a crystalline residue (80 mg), m.p. 114–115° (from benzene) which was possibly impure amide. (Found: C, 58·7; H, 7·3; N, 17·3. $C_7H_{10}N_2O$ requires: C, 60·8; H, 7·2; N, 20·3%.)

Pyrrole-3-carboxyhydrazide

Methyl pyrrole-3-carboxylate (4·2 g) in a mixture of water (10 ml) and EtOH (8 ml) was boiled under reflux with hydrazine hydrate (10 g) for 5 hr. The solvents were removed *in vacuo* leaving crude hydrazide (4·5 g), m.p. 135°. The hydrazide was conveniently characterized as *pyrrole-3-carboxy-(isopropylidenehydrazide)*, m.p. 202°, after treatment with acetone. (Found: C, 58·4; H, 6·8. $C_8H_{11}N_3O$ requires: C, 58·2; H, 6·7%.)

Pyrrole-3-carboxy-(benzenesulphonylhydrazide)

The hydrazide (4 g) in pyridine (75 ml) was treated with benzene sulphonyl chloride. After 2 hr the pyridine was removed *in vacuo* and the resultant syrup was poured into water, precipitating the *sulphonylhydrazide* (1·2 g), m.p. 216° from EtOH. (Found: C, 50·1; H, 4·0. $C_{11}H_{11}N_3O_2S$ requires: C, 49·8; H, 4·1%.)

The sulphonyl derivative (1·2 g) in ethylene glycol (20 g) was heated to 160° and Na_2CO_3 (4 g) was added in one batch.[19] Gas was evolved and after 3 min the reaction was stopped by adding hot water. The solution was extracted into ether (5 × 50 ml) and evaporation left an oil (300 mg), $\nu_{C=O}$ 1681 cm^{-1} ν_{N-H} 3448 cm^{-1} (CH_2Cl_2), which contained ethylene glycol. Extraction of the oil with light petroleum gave only a trace of a crystalline solid.

Attempted reactions with carboxylic acids

(i) *Action of lithium methyl.* A solution of LiMe (from Li (4·2 g), MeI (45 g) and ether (100 ml)) was added to a suspension of lithium pyrrole-2-carboxylate (4 g) in ether (100 ml) under N_2. The mixture was stirred and boiled under reflux for 72 hr and then ice–water was added. The ethereal layer was separated and the aqueous layer was extracted into ether (3 × 50 ml). The combined ethereal solution was dried and on evaporation gave a small amount of a pasty material (398 mg) which could not be crystallized and which did not show any carbonyl absorption in its IR spectrum. Acidification of the aqueous phase gave pyrrole-2-carboxylic acid (2·5 g).

Pyrrole-3-carboxylic acid was recovered from similar treatment of its Li salt with LiMe. No ether soluble material was obtained from the action of LiMe on lithium 1-ethoxycarbonyl-4-methoxy-Δ^3-pyrroline-3-carboxylate.

(ii) *Action of lithium aluminium hydride.* A solution of methyl pyrrole-3-carboxylate (2 g) in

ether (50 ml) was added dropwise to a solution of LAH (1·5 g) in ether (50 ml). The mixture was warmed under reflux for 15 min and then decomposed by the addition of water. The separated ether layer and ether extracts (3 × 50 ml) of the aqueous layer were combined and dried. Half of this solution was evaporated leaving an oil (0·8 g) which showed no carbonyl absorption; after 12 hr at room temp it was insoluble in ether.

The second half of the ethereal solution was treated[24] with MnO_2 B (6 g) and the mixture was stirred at room temp for 24 hr. The solution was filtered and evaporation of the ether left a pasty solid (600 mg) showing no carbonyl absorption.

Treatment of methylpyrrole-2-carboxylate and ethyl 1-ethoxycarbonyl-4-methoxy-Δ^3-pyrroline-3-carboxylate in a similar way gave no useful products.

Formylation of ethylpyrrole-2-carboxylate[20]

A solution of ethyl pyrrole-2-carboxylate (69·5 g) in ethylene chloride (125 ml) was added dropwise at 5° to dimethylformamide (40 g) in ethylene chloride (125 ml) containing $POCl_3$ (84·5 g). After standing 1 hr at 5° the mixture was boiled under reflux for 15 min and then cooled. AcOEt (375 g) in water (500 ml) was added to the mixture and the organic layer was separated. The aqueous layer was washed with ether (3 × 200 ml) and the combined organic layers were washed with 10% Na_2CO_3aq (5 × 100 ml). Evaporation of the solvents left a red oil which was distilled through a Vigreux column giving ethyl 5-formylpyrrole-2-carboxylate (42 g), b.p. 96–100°/0·1 mm, m.p. 75° (from light petroleum); and ethyl 4-formylpyrrole-2-carboxylate (12 g), b.p. 115–136°/0·1 mm, m.p. 104–106° (from light petroleum).

Formylation of methylpyrrole-2-carboxylate

Methylpyrrole-2-carboxylate (5 g) was similarly formylated giving methyl 5-formylpyrrole-2-carboxylate (3·9 g), m.p. 92–93° (from light petroleum); Anderson and Lee[21] quote m.p. 92–93° for methyl 4-formylpyrrole-2-carboxylate.

5-Formylpyrrole-2-carboxylic acid

(a) *From ethyl ester.* Ester (10 g) in EtOH (20 ml) was boiled under reflux with KOH (4 g) in EtOH (20 ml) for 3 hr. The yellow coloured K-salt was collected, dissolved in water (20 ml) and the solution washed with ether. Acidification with HCl then gave acid (7·1 g, 85%), m.p. 202–203° (from water).

(b) *From methyl ester.* Ester (3 g) was treated similarly giving acid (2·67 g, 97%), m.p. 202–203° (from water); mixed with acid from ethyl ester, m.p. 202–203°. The IR spectra of both samples of acid were identical.

Methyl 5-formylpyrrole-2-carboxylate

Acid (0·6 g), prepared by hydrolysis of ethyl ester, was treated with a 0·0059 M solution of diazomethane in ether (7 ml) giving methyl ester, m.p. 92–93°; mixed with the formylation product from methylpyrrole-2-carboxylate, m.p. 92–93°. The IR spectra of both samples of ester were identical.

By the action of a large excess of diazomethane on the acid *methyl 5-formyl-1-methylpyrrole-2-carboxylate*, m.p. 100–102° (from light petroleum) was obtained; the NMR spectrum had absorption at δ = 4·3 (N—CH_3) and 3·9 (OCH_3). The same compound was obtained by the action of diazomethane on the methyl ester. (Found: C, 57·3; H, 5·57; N, 8·4. $C_8H_9NO_3$ requires: C, 57·1; H, 5·4; N, 8·4%.)

4-Formylpyrrole-2-carboxylic acid

Ethyl ester (10 g) in EtOH (150 ml) was treated with KOH (3·5 g) in EtOH (50 ml) and the solution boiled under reflux for 5 hr. Acidification gave *4-formylpyrrole-2-carboxylic acid* (6·3 g, 75%) m.p. 220° from water. (Found: C, 51·5; H, 3·7; N, 10·2. $C_6H_5NO_3$ requires: C, 51·8; H, 3·6; N, 10·1%.)

[24] M. Harfenist, A. Bavley and W. A. Lazier, *J. Org. Chem.* **19**, 1608 (1954).

Pyrrole-3-aldehyde

A mixture of 4-formylpyrrole-2-carboxylic acid (2 g) copper chromite (0·6 g) and quinoline (3 ml) was heated at 180° for 30 min. The mixture was cooled and diluted with ether (50 ml). The filtered solution was washed with 1:1 HCl (20 ml) and then evaporated. The residual oil was dissolved in benzene and filtered through a column of silica gel. Evaporation of the eluate gave pyrrole-3-aldehyde (120 mg), m.p. 64° from CCl_4–light petroleum. Continuous extraction of the aqueous phase gave a small amount (20 mg) of aldehyde. (Found: C, 63·0; H, 5·5; N, 14·9. C_5H_5NO requires: C, 63·2; H, 5·3; N, 14·7%.)

Similar decarboxylation of 5-formylpyrrole-2-carboxylic acid (1 g) gave pyrrole-2-aldehyde (200 mg, 14·6%), m.p. 42–43°.

Spectral measurements. IR spectra were measured on P-E 237 or P-E 125 spectrometers. NMR spectra were measured on a P-E R10 spectrometer for solutions in $CDCl_3$.

Acknowledgements—The authors thank E. Cummins and M. Green for the NMR spectra. One of us (MKAK) thanks Pakistan C.S.R. and one of us (DPM) thanks SRC for maintenance grants.