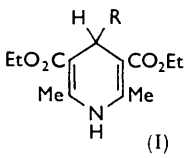
921. *Two Novel Rearrangement Reactions.*

By P. J. Brignell, E. Bullock, U. Eisner, B. Gregory, A. W. Johnson, and H. Williams.

Treatment of diethyl 4-chloromethyl-1,4-dihydro-2,6-lutidine-3,5-dicarboxylate (I; R = CH_2Cl) with potassium cyanide gives diethyl 4-cyano-2,7-dimethyl-4,5-dihydroazepine-3,6-dicarboxylate (VIII) and not the corresponding cyanomethyldihydropyridine (I; R = CH_2·CN) as claimed by Benary. An independent synthesis of the latter (I; R = CH_2·CN) is described. The pyrrole obtained by base-catalysed rearrangement of the dihydroazepine (VIII) is ethyl 3-cyano-2,5-dimethylpyrrole-4-carboxylate (IV), not ethyl 3-cyanomethyl-2-methylpyrrole-5-carboxylate (II; R = CH_2·CN) as reported. The related 3,5-dicyano-1,4-dihydro-2,6-lutidine derivatives have been investigated.

Ring-expansion of pyrroles to derivatives of pyridine is well known [1] though few examples of the reverse process have been reported.[2,3] Benary [2] claimed that treatment of the dihydropyridine (I; R = CH_2·CN) with base gave the pyrrole (II; R = CH_2·CN), a compound which would be a useful intermediate in the synthesis of pyrroles (*e.g.*, III [4]) related to the uroporphyrins. However, the failure of the product to give a colour with Ehrlich's reagent and its general lack of reactivity (cf. ref. 5) indicated that the structure (II; R = CH_2·CN) was incorrect. Further, the ultraviolet spectrum was expected to resemble that of the dimethyl analogue (II; R = Me),[6] whereas the observed spectrum was identical with that of the tetrasubstituted pyrrole (IV).[7] Mixed melting points and comparison of infrared spectra showed that the rearrangement product was in fact substance (IV). This was confirmed when its hydrolysis and decarboxylation yielded 3-cyano-2,5-dimethylpyrrole,[8] which has now been prepared by an unambiguous synthesis from 2,5-dimethylpyrrole by formylation [9] followed by dehydration of the corresponding oxime.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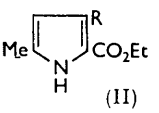
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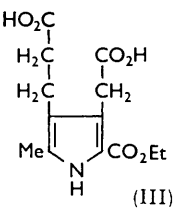
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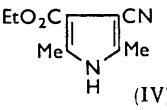

(IV)

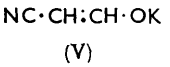
In Benary's method of preparation [2] of the supposed dihydropyridine (I; R = CH_2·CN) (termed " the cyano-compound " below) from the chloromethyl compound (I; R = CH_2Cl) with potassium cyanide in boiling aqueous alcohol, some of the pyrrole (IV) is always formed. Pyrrole formation can be avoided by carrying out the reaction in the cold, for an almost quantitative yield of the cyano-compound is then obtained. Dimethyl sulphoxide may also be used as a solvent in this reaction. The action of alcoholic alkali on the cyano-compound (cf. ref. 2) produces the pyrrole (IV), together

[1] *E.g.*, Rice and Londergan, *J. Amer. Chem. Soc.*, 1955, **77**, 4678; Closs and Schwartz, *J. Org. Chem.*, 1961, **26**, 2609.
[2] Benary, *Ber.*, 1920, **53**, 2218.
[3] Sasse, *J.*, 1959, 3046; Granelli, *Farm. ital.*, 1937, **5**, 708; *Chem. Abs.*, 1939, **33**, 4245; Süs, Möller, *et al.*, *Annalen*, 1953, **583**, 150; 1955, **593**, 91.
[4] MacDonald, *J.*, 1952, 4184.
[5] Fischer and Müller, *Z. physiol. Chem.*, 1937, **246**, 31; Fischer and Elhardt, *ibid.*, 1939, **257**, 61.
[6] Cookson, *J.*, 1953, 2789.
[7] Eisner and Gore, *J.*, 1958, 922; Eisner and Erskine, *J.*, 1958, 971.
[8] Bilton and Linstead, *J.*, 1937, 922.
[9] Kleinspehn and Briod, *J. Org. Chem.*, 1961, **26**, 1652.

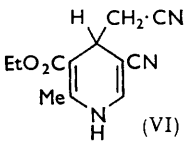
with ethyl acrylate which was identified by measurement of its retention time on a gas–liquid chromatography column and by comparison of its infrared spectrum with that of an authentic sample.

Comparison of the ultraviolet and infrared spectra of the cyano-compound with those of known 1,4-dihydropyridines (see Table), the lack of fluorescence in ultraviolet light, and the extreme lability to acid [10] caused us to suspect that the assigned structure (I; R = CH_2·CN) might be incorrect.

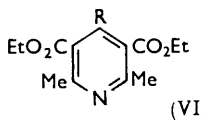
Synthesis of the authentic compound (I; R = CH_2·CN) from cyanoacetaldehyde * and ethyl α-amino-crotonate or -ethyl acetoacetate finally disproved this structure for the cyano-compound. Condensation of the potassium salt of cyanoacetaldehyde (V) with ethyl acetoacetate in ammonium carbonate buffer [16] afforded the authentic compound (I; R = CH_2·CN) in low yield, Reaction of the salt (V) with ethyl α-aminocrotonate in acetic acid [10] yielded a mixture of this compound (I; R = CH_2·CN) and the dihydropyridine (VI), produced by condensation of one mol. of the ester with two of cyanoacetaldehyde. The structure of compound (VI) follows from analytical and spectral data (see Experimental section).



(V)



(VI)



(VII)

The ultraviolet and infrared spectra of compound (I; R = CH_2·CN) are typical of the dihydropyridine structure (see Table). The nuclear magnetic resonance spectrum shows a doublet at τ 7·42, *J* 5·1 c./sec. (CH_2·CN) and a triplet centered at τ = 5·78 (≥CH) incompletely separated from the methylene quartet; it is essentially similar to that of the chloride (I; R = CH_2Cl) [17] which has a doublet (τ 6·48, *J* 5·8 c./sec.) and a triplet (τ 5·67, *J* 5·8 c./sec.).

Correlation of the dihydropyridines (I; R = CH_2Cl and CH_2·CN) was achieved by conversion into the pyridine (VII; R = CH_2·CN). This has been prepared by Benary [18] from the chloride (I; R = CH_2Cl) by dehydrogenation with nitric acid to the corresponding pyridine (VII; R = CH_2Cl) and conversion into the nitrile (VII; R = CH_2·CN). The dehydrogenation of the nitrile (I; R = CH_2·CN) proved to be unexpectedly complex but was finally achieved by heating with sulphur [19] which afforded the nitrile (VII; R = CH_2·CN), identical with the material obtained by Benary's route.[18] Dehydrogenation by nitrous acid gave the hydroxyimino-derivative [VII; R = C(CN):N·OH], also prepared by the action of nitrous acid on the nitrile (VII; R = CH_2·CN). Similarly the chloride (I; R = CH_2Cl) with nitrous acid yielded the oxime (VII; R = CH:N·OH), characterised as the benzoate, which was converted into the compound [VII; R = C(CN):N·OH] by

* The literature references to cyanoacetaldehyde and its derivatives are scant [11, 12] and sometimes contradictory.[13] We first attempted unsuccessfully to prepare it by a Wittig type synthesis.[14] The authors of the patent [14] have since informed us that the yield was erroneously quoted to be ten times that actually obtained and that they had been unable to repeat their original preparation. We subsequently used the method of Borsche and Manteuffel [15] which gave the potassium salt of cyanoacetaldehyde reproducibly in fair yield.

[10] Cf. Traber and Karrer, *Helv. Chim. Acta*, 1958, **41**, 2066.
[11] Claisen, *Ber.*, 1903, **36**, 3664; Quilico and Freri, *Gazzetta*, 1946, **76**, 3.
[12] Shaw, *J.*, 1955, 1834.
[13] Uhle and Jacobs, *J. Org. Chem.*, 1945, **10**, 76; Hartung and Adkins, *J. Amer. Chem. Soc.*, 1947, **69**, 1535; McElvain and Clarke, *ibid.*, p. 2657.
[14] B.P. 790,823/1958; *Chem. Abs.*, 1958, **52**, 16,411.
[15] Borsche and Manteuffel, *Annalen*, 1934, **512**, 97.
[16] Haley and Maitland, *J.*, 1951, 3155.
[17] Cf. Sims and Smith, *Proc. Chem. Soc.*, 1958, 282.
[18] Benary, *Ber.*, 1911, **44**, 489.
[19] Huntress and Shaw, *J. Org. Chem.*, 1948, **13**, 674.

Absorption bands of 1,4-dihydropyridines.

Compound	Ultraviolet maxima $\lambda_{max.}$ (mμ)	ε		N–H Non-bonded	N–H Bonded	Infrared bands (cm.$^{-1}$) C≡N		CO_2Et	Refs.
I; R = H [11]	230, 371	14,980	7470	3449	3350			1693	a
R = CH_3 [11, 12]	233, 351	18,500	8440	3439	3345			1690	12
R = CH_2Cl [13]	231, 349	19,400	7650	3447	3343			1694	b
R = CH_2Br	233, 345	17,900	7110	3449	3338			1695	
R = CH_2·CN	231, 349	19,500	7760						
R = CH_2·CH_3 [14]	234, 349	17,900	7790	3444	3347			1692	c
R = CH_2·CH_2Cl	234, 346	18,100	7700	3439	3343			1694	
R = CH_2·CH_2·CN	234, 347	18,650	8030	3441	3339	2253w		1695	
VIII	229, 326	15,100	15,400	3425	3370	2240w		1708	
IX; R = H * [10, 15, 16]	216, 346	23,400	5500	3450	3321		2206s		10, d, e
R = CH_3 [10, 15, 16]	216, 341	22,900	5880	3449	3316		2206s		10, d, e
R = CH_2Cl	216, 339	25,100	7760	3444	3311		2205s		
X	215, 315	20,900	15,140	3417	3343	2250w,	2210s		

* This compound (IX; R = H) has been reported (Bohlmann and Bohlmann, *Chem. Ber.*, 1953, **86**, 1419) to have $\lambda_{max.}$ 362·5 mμ, although other authors [a, e] record ultraviolet absorption data in agreement with ours. It was prepared (Bohlmann *et al.*, *loc. cit.*) by reduction of the corresponding pyridine with lithium aluminium hydride and the absorption was claimed to indicate 1,4-addition of hydrogen. We have dehydrogenated our sample of compound (IX; R = H) with diphenylpicrylhydrazyl (cf. Braude, Brook, and Linstead, *J.*, 1954, 3574) in chloroform–methanol and obtained the corresponding pyridine, m. p. 121° (Kofler) (lit., 112°,[d] 119—120° [e]). Reduction of the pyridine with lithium aluminium hydride gave, in our hands, compound (IX; R = H).

References: (a) Hofmann, Kosower, and Wallenfels, *J. Amer. Chem. Soc.*, 1961, **83**, 3314. (b) Benary, *Ber.*, 1911, **44**, 489. (c) Engelmann, *Annalen*, 1885, **231**, 37. (d) von Meyer, *J. prakt. Chem.*, 1908, **78**, 497. (e) Lukeš and Kuthan, *Coll. Czech. Chem. Comm.*, 1961, **26**, 1422; Kuthan, *ibid.*, 1962, **27**, 2175.

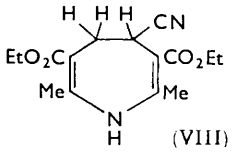
chlorination and treatment with cyanide. With chloranil in boiling toluene [20] the dihydropyridine (I; R = CH_2·CN) underwent loss of the CH_2·CN group with formation of the pyridine (VII; R = H) in 30% yield. It was shown by gas chromatography that no acetonitrile was formed in this reaction which possibly proceeds by C–C fission of a condensation product such as [VII; R = C(CN):C_6Cl_4:O].

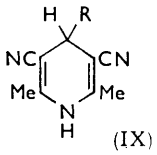
The infrared and ultraviolet spectra of the compound derived from the chloride (I; R = CH_2Cl) by treatment with cyanide exclude a dihydropyridine structure, whilst indicating certain structural features as essentially similar to those of the chloride (I; R = CH_2Cl). Thus in the nuclear magnetic resonance spectrum of the cyano-compound the grouping >CH·CH_2 appears to be an ABX system,[21] indicating that there is no free rotation round the methylene group. Furthermore, the bands associated with the methyl groups attached to the ring showed that these were non-equivalent (τ 7·60 and 7·63). We are indebted to Professor L. M. Jackman for pointing this out and for providing preliminary data. A further analysis of the spectra in benzene and chloroform revealed that the >CH·CH_2 system appears as two quartets (τ_X 5·45, J_{AX} 6·3, J_{BX} 1·6 c./sec.; and τ_A 6·46, J_{AB} 15·3, J_{AX} = 6·3 c./sec.) and a pair of complex resonances each with at least five lines (τ_B 7·57, J_{AB} ~15 c./sec.). The complexity of the third group of absorptions can be explained in terms of long-range interaction [22] of one proton with a methyl group which appears as a doublet under conditions of very high resolution (J ~1 c./sec.). The lack of symmetry in the molecule is emphasised by the spectrum in benzene in which the ester groups appear to be non-equivalent, possibly an indication that one of them is in a favourable orientation for a specific interaction with the solvent.

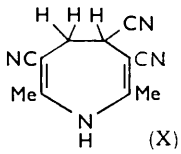
We therefore formulate the cyano-compound as the dihydroazepine [23] (VIII) which could arise from a Wagner–Meerwein type of rearrangement of the chloromethyl derivative

[20] Braude, Hannah, and Linstead, *J.*, 1960, 3249.
[21] Bernstein, Pople, and Schneider, *Canad. J. Chem.*, 1957, **35**, 65.
[22] Davis, Lutz, and Roberts, *J. Amer. Chem. Soc.*, 1961, **83**, 246.
[23] Bullock, Gregory, Johnson, Brignell, Eisner, and Williams, *Proc. Chem. Soc.*, 1962, 122.

(I; R = CH_2Cl). A number of analogous ring expansions of heterocyclic [24] and homocyclic [25] systems have been described. In accordance with this postulate the action of a number of nucleophiles (methoxide, hydroxide, *p*-tolylthio, azide, and acetate, but not


(VIII)


(IX)


(X)

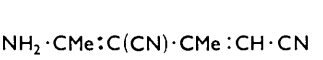
iodide or benzenesulphonate) on the chloromethyl compound (I; R = CH_2Cl) produces spectral changes similar to those due to cyanide. Moreover, no reaction occurs when the homologue (I; R = $CH_2{\cdot}CH_2Cl$) is treated with cyanide under conditions whereby the chloromethyl compound (I; R = CH_2Cl) is converted into the azepine (VIII), and the replacement reaction producing the cyanoethyl derivative (I; R = $CH_2{\cdot}CH_2{\cdot}CN$) requires forcing conditions and acetamide as solvent.

The conversion of the dihydroazepine (VIII) into the pyrrole (IV) and ethyl acrylate by base may be provisionally formulated [23] as involving ring opening by a retro-Claisen reaction, cyclisation to a pyrroline, and fragmentation.

A related group of dihydropyridines (IX) was examined and a second dihydroazepine (X) was isolated by treatment of the chloromethyl member (IX; R = CH_2Cl) with potassium cyanide.[26] The chloro-compound (IX; R = CH_2Cl) was the main product from the reaction of the nitrile [27] (XI) with 1,2-dichloroethyl ethyl ether, which also yielded some of the aliphatic dinitrile (XII).

We have been unable to repeat Benary and Löwenthal's observation [26] that the reaction of the chloromethyl compound (IX; R = CH_2Cl) with potassium cyanide produces two substances, the amide (IX; R = $CH_2{\cdot}CO{\cdot}NH_2$), m. p. 109°, and the nitrile (IX; R = $CH_2{\cdot}CN$), m. p. 220°. We obtained a single product, m. p. 153°, which was


(XI)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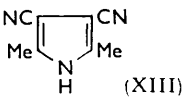
(XIII)

unchanged after repeated crystallisation. The infrared and ultraviolet (Table) data are consistent with structure (X) for this material. This compound yielded a small amount of the expected pyrrole (XIII) [8] on treatment with base, although difficulties were experienced in reproducing this reaction. The kinetics and mechanism of these and related rearrangements are under investigation.

Experimental

Ultraviolet spectra were determined on ethanolic solutions with Unicam S.P. 500 and S.P. 700 instruments. Infrared spectra were measured for chloroform solutions (except where otherwise stated) with Unicam S.P. 100 (corrected values are given for all spectra obtained on this instrument) and Hilger H 800 instruments. Most of the nuclear magnetic resonance spectra were measured on an AEI RS2 instrument operating at 60 Mc/sec.

Diethyl 4-Chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate [18] (I; R = CH_2Cl).

[24] Bergmann and Rabinovitz, *J. Org. Chem.*, 1960, **25**, 827, 828; Craig, Lester, Saggiomo, Kaiser, and Zirkle, *J. Org. Chem.*, 1961, **26**, 135; Whitlock, *Tetrahedron Letters*, 1961, 593; Sternbach and Reeder, *J. Org. Chem.*, 1961, **26**, 4936; Bell, Sulkowski, Gochman, and Childress, *J. Org. Chem.*, 1962, **27**, 562.

[25] Nelson, Fassnacht, and Piper, *J. Amer. Chem. Soc.*, 1961, **83**, 206; Schreiber, Pesaro, Leimgruber, and Eschenmoser, *Helv. Chim. Acta*, 1958, **41**, 2103; van Tamelen and Hildahl, *J. Amer. Chem. Soc.*, 1956, **78**, 4405.

[26] Benary and Löwenthal, *Ber.*, 1922, **55**, 3429.

[27] Moir, *J.*, 1902, **81**, 100.

—(i) Molten ethyl α-aminocrotonate [28] (50 g.) and 1,2-dichloroethyl ethyl ether [29] (58·6 g.) were mixed and then treated with 10% aqueous ammonia (300 ml.). After a vigorous exothermic reaction, the mixture was kept for 1—2 hr. The semi-solid product was separated and washed with small amounts of ethanol and ether, affording yellow crystals (36·8 g., 63%), m. p. 134—136° (lit.,[18] 133—134°) (from ethanol), $\nu_{max.}$ 1031, 1107, 1160, 1281, 1305, 1328, 1373, 1478, 1621, 1694, 2940, 3343, and 3515 cm.$^{-1}$.

(ii) Ethyl α-aminocrotonate (23 g.) in benzene (190 ml.) was treated with 1,2-dichloroethyl ethyl ether (29 ml.) and kept at room temperature for 3 days. The mixture was washed with water, and the product (1·5 g.) was filtered off. Concentration of the filtrate and addition of light petroleum afforded the main crop (14·5 g., total 60%). Recrystallisation from aqueous acetone gave the diester as a yellow solid (9·7 g.), m. p. 131—132°.

Diethyl 4-Bromomethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (I; R = CH_2Br). —1 2-Dibromoethyl ethyl ether [30] (9·5 g., 6·35 ml.) was added to a cooled solution of ethyl α-aminocrotonate (5 g.) in benzene (15 ml.) and after 30 min. a precipitate of ammonium bromide was separated. Removal of the benzene from the filtrate gave a solid which was washed with water and then dried. It was further washed with cold benzene and the yellow solid so obtained was crystallised from benzene containing a small quantity of ethanol. The colourless *product* (2 g., 15%) had m. p. 131·5—133° (Found: C, 48·8; H, 6·1; Br, 23·4; N, 4·15. $C_{14}H_{20}BrNO_4$ requires C, 48·55; H, 5·8; Br, 23·1; N, 4·05%). It was unstable and became orange on exposure to air or on prolonged heating of its solutions. The infrared spectrum showed max. at 519, 595, 616, 867, 933, 973, 1025, 1056, 1104, 1162, 1281, 1302, 1325, 1374, 1386, 1479, 1622, 1652, 1695, 2876, 2910, 2940, 2970, 3040, 3338, and 3449 cm.$^{-1}$.

Diethyl 4-Cyano-4,5-dihydro-2,7-dimethylazepine-3,6-dicarboxylate (VIII).—(i) The chloro-compound (I; R = CH_2Cl) (36·8 g.) and potassium cyanide (36·8 g.) were heated under reflux in ethanol (92 ml.) for 5 hr. A large excess of water precipitated the product which was separated and fractionally crystallised from ethanol, yielding two compounds. The less soluble material (VIII) formed colourless leaflets, m. p. 106—107° (lit.,[2] 106—107°) (Found: C, 62·0; H, 7·0; N, 9·45. Calc. for $C_{15}H_{20}N_2O_4$: C, 61·65; H, 6·9; N, 9·6%), $\nu_{max.}$ 870, 943, 965, 1030, 1096, 1109, 1137, 1175, 1272, 1305, 1317, 1376, 1387, 1455, 1466, 1508, 1523, 1635, 1652, 1708, 2240, 2942, 2986, 3045, and 3425 cm.$^{-1}$ (concn. 11·6 mg./ml.; the spectrum varies somewhat with concentration).

The more soluble material (IV) formed colourless needles (from aqueous ethanol), m. p. 149·5—151° (Kofler), mixed m. p. with authentic material [8] 150—151° (Found: C, 62·7; H, 6·0; N, 14·1. Calc. for $C_{10}H_{12}N_2O_2$: C, 62·5; H, 6·3; N, 14·6%), $\lambda_{max.}$ 263 mμ (ε 8870), shoulder 234 mμ (ε 4470), $\nu_{max.}$ 1097, 1142, 1280, 1550, 1703, 2224, 3255, and 3443 cm.$^{-1}$ (cf. ref. 7).

(ii) The chloro-compound (I; R = CH_2Cl) (5 g.) and potassium cyanide (5 g.) were shaken at room temperature in ethanol (250 ml.) for 28 hr. Much of the ethanol was removed *in vacuo* and addition of a large excess of water precipitated the cyano-compound (4·5 g.) identical, after purification, with the material prepared as above.

(iii) The chloro-compound (I; R = CH_2Cl) (1·5 g.) was added to a stirred suspension of sodium cyanide (0·5 g.) in dimethyl sulphoxide [31] (5 ml.), and stirring continued for 16 hr. Addition of water to the brown suspension gave a pale brown solid which, on crystallisation from ethanol, gave the cyano-derivative as colourless plates in almost quantitative yield.

Rearrangement of Diethyl 4-Cyano-4,5-dihydro-2,7-dimethylazepine-3,6-dicarboxylate (VIII).—(i) Carefully purified cyano-compound (VIII) (38·6 mg.) was dissolved in ethanol (0·32 ml.) containing potassium hydroxide (7·7 mg.) and heated on the steam-bath for 10 min. The solution was evaporated to dryness. Addition of water then afforded white crystals (3·4 mg.) that had m. p. 150—151° after repeated crystallisation from ethanol, identical with that of ethyl 4-cyano-2,5-dimethylpyrrole-3-carboxylate.[8] In another experiment, a 62% yield of material, m. p. 144—146°, was obtained.

(ii) The cyano-compound (VIII) (1 g.) was dissolved in ethanol (6 ml.), and potassium hydroxide (0·02 g.) in ethanol (4 ml.) was added. The solution was heated under reflux for 50 min. and then alcohol was distilled off at atmospheric pressure until 6 c.c. of distillate had

[28] Glickman and Cope, *J. Amer. Chem. Soc.*, 1945, **67**, 1017.
[29] Johnson, *J.*, 1946, 895.
[30] Baganz and Brinckmann, *Chem. Ber.*, 1953, **86**, 1318.
[31] Friedman and Shechter, *J. Org. Chem.*, 1960, **25**, 877.

been collected. The distillate was fractionated by gas–liquid chromatography on a Perkin-Elmer Fraktometer instrument (2 m. Perkin-Elmer Apiezon column at 88° with a flow rate of 15 ml./min. of nitrogen as carrier gas), and a fraction with retention time 12·0 min. was collected. This was shown to be ethyl acrylate by comparison of its infrared spectrum (in chloroform) with that of an authentic sample.

3-*Cyano*-2,5-*dimethylpyrrole*.—The pyrrole ester (above; 2 g.) was hydrolysed and decarboxylated according to the method of Benary,[2] 3-cyano-2,5-dimethylpyrrole (32 mg.) being obtained as very pale pink crystals, m. p. 87·5—88·5° (lit.,[8] 89°), $\nu_{max.}$ 1006, 1133, 1149, 1314, 1537, 1600, 2218, 3297, and 3455 cm.$^{-1}$ (cf. ref. 7).

2,5-*Dimethylpyrrole*-3-*aldoxime*.—Dimethylformamide (8 g.) was treated with phosphorus oxychloride (10 ml.) at 0° and the mixture was stirred at room temperature for 15 min. Dichloroethylene (25 ml.) was added, the solution was cooled to 0°, and 2,5-dimethylpyrrole (9·1 g.) in dichloroethylene (25 ml.) was added dropwise with stirring and cooling. The mixture was boiled under reflux for 1 hr., cooled, and decomposed with sodium acetate trihydrate (75 g.) in water (100 ml.). The aldehyde isolated by continuous ether-extraction (3 days) (8·0 g., 68%), had m. p. 135—139° (lit.,[32] m. p. 142—143°).

The above aldehyde (2·46 g.) in aqueous ethanol was treated with hydroxylamine hydrochloride (1·4 g.) and sodium acetate trihydrate (2·72 g.) in water, and the solution was heated on a steam-bath for 30 min. On cooling, the product (1·40 g.) separated. Repeated crystallisation from toluene, ethyl acetate, and water afforded the *oxime*, m. p. 157° (Found: C, 60·5; H, 7·2; N, 19·85. $C_7H_{10}N_2O$ requires C, 60·8; H, 7·3; N, 20·3%).

3-*Cyano*-2,5-*dimethylpyrrole*.—The above oxime (512 mg.) and anhydrous sodium acetate (0·5 g.) in acetic anhydride (25 ml.) were boiled under reflux for 30 min. The solution was poured into hot water and evaporated to dryness under reduced pressure. Water was added to the residue and the black solid separated. It was taken up in boiling water, filtered from an oily impurity, and allowed to crystallise (yield, 210 mg.). Recrystallisation from cyclohexane afforded the cyanopyrrole, m. p. 91—92°, undepressed on admixture with the specimen obtained as above.

Cyanoacetaldehyde.—The *potassium salt* (V) was obtained as a hygroscopic solid (Found: K, 37·5. C_3H_2KNO requires K, 36·5%), by the method of Borsche and Manteuffel.[15] The *semicarbazone*, m. p. 152—153°, formed colourless crystals (Found: C, 38·1; H, 4·85; N, 44·7. $C_4H_6N_4O$ requires C, 38·1; H, 4·8; N, 44·4%) from aqueous ethanol. The 2,4-dinitrophenylhydrazone, m. p. 172—174° (lit.,[12] 170—171°) (Found: C, 43·6; H, 3·1; N, 27·7. Calc. for $C_9H_7N_5O_4$: C, 43·4; H, 2·8; N, 28·1%), crystallised from aqueous ethanol.

Diethyl 4-*Cyanomethyl*-1,4-*dihydro*-2,6-*dimethylpyridine*-3,5-*dicarboxylate* (I; R = CH_2·CN).—(i) The potassium salt of cyanoacetaldehyde (2·16 g.) and ethyl α-aminocrotonate [28] (5·63 g.) were dissolved in glacial acetic acid (30 ml.) by shaking at room temperature for 15 min. The mixture was heated on a water-bath for 30 min. and poured on ice. The solid product (1·92 g.) was separated and dried. A portion (0·48 g.) was chromatographed in benzene on neutral alumina (Woelm, activity I; 14 g.). Elution with ether–benzene (1 : 19) gave 0·277 g. of compound (A) and elution with ether–benzene (1 : 9) gave 0·087 g. of compound (B). Compound (A) was crystallised four times from aqueous ethanol, to give *diethyl* 4-*cyanomethyl*-1,4-*dihydro*-2,6-*dimethylpyridine*-3,5-*dicarboxylate*, m. p. 121·5—122° (previously [23] incorrectly given as 141—143°) (Found: C, 61·35; H, 6·85; N, 9·3. $C_{15}H_{20}N_2O_4$ requires C, 61·6; H, 6·9; N, 9·1%), $\lambda_{max.}$ 231 and 349 mμ (ε 19,500 and 7760), $\nu_{max.}$ 3400, 3320, 2980, 2250, 1690, 1620, 1490, 1470, 1440, 1415, 1380, 1365, 1340, 1310, 1300, 1275, 1230, 1190, 1170, 1150, 1120, 1100, 1050, 1025, and 960 cm.$^{-1}$. Compound (B) was crystallised from benzene and four times from aqueous ethanol, to give *ethyl* 5-*cyano*-4-*cyanomethyl*-1,4-*dihydro*-2-*methylpyridine*-3-*carboxylate* (VI), m. p. 130·5—133° (Found: C, 62·5; H, 5·6; N, 18·2. $C_{12}H_{13}N_3O_2$ requires C, 62·3; H, 5·7; N, 18·2%), $\lambda_{max.}$ 216·5 and 344 mμ (ε 33,100 and 7590), $\nu_{max.}$ 3420, 3300, 2960, 2250, 2220, 1690, 1675, 1610, 1475, 1410, 1375, 1360, 1320, 1275, 1255, 1225, 1160, 1110, 1070, 1015, and 965 cm.$^{-1}$.

(ii) The potassium salt of cyanoacetaldehyde (0·995 g.) was dissolved in 10% aqueous ammonium carbonate (100 ml.), and ethyl acetoacetate (8·6 ml.) was added. When the mixture was kept at room temperature for 6 days the dihydropyridine (I; R = CH_2·CN) (0·134 g.), m. p. 122°, undepressed on admixture of a sample prepared as above, was obtained.

[32] Piloty, Krannich, and Will, *Ber.*, 1914, **47**, 2531.

Dehydrogenation of Diethyl 4-Cyanomethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate. —(*a*) *With sulphur.* A mixture of the dihydro-ester (55·4 mg.) and sulphur (6·2 mg.) was heated at 206° for 30 min., then was cooled, dissolved in ethanol (4 ml.), treated with hydrochloric acid (10 ml.), and extracted with ether (10 ml.). The aqueous layer was made alkaline with 2N-sodium hydroxide and extracted with ether (3 × 10 ml.). The ethereal layers were dried and the solvent removed under reduced pressure, to yield the product (37·5 mg.), m. p. 59—63°. Two crystallisations from aqueous ethanol afforded material of m. p. 65·5—66·5°, undepressed on admixture with diethyl 4-cyanomethyl-2,6-dimethylpyridine-3,5-dicarboxylate prepared by Benary's route (see below). The infrared spectra of the two samples were identical.

(*b*) *With nitrous fumes.* Nitrous fumes were passed through a solution of the dihydropyridine (0·1 g.) in ethanol (10 ml.) for 30 min. The solution was then poured into water (10 ml.), made alkaline with sodium hydrogen carbonate solution, and extracted with ether (4 × 15 ml.). The ethereal extracts were evaporated under reduced pressure to a viscous oil (0·091 g.) which was distilled at 150°/0·02 mm. The product crystallised from benzene–light petroleum (b. p. 40—60°). Two further recrystallisations from aqueous ethanol yielded the *hydroxyimino-derivative*, [VII; R = C(CN):N·OH], m. p. 139—141° (see below) (Found: C, 56·0; H, 5·6; N, 12·8. $C_{15}H_{17}N_3O_5$ requires C, 56·4; H, 5·4; N, 13·15%).

(*c*) *With nitric acid.* The dihydropyridine (89·1 mg.) was heated with 25% nitric acid (1 ml.) on a water-bath for 4 min., poured into water (10 ml.), made alkaline with sodium hydrogen carbonate solution, and extracted with ether (3 × 15 ml.). The ethereal extract was dried and evaporated under reduced pressure, to yield the product (68·9 mg.) which after two recrystallisations from benzene–light petroleum had m. p. 140·5—143° and was identical with that from the preceding experiment.

Diethyl 4-cyanomethyl-2,6-dimethylpyridine-3,5-dicarboxylate (25·8 mg.), concentrated nitric acid (0·25 ml.), and saturated sodium nitrite solution (0·25 ml.) were heated on a water-bath for 3 min., then made alkaline with aqueous ammonia (*d* 0·88) and extracted with ether (4 × 5 ml.). The ethereal layer was dried and evaporated under reduced pressure to yield the product (7·2 mg.) which after two recrystallisations from benzene–light petroleum had m. p. 139—140·5°, undepressed on admixture of the product from the previous experiment. The two materials had identical infrared spectra.

(*d*) *With chloranil.* The dihydro-ester (0·32 g.) and chloranil (0·27 g.) in toluene (17 ml.) were heated under reflux for 3 hr., cooled, and extracted with hydrochloric acid (3 × 5 ml.). The acid layer was made alkaline with aqueous ammonia (*d* 0·88) and filtered, to yield the product (0·085 g., 31%). A portion of the product (39·4 mg.) was sublimed at 100°/7 mm., to give material (34·1 mg.), m. p. 68·5—69°, which formed white needles, m. p. 71—72·5°, after two crystallisations from aqueous ethanol. A mixed m. p. with diethyl 2,6-dimethylpyridine-3,5-dicarboxylate was undepressed and the two materials had identical infrared spectra.

In a further experiment the mixture was distilled and the distillate examined for acetonitrile by gas chromatography (Perkin-Elmer Fraktometer; 1 m. column, 16% dinonyl phthalate on 60—80 mesh Celite, with hydrogen as carrier) but none was detected. It was shown that under the conditions of the experiment 0·5% of the calculated quantity of acetonitrile could have been detected.

Dehydrogenation of Diethyl 4-Chloromethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate. —(*a*) *With nitrous acid.* Sodium nitrite (0·92 g.) was added in small portions to a stirred solution of the above chloro-compound (I; R = CH_2Cl) (4 g.) in acetic acid (72 ml.). The stirring was continued for 6 hr. and the precipitate of sodium chloride removed. The filtrate was neutralised with saturated aqueous sodium carbonate, and the solid which separated was removed, dried, and chromatographed in chloroform–benzene (1 : 1) on alumina (Spence type H), the first yellow band being collected. Removal of the solvent gave the *oxime* (VII; R = CH:N·OH), colourless prisms (2·11 g., 44%) (from aqueous ethanol), m. p. 125—126° (Found: C, 57·0; H, 5·6; N, 9·5. $C_{14}H_{18}N_2O_5$ requires C, 57·1; H, 6·15; N, 9·5%), $\lambda_{max.}$ 223 and 259 mμ (ε 19,700 and 10,900), $\nu_{max.}$ 1114, 1123, 1299, 1560, 1567, 1718, 1731, and 3577 cm.$^{-1}$. The derived *benzoate* (Schotten–Baumann) formed needles, m. p. 102—103°, from aqueous ethanol (Found: C, 63·5; H, 5·5; N, 6·8. $C_{21}H_{22}N_2O_6$ requires C, 63·3; H, 5·6; N, 7·0%), whose infrared spectrum showed no NH absorption but had two ester bands at 1730 and 1758 cm.$^{-1}$.

A slow stream of chlorine was passed through a solution of the aldoxime (100 mg.) in methanol (2 c.c.) for 15 min. The white hydrochloride so formed was separated and added to a

stirred solution of potassium cyanide (72·1 mg.) in methanol (5 ml.).[33] After being stirred for a further hour at 60°, the solution was cooled and adjusted to pH 5·0 with 10% hydrochloric acid. The separated potassium chloride was removed and the filtrate evaporated *in vacuo* at room temperature. Trituration of the residue with water gave a colourless solid (16·5 mg.) [VII; R = C(CN):N·OH] which was crystallised from ethanol and then had m. p. 144—147·5°. No depression of the m. p. was observed when this (hydroxyimino)acetonitrile derivative was mixed with the nitrous acid dehydrogenation product recorded above and the infrared and ultraviolet spectra of the products were identical [λ_{infl} 226 and 278 mμ (ε 14,500 and 5030, respectively); $\nu_{max.}$ 827, 843, 865, 878, 979, 1016, 1058, 1111m, 1263, 1300m, 1333, 1395m, 1449, 1479, 1567, 1732s, 2231, 2644, 2877, 2911, 2941, 3045, 3144, 3228, and 3543 cm.$^{-1}$].

(*b*) *With nitric acid.* The dihydro-ester (5 g.) and nitric acid (20 ml. of 1 : 4 concentrated acid–water) were warmed together with shaking until a clear solution was obtained. The product was then basified with aqueous sodium hydrogen carbonate and extracted three times with ether. The combined extracts were washed, dried ($MgSO_4$), and evaporated *in vacuo* at room temperature. The yellow oily product was chromatographed in chloroform–benzene (1 : 1) on alumina (Spence grade H), and the eluate up to and including the first yellow band was separated. Removal of the solvent gave a yellow chlorine-containing oil (1·83 g., 37%) which from its spectrum was mainly the corresponding lutidine. It was identified by conversion into the iodo-analogue by treating it (1·83 g.) in acetone (45 ml.) with sodium iodide (1·83 g.). Next morning sodium chloride was removed and the filtrate evaporated *in vacuo* at room temperature. Addition of water to the residue gave pale brown crystals which were crystallised twice from ethanol, to give diethyl 4-iodomethyl-2,6-dimethylpyridine-3,5-dicarboxylate (0·97 g., 41%) as colourless needles, m. p. 77—78° (lit.,[18] 77—78°) (Found: C, 42·5; H, 4·55; I, 32·8; N, 3·15. Calc. for $C_{14}H_{18}INO_4$: C, 42·95; H, 4·65; I, 32·45; N, 3·6%) $\lambda_{max.}$ 213 and 288 mμ (ε 21,200 and 3500, respectively).

Diethyl 4-Cyanomethyl-2,6-dimethylpyridine-3,5-dicarboxylate.—The foregoing compound (140 mg.) and potassium cyanide (140 mg.) in 1 : 9 aqueous ethanol (20 ml.) were heated on the water-bath for 30 min., then quickly concentrated *in vacuo*. Addition of water to the residue gave a semi-solid which was extracted in ether and recovered as a highly fluorescent, pale violet solid. This sublimed at 60°/0·1 mm. to yield colourless needles (20 mg.), m. p. 66·5—67° (lit.,[34] 66—67°), identical with the product obtained by sulphur dehydrogenation of the 1,4-dihydro-compound (see above). It had $\lambda_{max.}$ at 273 mμ (ε 4730), λ_{infl} 220 and 280 mμ (ε 7430 and 4320, respectively).

Dimethyl sulphoxide was used as solvent in this reaction in another experiment.

Diethyl 4-2′-Chloroethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (I; R = $CH_2{\cdot}CH_2Cl$).—2-Chloropropionaldehyde [35] (5 ml.) and molten ethyl α-aminocrotonate (8·8 g.) were mixed and after 30 min. ammonium chloride was separated. After 3 days, the sticky *pyridine derivative* was removed and crystallised from ethanol; it (4·6 g.) had m. p. 136—137° (Found: C, 56·9; H, 6·8; Cl, 11·2; N, 4·2. $C_{15}H_{22}ClNO_4$ requires C, 57·05; H, 7·05; Cl, 11·25; N, 4·45%), $\nu_{max.}$ 1030, 1100s, 1150, 1260, 1290s, 1308, 1358, 1370, 1458s, 1610, 1680s, 2950, 3340, and 3450 cm.$^{-1}$.

Diethyl 4-2′-Cyanoethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (I; R = $CH_2{\cdot}CH_2{\cdot}CN$).—Acetamide (1·5 g.) and potassium cyanide (1·5 g.) were heated to 130° and then allowed to cool to 90°. The above chloro-compound (I; R = $CH_2{\cdot}CH_2Cl$) (0·3 g.) was added in small quantities.[36] The temperature was kept at 90° for 7½ hr. and the cooled residue was treated with water. The precipitated *nitrile* was separated and crystallised from aqueous ethanol; it (0·12 g.) had m. p. 114·5—115° (Kofler block) (Found: C, 62·6; H, 7·15; N, 9·4. $C_{16}H_{22}N_2O_4$ requires C, 62·75; H, 7·2; N, 9·15%), $\nu_{max.}$ 987, 1063, 1105s, 1125s, 1157, 1281, 1302, 1319, 1373, 1386, 1475s, 1623, 1652, 1695s, 2253, 2910, 2939, 3025, 3339, 3441, and 3521 cm.$^{-1}$. The product was recovered unchanged after being heated with an excess of ethanolic potassium hydroxide for 50 min.

3,5-Dicyano-1,4-dihydro-2,6-dimethylpyridine (IX; R = H).—Prepared by von Meyer's method,[37] this product had m. p. 232·5—233° (Kofler block) (lit., 222°, 219—220°, 225—228°) (Found: C, 67·7; H, 5·2; N, 26·7. Calc. for $C_9H_9N_3$: C, 67·9; H, 5·7; N, 26·4%), $\nu_{max.}$ 885,

[33] Cf. Poziomek and Melvin, *J. Org. Chem.*, 1961, **26**, 3769.
[34] Benary, *Ber.*, 1918, **51**, 567.
[35] Kirrmann, Goudard, and Chahidzadeh, *Bull. Soc. chim. France*, 1935, 2143.
[36] Klötzer, *Monatsh*, 1956, **87**, 526.
[37] von Meyer, *J. prakt. Chem.*, 1908, **78**, 497.

933, 1024, 1142, 1290, 1320, 1348, 1395, 1448, 1503, 1523, 1609, 1647, 1680, 2206, 2758, 2873, 3146, 3270, 3321, 3450, and 3510 cm.$^{-1}$.

Dehydrogenation of 3,5-*Dicyano*-1,4-*dihydro*-2,6-*dimethylpyridine*.—The dihydro-compound (0·2 g.) was dissolved in a mixture of chloroform (20 ml.) and methanol (5 ml.), diphenylpicrylhydrazyl (0·93 g.) was added and the mixture heated under reflux in nitrogen for 30 min. The colour changed from violet to orange-brown. Light petroleum (250 ml.; b. p. 40—60°) was added and the precipitate of diphenylpicrylhydrazine separated. The solvent was removed from the filtrate, and the residue chromatographed in light petroleum containing a small amount of chloroform on alumina (Spence type H). 1 : 1 Benzene–chloroform as eluant gave a red amorphous product which was sublimed *in vacuo* at 70° to yield 3,5-dicyano-2,6-dimethylpyridine as pale yellow cubes (0·05 g., 25%), m. p. 121° (Kofler block) (lit., 112°, 119—120°). The infrared spectrum of the product showed no NH stretching band but a strong band at 2200 cm.$^{-1}$ (aromatic nitrile). Reduction of the product with lithium aluminium hydride (method of Bohlmann and Bohlmann [38]) yielded the original 1,4-dihydrolutidine, m. p. 230—232°, having infrared and ultraviolet spectra identical with those of the starting product.

3,5-*Dicyano*-1,4-*dihydro*-2,4,6-*trimethylpyridine* (IX; R = Me).—Prepared by von Meyer's method,[37] this product had m. p. 185—187° (Kofler block) (lit., 170°, 184—185°), $\nu_{max.}$ 853, 884, 935, 996, 1291, 1315, 1337, 1395, 1456, 1502, 1522, 1642, 1674, 2206, 2255w, 2881, 2932, 3135, 3261, 3316, and 3449 cm.$^{-1}$.

4-*Chloromethyl*-3,5-*dicyano*-1,4-*dihydro*-2,6-*dimethylpyridine* (IX; R = CH_2Cl).—β-Aminocrotononitrile [27] (29 g.) was treated in benzene (30 ml.), whilst cooled in ice, with 1,2-dichloroethyl ethyl ether (25 ml.). On removal from the ice-bath a vigorous reaction took place. The mixture was kept for 2 hr., then the precipitated yellow solid was separated, washed with ether and water, and fractionally crystallised from aqueous ethanol, yielding two components. The less soluble product formed colourless granules, m. p. 178—180° (lit.,[26] 170°) (Found: C, 58·1; H, 5·4; Cl, 16·8; N, 20·4. $C_{10}H_{10}ClN_3$ requires C, 57·8; H, 4·9; Cl, 17·1; N, 20·25%), and was 4-*chloromethyl*-3,5-*dicyano*-1,4-*dihydro*-2,6-*dimethylpyridine*. It had $\lambda_{max.}$ 216 and 339 mμ (ε 25,200 and 7850), and $\nu_{max.}$ 1280, 1293, 1314, 1327, 1347, 1447, 1500, 1521, 1607, 1643, 1670, 1676, 2205, 3133, 3252, 3311, and 3444 cm.$^{-1}$.

3 4,5-*Tricyano*-4,5-*dihydro*-2,7-*dimethyl*-1H-*azepine* (X).—(i) 4-Chloromethyl-3,5-dicyano-1,4-dihydro-2,6-dimethylpyridine (above; 2·0 g.) and potassium cyanide (2·0 g.) in methanol (25 ml.) were heated on the steam-bath for 45 min. The methanol was removed *in vacuo* and on addition of water an oil was precipitated. The oil soon solidified and was crystallised from ethanol. Only one component (100 mg.) could be isolated: this had m. p. 153—153·5° (Kofler block), and did not correspond to any material isolated by Benary [26] from a similar reaction (Found: C, 66·4; H, 5·25; N, 28·3. $C_{11}H_{10}N_4$ requires C, 66·65; H, 5·1; N, 28·25%). This *tricyano-compound* had $\nu_{max.}$ 881, 936, 1089, 1317, 1398, 1449, 1555, 1560, 1609, 1643, 1654, 2210, 2250, 3079, 3160, 3269, 3343, 3417, and 3520 cm.$^{-1}$ and $\lambda_{max.}$ 215 and 315 mμ (ε 20,800 and 15,000).

(ii) The chloro-compound (492 mg.) was added to a stirred suspension of sodium cyanide (250 mg.) in dimethyl sulphoxide (6 ml.), a green colour being obtained. After 17 hours' stirring, the solution was brown and turbid (sodium chloride). Water was added, a crystalline product being gradually precipitated. This crystallised from aqueous ethanol as colourless prisms, m. p. 153—153·5°, identical with those obtained in the previous experiment.

Rearrangement of 3,4,5-*Tricyano*-4,5-*dihydro*-2,7-*dimethylazepine* (X).—The cyano-compound (X) (22·9 mg.) in ethanol (0·2 ml.), and potassium hydroxide (33·0 mg.) in ethanol (1 ml.), were mixed and heated on a steam-bath for 2 hr. The solvent was removed and water added, crystals separating. These were largely starting material. The mother-liquors, during several days, deposited white needles (2 mg.), m. p. 237—239°, whose infrared and ultraviolet spectra suggested a slightly impure sample of 3,4-dicyano-2,5-dimethylpyrrole (XIII), lit.,[8] m. p. 239°, $\lambda_{max.}$ 249 mμ (log ε 3·78), $\nu_{max.}$ 1540, 1600, 2245, 2430, 2720, 2870, 3180, 3250, and 3460 cm.$^{-1}$ (cf. ref. 7).

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Department of Chemistry, Sir John Cass College, London E.C.3.
Department of Chemistry, University of Nottingham. [*Received, March* 13*th*, 1963.]

[38] Bohlmann and Bohlmann, *Chem. Ber.*, 1953, **86**, 1419.