422. *Experiments towards the Synthesis of Corrins. Part I. The Preparation and Reactions of Some Δ^1-Pyrrolines. A Novel Proline Synthesis.*

By R. Bonnett, V. M. Clark, A. Giddey, and Sir Alexander Todd.

Several Δ^1-pyrrolines have been prepared by cyclisation of γ-amino-carbonyl compounds and by dehydrogenation of pyrrolidines with mercuric acetate. Their reactions with various nucleophiles have been studied. Addition of hydrogen cyanide to Δ^1-pyrrolines unsubstituted in the 2-position gives 2-cyanopyrrolidines which can be hydrolysed to the corresponding proline derivatives.

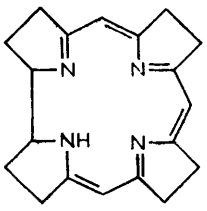
The molecule of vitamin B_{12} contains a planar quadridentate ligand bearing a resemblance to the porphyrins, though at a lower level of oxidation.[1] For the basic ring system (I) of this ligand the name " corrin " has been proposed.[2] This ring system has as yet been found only in the B_{12} group of vitamins and in an endeavour to further our understanding of the vitamin and its mode of action experiments towards the synthesis of corrin derivatives have been initiated and will be reported in this and subsequent papers.

The unit ring system of the corrin nucleus is related to the Δ^1-pyrrolines, about which little is known. This lack of knowledge is doubtless due in part to the difficulty encountered by earlier workers in determining the true position of the double bond in their products. The reduction of pyrroles with zinc in acid solution [3] appears to yield Δ^3-pyrrolines as major products, together with some of the Δ^1-form, though catalytic isomerisation using Raney nickel [4] converts Δ^3- into the Δ^1-isomers. A more widely applicable preparative method has been that based upon the cyclisation of γ-amino-carbonyl compounds.[5] Using this route we have prepared a series of Δ^1-pyrrolines (III, a, b, c). In each case, before reduction of the nitro-group, the carbonyl group was protected as the 1 : 3-dioxolan derivative in order to avoid formation of the corresponding pyrrolidine and Δ^1-pyrroline 1-oxide.[6] The Δ^1-pyrrolines so obtained are colourless volatile liquids having a penetrating and unpleasant odour. They can be readily characterised as their picrates. The infrared spectra of the liquid bases show a strong absorption band, attributable to the C=N stretching mode, appearing near 1650 or 1620 cm.$^{-1}$ depending on whether or not the =C– atom bears an alkyl substituent. Protonation of the azomethine group gives rise to a

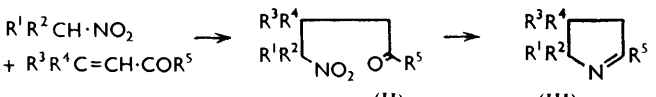
[1] Bonnett, Cannon, Clark, Johnson, Parker, Lester Smith, and Todd, *J.*, 1957, 1158, and references therein cited.
[2] I.U.P.A.C. " Nomenclature of Organic Chemistry, 1957," Butterworths, 1958, p. 85.
[3] Ciamician and Dennstedt, *Ber.*, 1882, **15**, 1831.
[4] Evans, *J. Amer. Chem. Soc.*, 1951, **73**, 5230.
[5] Kohler and Drake, *ibid.*, 1923, **45**, 2144; Cloke, *ibid.*, 1929, **51**, 1174; Rupe and Gisiger, *Helv. Chim. Acta*, 1925, **8**, 338.
[6] Cf. Knott, *J.*, 1948, 186; Kloetzel and Pinkus, *J. Amer. Chem. Soc.*, 1958, **80**, 2332.

hypsochromic shift of approximately 35 cm.$^{-1}$, the band being readily observable with hydrochlorides though not always with picrates where absorption due to the anion tends to be superimposed upon it. In conformity with the Δ^1-formulation the infrared spectra of the free bases show no absorption of an N–H stretching mode and electrometric titration in aqueous solution gives pK_a values of 6·7—7·7, as would be expected of Schiff bases.[7]

In the absence of specific evidence to the contrary, it might be assumed that those pyrrolines formed by the cyclisation of γ-amino-ketones would have been formulated in the existing literature as the Δ^1-isomers. However, both Hielscher [8] and Gabriel [9] assigned



(I)



	R^1	R^2	R^3	R^4	R^5
(a)	Me	Me	H	H	H
(b)	Me	Me	Me	H	H
(c)	H	H	Me	Me	Me

(II) (III)

the Δ^2-structure to such products and Sonn,[10] although expressing the possibility of tautomerism between Δ^1- and Δ^2-forms, formulated the stable product as the Δ^2-isomer. As a result the very existence of Δ^1-pyrrolines was denied in some texts [11] and it is only recently that compelling spectral evidence for the Δ^1-formulation of these reduction products has been presented.[4,12]

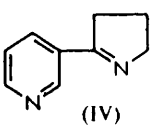
In addition to the above reductive methods it has now proved possible to obtain Δ^1-pyrrolines by dehydrogenation of the corresponding pyrrolidines. The dehydrogenation of tertiary amines has been extensively investigated by using a variety of reagents; [13-18] secondary amines have, however, received much less attention. *N*-Methylbenzylamine has been dehydrogenated with manganese dioxide in chloroform,[19] and evidence for the formation of an azomethine group obtained though the Schiff base was not isolated; the same reagent has been shown to convert *N*-methylaniline into formanilide.[18] Piperidine, on attempted conversion into Δ^1-piperideine, yielded a series of trimers [20] and analogous behaviour in the case of pyrrolidine has been reported.[21]

In the present work we have found that a number of cyclic secondary amines can be dehydrogenated by mercuric acetate in dilute aqueous acetic acid. This reagent, under somewhat milder conditions, has been used by Leonard and his co-workers [14] for the dehydrogenation of cyclic tertiary amines, their conditions being such that secondary amines were unaffected.[22] In our experiments the reaction was conveniently followed by

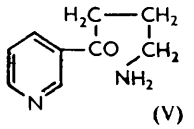
[7] Starr, Bulbrook, and Hixon, *J. Amar. Chem. Soc.*, 1932, **54**, 3971.
[8] Hielscher, *Ber.*, 1898, **31**, 277.
[9] Gabriel and Colman, *Ber.*, 1908, **41**, 513; Gabriel, *ibid.*, 1909, **42**, 1238.
[10] Sonn, *Ber.*, 1935, **68**, 148; 1939, **72**, 2150.
[11] Sidgwick, Taylor, and Baker, " The Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1937, p. 491; Corwin in " Heterocyclic Compounds," ed. Elderfield, Wiley, New York, 1950, Vol. I, p. 339.
[12] Eddy and Eisner, *Analyt. Chem.*, 1954, **26**, 1428; Witkop, *J. Amer. Chem. Soc.*, 1954, **76**, 5597.
[13] Julian and Printy, *ibid.*, 1949, **71**, 3206; Buckley, Dunstan, and Henbest, *J.*, 1957, 4880.
[14] Leonard and Hauck, *J. Amer. Chem. Soc.*, 1957, **79**, 5279, and references therein.
[15] Buckley, Dunstan, and Henbest, *J.*, 1957, 4901.
[16] Dunstan and Henbest, *ibid.*, 4905.
[17] Godtfredsen and Vangedal, *Acta Chem. Scand.*, 1956, **10**, 1414.
[18] Henbest and Thomas, *J.*, 1957, 3032.
[19] Highet and Wildman, *J. Amer. Chem. Soc.*, 1955, **77**, 4399.
[20] Lehmann and Schwaderer, *Ber.*, 1889, **22**, 1318, 1328; Schöpf, Komak, Braun, and Jacobi, *Annalen*, 1948, **559**, 1, and later papers.
[21] Schöpf, F.I.A.T. Review, " Preparative Organic Chemistry," 1948, Part 2, p. 117.
[22] Leonard and Morrow, *J. Amer. Chem. Soc.*, 1958, **80**, 371.

observing the precipitation of mercurous acetate, and the products were examined by gas-chromatography which separated the 2-alkylpyrrolidines clearly from the corresponding Δ^1-pyrrolines: the latter were readily isolated as picrates. In this fashion, 2-methylpyrrolidine, 2 : 5-dimethylpyrrolidine, and 2 : 4 : 4-trimethylpyrrolidine were dehydrogenated, the crude product in each case containing the original base and the corresponding Δ^1-pyrroline in approximate ratio 3 : 2. The nature of the unsaturated products was confirmed by their electrometric titration curves and infrared spectra, and by the mixed melting points of their picrates. In the case of pyrrolidine itself, mercurous acetate was precipitated during the reaction but no new volatile base could be isolated: presumably the product polymerised.[23] 2 : 2-Dimethylpyrrolidine and 2 : 2 : 3-trimethylpyrrolidine were not dehydrogenated under these conditions, whilst 2-methylpiperidine gave a low yield of 2-methylpiperideine. In the pyrrolidine series, not only is a planar *transoid* arrangement unfavourable, but initial mercuration is subject to considerable steric hindrance when an α-position is completely substituted.

The Δ^1-pyrrolines, on the basis of their analyses, infrared spectra, and low basicity, exist in the cyclic form rather than as acyclic γ-amino-carbonyl compounds, although with acylating agents derivatives of the acyclic form are obtained.[9] The tobacco-smoke constituent, myosmine [24] (IV), readily yields carbonyl derivatives [25] although the existence of the amino-ketone poikiline [26] (V) as such is open to question.

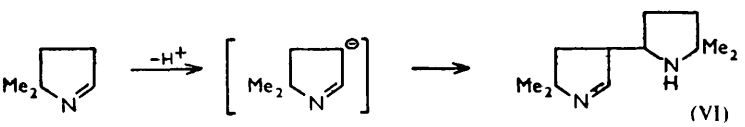


(IV)



(V)

Δ^1-Pyrrolines are slowly reduced by tin and hydrochloric acid and, more rapidly, by lithium aluminium hydride to yield, in each case, the pyrrolidine. The azomethine link is much less susceptible to nucleophilic addition than the carbonyl group, though under acid conditions reactivity is enhanced. Under basic conditions, nitromethane and nitroethane did not react with any of the Δ^1-pyrrolines investigated, nor did addition of the Grignard reagent occur. Previous workers have used the Grignard reagent in attempted Zerewitinow determinations on 2-substituted Δ^1-pyrrolines: the formation of a 1 : 1 complex has been reported [27] and in some instances the pyrroline has been recovered.[27,28]



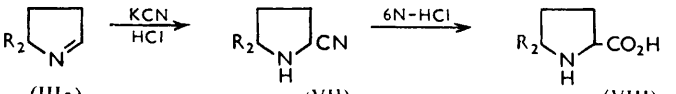
(VI)

In the present work, attempted addition of ethylmagnesium bromide to 2 : 4 : 4-trimethyl-Δ^1-pyrroline led to a trace of high-boiling material and 40% recovery of the base. 5 : 5-Dimethyl-Δ^1-pyrroline behaved differently, and there is evidence that the high-boiling product contained the dimeric compound (VI) formed, probably, as a result of initial abstraction of a proton followed by addition to a second pyrroline molecule.[29]

The addition of cyanide ion to a protonated or quaternised azomethine is well

[23] Fuhlhage and VanderWerf, *J. Amer. Chem. Soc.*, 6249.
[24] Späth, Wenusch, and Zajic, *Ber.*, 1936, **69**, 393; Stein and Burger, *J. Amer. Chem. Soc.*, 1957, **79**, 154.
[25] Haines, Eisner, and Woodward, *ibid.*, 1945, **67**, 1258.
[26] Wenusch and Schöller, quoted by Marion, "The Alkaloids," ed. Manske and Holmes, Academic Press, New York, 1950, Vol. I, p. 256.
[27] Maginnity and Cloke, *J. Amer. Chem. Soc.*, 1951, **73**, 49; Maginnity and Gair, *ibid.*, 1952, **74**, 4958.
[28] Kloetzel, Pinkus, and Washburn, *ibid.*, 1957, **79**, 4222.
[29] Cf. Short and Watt, *J.*, 1930, 2293; Plancher and Ravenna, *Atti R. Accad. Lincei*, 1906, **15**, ii, 555

known [14,30] and it has been found to proceed with Δ^1-pyrrolines in which the 2-position is unsubstituted: for example, 5 : 5-dimethyl-Δ^1-pyrroline readily gave 5-cyano-2 : 2-dimethylpyrrolidine (VII; R = Me) which was reduced by lithium aluminium hydride to the corresponding diamine and hydrolysed with hydrochloric acid to 5 : 5-dimethylproline (VIII; R = Me).



(IIIa) (VII) (VIII)

A similar series of reactions was performed with 4 : 5 : 5-trimethyl-Δ^1-pyrroline although the separation of the various diastereoisomers was not attempted. The formulation of the products follows from the analyses of the nitriles, the prolines, and the salts of the diamines, together with the electrometric titration of the latter.[31]

The addition of hydrogen cyanide to Δ^1-pyrrolines thus provides a novel and convenient route to various substituted prolines, some of which occur naturally.[32] Proline, too, can be made by this method, for on treatment of 4-amino-1 : 1-diethoxybutane with hydrochloric acid and potassium cyanide the amino-nitrile (VII; R = H) was obtained: subsequent hydrolysis then gave proline (VIII; R = H).

Experimental

The organic bases were isolated by adjusting their aqueous solutions to pH 11 with aqueous potassium hydroxide and extracting these solutions continuously with ether for several hours. Drying ($MgSO_4$) of the extract followed. Unless otherwise stated, the picrates were yellow, were prepared in moist ether, and were recrystallised from ethanol or propan-1-ol. Infrared spectra were measured by using Nujol or hexachlorobutadiene mulls or liquid films.

Preparation of Δ^1-Pyrrolines from γ-Nitro-carbonyl Compounds (with Drs. R. F. C. Brown and M. Lamchen).—(a) 5 : 5-*Dimethyl-Δ^1-pyrroline.* 4-Methyl-4-nitropentan-1-al (70 g.; prepared by condensation of 2-nitropropane and acraldehyde in presence of sodium methoxide [33]), dry ethylene glycol (35 g.), and toluene-*p*-sulphonic acid (1 g.) were heated under reflux in benzene (200 ml.), the water produced (9 ml.) being retained in a Dean–Stark trap. The benzene solution was washed with aqueous sodium hydrogen carbonate, dried, and fractionated to give 2-(3-*methyl*-3-*nitrobutyl*)-1 : 3-*dioxolan* (68 g., 75%), b. p. 105°/0·5 mm. (Found: C, 51·0; H, 8·2; N, 7·35. $C_8H_{15}O_4N$ requires C, 50·8; H, 8·0; N, 7·4%). The dioxolan (63 g.) was hydrogenated in methanol (30 ml.) over Raney nickel (5 g.) at room temperature and 115 atm. for 20 hr., the catalyst removed, solvent evaporated, and the residue heated under reflux with 7·5N-hydrochloric acid (65 ml.) for 20 min. The cooled solution was made alkaline with aqueous potassium hydroxide and extracted with ether. Fractionation of the dried extract gave 5 : 5-*dimethyl-Δ^1-pyrroline*, b. p. 104—108° (17 g., 53%), whose infrared spectrum showed peaks at 1621, 1378, and 1361 cm.$^{-1}$. The *hydrochloride*, a hygroscopic solid, exhibited a band at 1655 cm.$^{-1}$. The *picrate* crystallised as yellow prisms (from ethanol–ether), m. p. 120—124° (Found: C, 44·5; H, 4·6; N, 17·1. $C_{12}H_{14}O_7N_4$ requires C, 44·2; H, 4·3; N, 17·2%).

(b) 4 : 5 : 5-*Trimethyl-Δ^1-pyrroline.* 3 : 4-Dimethyl-4-nitropentan-1-al, prepared according to Warner and Moe's instructions,[33] was converted in 63% yield into the 1 : 3-*dioxolan*, b. p. 100°/0·4 mm. (Found: C, 53·5; H, 8·2; N, 7·1. $C_9H_{17}O_4N$ requires C, 53·2; H, 8·4; N, 7·0%). The dioxolan was hydrogenated and hydrolysed, yielding 4 : 5 : 5-*trimethyl-Δ^1-pyrroline*, b. p. 127—130°, in 61% yield (Found: C, 75·2; H, 12·3; N, 12·9. $C_7H_{13}N$ requires C, 75·6; H, 11·8; N, 12·6%). The infrared band of C=N was at 1617 cm.$^{-1}$. The *picrate* formed prisms, m. p. 173° (Found: C, 46·0; H, 4·8; N, 16·6. $C_{13}H_{16}O_7N_4$ requires C, 45·9; H, 4·7; N, 16·5%).

[30] Dornow and Lüpfert, *Chem. Ber.*, 1956, **89**, 2718.
[31] Rometsch, Marxer, and Miescher, *Helv. Chim. Acta*, 1951, **34**, 1611.
[32] Hulme and Arthington, *Nature*, 1954, **174**, 588; Hulme, *ibid.*, 1055; Kenner and Sheppard, *ibid.*, 1958, **181**, 48.
[33] Shechter, Ley, and Zeldin, *J. Amer. Chem. Soc.*, 1952, **74**, 3664; Warner and Moe, *ibid.*, p. 1064.

(c) 2 : 4 : 4-*Trimethyl*-Δ^1-*pyrroline*. 4 : 4-Dimethyl-5-nitropentan-2-one [34] was converted into the corresponding *dioxolan*, b. p. 90°/0·7 mm. (81%) (Found: C, 53·0; H, 8·2; N, 6·9. $C_9H_{17}O_4N$ requires C, 53·2; H, 8·4; N, 7·0%), from which 2 : 4 : 4-*trimethyl*-Δ^1-*pyrroline*, b. p. 126—129°, was prepared in 38% yield. The infrared band of the C=N group was at 1644 cm.$^{-1}$. The *picrate*, needles, m. p. 195°, exhibited a band at 1684 cm.$^{-1}$ (Found: C, 45·8; H, 4·9; N, 16·5. $C_{13}H_{16}O_7N_4$ requires C, 45·9; H, 4·7; N, 16·5%).

Preparation of Pyrrolidines.—(a) 2-*Methylpyrrolidine*. Lævulic acid oxime [35] (50 g.) in methanol (200 ml.) was hydrogenated over Raney nickel (8 g.) in an autoclave at 100°/100 atm. for 2 hr.; after removal of the catalyst, fractionation gave 5-methylpyrrolid-2-one (26 g., 69%), b. p. 135—143°/15 mm. Reduction of this with lithium aluminium hydride [36] yielded 2-methylpyrrolidine (65%), b. p. 92—93°, whose chloroplatinate [37] formed orange needles, m. p. 208°, from aqueous ethanol. Picric acid gave a *picrate–picric acid complex* as orange prisms, m. p. 89°, after recrystallisation from ethanol (Found: C, 37·6, 37·9; H, 3·1, 3·1; N, 18·3, 18·0; equiv., 566, 553. $C_5H_{11}N,2C_6H_3O_7N_3$ requires C, 37·6; H, 3·15; N, 18·1%; equiv., 543. $C_5H_{11}N,C_6H_3O_7N_3$ requires C, 42·2; H, 4·2; N, 17·9%; equiv., 314). This compound is probably identical with that reported [38] as the picrate, m. p. 88·5—89·5°, for which only a nitrogen analysis (N, 17·84%) was given.

(b) 2 : 5-*Dimethylpyrrolidine*. The mixture of Δ^1- and Δ^3-pyrrolines from the reduction of 2 : 5-dimethylpyrrole with zinc and hydrochloric acid was catalytically hydrogenated over platinum oxide to give 2 : 5-dimethylpyrrolidine, b. p. 101—109°, whose picrate formed yellow needles, m. p. 120°. Evans [4] records m. p. 120—121° for the picrate of the *cis*-isomer.

(c) 2 : 2-*Dimethylpyrrolidine*. (i) 5 : 5-Dimethyl-Δ^1-pyrroline (3 g.) was heated under reflux in 6N-hydrochloric acid (40 ml.) with granulated tin (15 g.) for 5 hr. The solution was then made strongly alkaline with aqueous potassium hydroxide and steam-distilled. Ether-extraction of the distillate followed by fractionation of the dried extract gave 2 : 2-dimethylpyrrolidine (0·87 g., 29%), b. p. 102—105°. The picrate [39] formed yellow needles, m. p. 189° after recrystallisation from ethanol.

(ii) To a stirred slurry of lithium aluminium hydride (2 g.) in dry ether (25 ml.) at 0° a solution of 5 : 5-dimethyl-Δ^1-pyrroline (3 g.) in dry ether (25 ml.) was slowly added. The mixture was stirred for 30 min. and then heated under reflux for 3 hr. Excess of hydride was decomposed with saturated aqueous potassium carbonate, and the ether layer separated, washed, dried, and fractionated to give 1·85 g. (60%) of 2 : 2-dimethylpyrrolidine, b. p. 103—106°; the picrate had m. p. 188—189° undepressed on admixture with the specimen prepared as under (i) above.

(d) 2 : 2 : 3-*Trimethylpyrrolidine*. 4 : 5 : 5-Trimethyl-Δ^1-pyrroline was similarly reduced with tin and hydrochloric acid to 2 : 2 : 3-trimethylpyrrolidine (65%), b. p. 128—132°. The *picrate*, yellow needles from ethanol, had m. p. 221° (Found: C, 45·8; H, 5·1; N, 16·5. $C_{13}H_{18}O_7N_4$ requires C, 45·6; H, 5·3; N, 16·4%).

(e) 2 : 4 : 4-*Trimethylpyrrolidine*. (i) Reduction of 2 : 4 : 4-trimethyl-Δ^1-pyrroline by lithium aluminium hydride gave 2 : 4 : 4-*trimethylpyrrolidine*, b. p. 120—124°, in 50% yield. The *picrate* formed yellow prisms, m. p. 162—163°, from ethanol (Found: C, 45·6; H, 5·1; N, 16·6. $C_{13}H_{18}O_7N_4$ requires C, 45·6; H, 5·3; N, 16·4%).

(ii) Reduction of 2 : 4 : 4-trimethyl-Δ^1-pyrroline by tin and hydrochloric acid was slow. After 5 hr., gas chromatography indicated 60% conversion into the pyrrolidine and even after 18 hr. 10% of the pyrroline appeared unreduced.

Dehydrogenation of Pyrrolidines to Δ^1-*Pyrrolines* (cf. ref. 14).—The pyrrolidine (2—5 g.) and mercuric acetate (4 mol.) were heated under reflux in 10% aqueous acetic acid (100 ml.) for 20 hr. Mercurous acetate (sometimes accompanied by free mercury) slowly separated. After removal of the precipitate the filtrate was treated with hydrogen sulphide, again filtered, and excess of hydrogen sulphide removed under reduced pressure. The bases were extracted in the usual way, and a portion of the dried extract examined by gas chromatography (see below). Addition of a moist ethereal solution of picric acid to the bulk of the dried extract gave the

[34] Kloetzel, *J. Amer. Chem. Soc.*, 1947, **69**, 2270.
[35] Müller, *Ber.*, 1883, **16**, 1618.
[36] Cf. Karrer and Erhardt, *Helv. Chim. Acta*, 1951, **34**, 2209.
[37] Fenner and Tafel, *Ber.*, 1898, **31**, 906.
[38] Terentiev and Votadina, *Doklady Akad. Nauk S.S.S.R.*, 1953, **88**, 845.
[39] Cf. Buckley and Elliott, *J.*, 1947, 1508.

pyrroline picrate, the pyrrolidine salts usually remaining in solution. The successful dehydrogenations are summarised in the Table.

Dehydrogenation of cyclic secondary amines.

Pyrrolidine	Picrate, m. p.	Yield (%)	Δ^1-Pyrroline pK_a [b]	Picrate, m. p.	Infrared band of C=NH$^+$ (cm.$^{-1}$)
2-Methyl	89° [a]	25	7·7	121°	1679
2 : 5-Dimethyl	121	30	8·0	135	1673
2 : 4 : 4-Trimethyl	162	47	7·6	195	1684

[a] (1 : 1) Picrate–picric acid complex. [b] Apparent pH recorded at 20° by a Pye glass electrode and meter for a 30% aqueous ethanol solution at the half-neutralisation point. The meter was standardised with aqueous buffer at pH 7.

Although a copious precipitate of mercurous acetate was formed, no low-boiling product was isolable when pyrrolidine itself was investigated. The reaction did not appear to proceed easily with 2 : 2-di- or 2 : 2 : 3-tri-methylpyrrolidine, little or no mercurous acetate being precipitated.

Attempted Addition of Various Nucleophilic Reagents to Δ^1-Pyrrolines.—(a) *Nitroalkanes.* No product was isolated from the interaction of 5 : 5-dimethyl-Δ^1-pyrroline with (i) nitroethane in the presence of sodium methoxide or (ii) nitromethane in the presence of the ion-exchange resin Dowex-2 (hydroxide form).

(b) *Ethylmagnesium bromide.* (i) To a stirred ethereal solution of ethylmagnesium bromide (from 7 g. of ethyl bromide) 5 : 5-dimethyl-Δ^1-pyrroline (4 g.) in dry ether (20 ml.) was added. The mixture rapidly became viscous; after being heated under reflux for 1½ hr. the solution was cooled and 6N-hydrochloric acid (30 ml.) added. Two hours later the mixture was made alkaline with potassium hydroxide and extracted with ether. Fractionation of the extract furnished a viscous liquid (0·9 g.), b. p. 90°/0·5 mm., showing two basic groups, pK_{a_1} 5·4, pK_{a_2} 9·9 on electrometric titration. Further attempts at purification met with no success.

(ii) From an attempt to add ethylmagnesium bromide to 2 : 4 : 4-trimethyl-Δ^1-pyrroline 40% of the starting material was recovered and only a trace of high-boiling material was formed.

Addition of Hydrogen Cyanide to Δ^1-Pyrrolines.—(i) *5-Cyano-2 : 2-dimethylpyrrolidine.* To a stirred solution of potassium cyanide (4·5 g.) and 5 : 5-dimethyl-Δ^1-pyrroline (5 g.) in water (20 ml.) at 0° 2N-hydrochloric acid (50 ml.) was added during 2 hr. The mixture (which had pH 6) was left at room temperature overnight, then made alkaline with potassium hydroxide and extracted with ether. Fractionation of the dried extract gave *5-cyano-2 : 2-dimethylpyrrolidine* (2·84 g., 44%), b. p. 164—166° (Found: C, 67·5; H, 10·0; N, 22·5. $C_7H_{12}N_2$ requires C, 67·7; H, 9·7; N, 22·6%). The infrared spectrum (liquid film) showed peaks at 3310, 2245, 1385, and 1368 cm.$^{-1}$.

Reduction of the nitrile in ether by lithium aluminium hydride gave 5-aminomethyl-2 : 2-dimethylpyrrolidine isolated as the *dipicrate*, yellow needles, m. p. 225° (decomp.) after recrystallisation from ethanol (Found: C, 39·0; H, 4·05; N, 19·3. $C_{19}H_{22}O_{14}N_8$ requires C, 38·9; H, 3·8; N, 19·1%).

(ii) *5-Cyano-2 : 2 : 3-trimethylpyrrolidine.* Addition of hydrogen cyanide to 4 : 5 : 5-trimethyl-Δ^1-pyrroline furnished *5-cyano-2 : 2 : 3-trimethylpyrrolidine* (48%), b. p. 178—180°, presumably as a mixture of diastereoisomers (Found: C, 69·5; H, 10·8; N, 19·4. $C_8H_{14}N_2$ requires C, 69·5; H, 10·2; N, 20·3%). The infrared spectrum (liquid film) showed max. at 3320 and 2240 cm.$^{-1}$. Reduction of this nitrile with lithium aluminium hydride yielded *5-aminomethyl-2 : 2 : 3-trimethylpyrrolidine* (42%), b. p. 192—196°, pK_{a_1} 6·8, pK_{a_2} 10·5 (cf. ref. 31); the *diperchlorate* formed prisms, m. p. 250—254° (decomp.) after recrystallisation from ethanol–ether (Found: C, 28·1; H, 6·0; N, 8·0. $C_8H_{20}O_8N_2Cl_2$ requires C, 28·0; H, 5·9; N, 8·2%). The dipicrate could not be recrystallised to constant m. p.

(iii) Attempted addition of hydrogen cyanide to 2 : 4 : 4-trimethyl-Δ^1-pyrroline led only to a 63% recovery of the starting material.

Preparation of Prolines.—(a) *5 : 5-Dimethylproline.* 5-Cyano-2 : 2-dimethylpyrrolidine (0·95 g.) in 6N-hydrochloric acid (20 ml.) was heated under reflux for 6 hr. Evaporation to dryness under reduced pressure gave a residue which was dissolved in water (10 ml.) and percolated through a column (10 cm. × 1·5 cm.^{2}) of Dowex-1 resin (acetate form). The residue obtained

on evaporation of the eluate was dried *in vacuo* at 90° for 2 hr., and then recrystallised from ethanol–ether (charcoal) to give 5 : 5-*dimethylproline* (0·81 g., 74%) as needles, m. p. 190—195°, raised to 194—196° on further recrystallisation (Found: C, 58·5; H, 9·4; N, 9·8. $C_7H_{13}O_2N$ requires C, 58·7; H, 9·15; N, 9·8%). The infrared spectrum (mull) of the freshly dried material showed maxima at 3420, 3100, 2725, 1620, and 1580 cm.$^{-1}$; on exposure of the material to the atmosphere for 30 min. the maxima moved to 3440, 3360, 3245, 3135, 2725, 2420, 1684, and 1609 cm.$^{-1}$. In paper chromatography, butan-1-ol–acetic acid–water (4 : 1 : 5, upper phase) gave R_F 0·52; phenol saturated with water (hydrogen cyanide atmosphere) gave R_F 0·87. The amino-acid gave no colour on paper when sprayed with isatin; with ninhydrin a purple-brown colour slowly developed during 30 min. at 90°. In alkaline solution, 5 : 5-dimethylproline gave a blue colour with acetaldehyde and sodium nitroprusside.[40]

(b) 4 : 5 : 5-*Trimethylproline*. Hydrolysis of 5-cyano-2 : 2 : 3-trimethylpyrrolidine yielded 4 : 5 : 5-*trimethylproline* (mixture of diastereoisomers?) as rosettes, m. p. 226—228° (from ethanol–ether) (Found: C, 60·8; H, 10·1; N, 8·75. $C_8H_{15}O_2N$ requires C, 61·1; H, 9·6; N, 8·9%). The infrared spectrum had maxima at 3400, 2710, 2465, and 1620 cm.$^{-1}$. On paper chromatography, the R_F value in the butanol system (above) was 0·61; in the phenol system (above) 0·86. Colour reactions with various reagents were similar to those of 5 : 5-dimethylproline.

(c) *Proline*. 2N-Hydrochloric acid (25 ml.) was slowly added at 0° to a stirred mixture of 4-amino-1 : 1-diethoxybutane [41] (3 g.) and potassium cyanide (1·8 g.) in water (15 ml.). The final pH was 2. The mixture was left at room temperature overnight and then a further addition of 2N-hydrochloric acid (10 ml.) was made and the solution warmed to 50° for 20 min. After cooling, the solution was made alkaline with potassium hydroxide solution and extracted with ether. Fractionation of the dried extract gave crude 2-*cyanopyrrolidine* (0·55 g., 29%), b. p. 168—172°. The infrared spectrum (liquid film) had maxima at 3340 and 2250 cm.$^{-1}$; electrometric titration gave an equivalent of 104 (theory, 96). The nitrile was hydrolysed in the usual way to yield proline (69%) as needles, m. p. 208—210° (from ethanol) (Found: C, 52·3; H, 8·0; N, 12·05. Calc. for $C_5H_9O_2N$: C, 52·2; H, 7·9; N, 12·2%). The infrared spectrum of the dry material showed maxima at 3170, 2715, 2402, and 1613 cm.$^{-1}$: after 2 hr. in moist air the maxima appeared at 3500, 3350, 3180, 2710, 2402, 1645, 1609, and 1589 cm.$^{-1}$. Identical values were observed on using an authentic sample of proline. Paper chromatography in the butanol system (above) gave R_F 0·35; and in the phenol system (above) R_F 0·83.

Gas Chromatography of Pyrrolidines and Δ^1-*Pyrrolines*.—Chromatograms were obtained by using a Perkin–Elmer vapour fractometer (Model 154), the column (200 cm. × 0·12 cm.^{2}) being packed with polyethylene glycol (average mol. wt. 400) (1 part) on Silocell (60—70 mesh) (5 parts).

Samples (*ca.* 0·01 ml. of liquid) were applied with nitrogen as the carrier gas at an excess pressure of 12·2 lb./sq. in. At 97°, the uncorrected retention volumes (ml.) were: pyrrolidine, 36; 2-methylpyrrolidine, 34; 2-methyl-Δ^1-pyrroline, 55; 2 : 5-dimethylpyrrolidine, 32; 2 : 5-dimethyl-Δ^1-pyrroline, 60; 2 : 4 : 4-trimethylpyrrolidine, 38; 2 : 4 : 4-trimethyl-Δ^1-pyrroline, 66; 5 : 5-dimethylpyrrolidine, 32; 5 : 5-dimethyl-Δ^1-pyrroline, 34; 2 : 2 : 3-trimethylpyrrolidine, 55; 4 : 5 : 5-trimethyl-Δ^1-pyrroline, 60; ether, 4; acetone, 8·5; benzene, 15; methanol, 17; ethanol, 17; water, 45.

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[40] Cf. Feigl, " Spot Tests, II. Organic Applications," Elsevier, Amsterdam, 1954, p. 189.
[41] *Org. Synth.*, 1931, **11**, 26; Manske, *Canad. J. Res.*, 1931, **5**, 592.