423. *Experiments towards the Synthesis of Corrins. Part II.* The Preparation and Reactions of Δ^1-Pyrroline 1-Oxides.*

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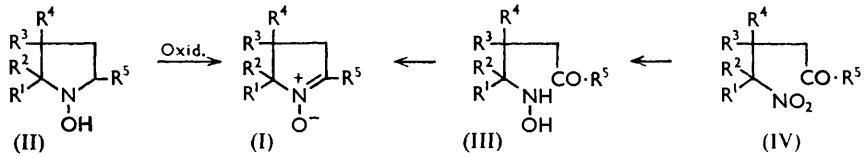
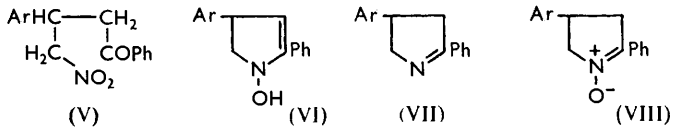
The reduction of γ-nitro-carbonyl compounds to give Δ^1-pyrroline 1-oxides is described and the reactions of several such *N*-oxides are reported.

The corrin nucleus, parent of the macrocyclic component of the vitamin B_{12} molecule, is at an oxidation level between that of the pyrroles and the Δ^1-pyrrolines and, in our synthetical studies in this field, it became apparent that the Δ^1-pyrroline 1-oxides might offer a flexibility in synthesis somewhat greater than the parent Schiff bases.

The Δ^1-pyrroline 1-oxides (I) are cyclic nitrones [1] derivable by oxidation of hydroxylamines [2] (II) or by cyclisation of a γ-hydroxyamino-carbonyl compound (III). As



γ-nitro-aldehydes and ketones (IV) are readily available the generation of Δ^1-pyrroline 1-oxides depends upon the reduction of the nitro- to the hydroxyamino-group. Kohler and Drake in their early work [3] upon the catalytic hydrogenation of 3-(3 : 4-methylenedioxyphenyl)-4-nitro-1-phenylbutan-1-one (V) obtained an oxygenated product to which they assigned the hydroxylated pyrroline structure (VI). Recently, Kloetzel and Pinkus [4] have repeated this work and, using zinc dust and aqueous ammonium chloride, have



Ar = 3 : 4-methylenedioxyphenyl

obtained the pyrroline (VII), but no trace of (VI). In our hands, the zinc dust method has given Kohler and Drake's oxygenated product, to which we now assign the Δ^1-pyrroline 1-oxide formulation (VIII).

The use of zinc dust in cold aqueous ammonium chloride has proved of general utility in the reduction of γ-nitro-carbonyl compounds to the Δ^1-pyrroline 1-oxides though, on occasion, the carbonyl function has to be protected as an acetal. Thus, reduction of 4 : 4-dimethyl-5-nitropentan-2-one [5] (IV; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$) gave 2 : 4 : 4-trimethyl-Δ^1-pyrroline 1-oxide (I; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$) in 75% yield, and 3 : 4-dimethyl-4-nitropentanal gave 51% of the 4 : 5 : 5-trimethylpyrroline oxide. 4-Methyl-4-nitropentanal (IV; $R^3 = R^4 = R^5 = H$; $R^1 = R^2 = Me$), however, gave only a low yield of the pyrroline 1-oxide, and the required 5 : 5-dimethyl-Δ^1-pyrroline 1-oxide (I; $R^3 = R^4 = R^5 = H$; $R^1 = R^2 = Me$) was subsequently obtained by reduction of the nitro-aldehyde diethyl acetal to the corresponding hydroxylamine followed by hydrolysis

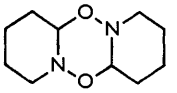
* Part I, preceding paper.

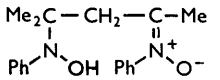
[1] Smith, *Chem. Rev.*, 1938, **23**, 193.
[2] Cf. Rupe and Wittwer, *Helv. Chim. Acta*, 1922, **5**, 217; Utzinger, *Annalen*, 1944, **556**, 50; Thesing, *Chem. Ber.*, 1954, **87**, 507.
[3] Kohler and Drake, *J. Amer. Chem. Soc.*, 1923, **45**, 2144.
[4] Kloetzel and Pinkus, *ibid.*, 1958, **80**, 2332.
[5] Kloetzel, *ibid.*, 1947, **69**, 2271.

of the protecting acetal group. 5-Ethoxycarbonyl-5-methyl-Δ^1-pyrroline 1-oxide was prepared from the ethylene acetal of 4-ethoxycarbonyl-4-nitropentanal by a similar method.

The *N*-oxides were extremely hygroscopic oils whose satisfactory analysis proved difficult but, being weakly basic, they were readily characterised as picrates. Each showed a single ultraviolet absorption maximum, at 229—235 mμ (ε ~9000), attributable to the $>C=^{+}N-O^{-}$ chromophore. This group exhibited strong infrared absorption, the frequency ranging from 1600 to 1620 cm.$^{-1}$ for those compounds bearing a 2-alkyl substituent and from 1570 to 1590 cm.$^{-1}$ when no such substituent was present (*i.e.*, I; $R^5 = H$).

These Δ^1-pyrroline 1-oxides are the first monomeric non-aromatic nitrones to be reported,[6] their formation being closely parallel to that of the amino-Δ^1-pyrroline 1-oxide (I; $R^1 = R^2 = Me$, $R^3 = R^4 = H$, $R^5 = NH_2$) resulting from the reduction of 3-methyl-3-nitrobutyl cyanide.[7] The aliphatic and alicyclic nitrones so far reported have generally been obtained as dimers; thus, oxidation of 1-hydroxypiperidine does not give the expected cyclic nitrone but a product to which the dimeric structure (IX) has been assigned.[8] In other cases aldol-type dimers are formed; acetone and phenylhydroxylamine give the dimer (X),[9] and the condensation product of *n*-butyraldehyde and phenylhydroxylamine has been reported [10] to be of the same type. The condensation product of formaldehyde and phenylhydroxylamine dimerises in yet another manner [11] which will be considered in a subsequent paper.

(IX) 


(X)

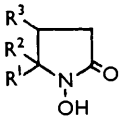
The ease of preparation of the Δ^1-pyrroline 1-oxides and their relative stability has afforded an opportunity to examine their reactions in some detail. The analogy between the $>C=^{-}N-O^{-}$ group and the carbonyl group is striking and well known in the aryl-substituted nitrones where addition of nucleophilic reagents, *e.g.*, phenylhydrazine or semicarbazide, has often led to a derivative of the parent carbonyl compound with loss of the hydroxyamino-residue.[12] With the Δ^1-pyrroline 1-oxides addition of cyanide ion, a Grignard reagent, or the anion of a nitroalkane proceeds smoothly; moreover, activation of an α-methyl group (*e.g.*, in the condensation with an aldehyde under basic conditions) is readily observed. Reactions depending on the back-polarisation of the system $>C=^{+}N-O^{-} \longleftrightarrow >C^{-}-^{+}N=O$ will be discussed in a later paper.

Δ^1-Pyrroline 1-oxides (I) were readily reduced to the cyclic secondary hydroxylamines (II) by aqueous potassium borohydride. These hydroxylamines, on treatment with toluene-*p*-sulphonyl chloride and triethylamine in ether, afforded Δ^1-pyrrolines in moderate yield (30—40%), presumably through the elimination of toluene-*p*-sulphonic acid from an intermediate *O*-toluene-*p*-sulphonyl compound in a manner analogous to that by which Schöpf obtained Δ^1-piperideine derivatives from 1-chloropiperidine.[13] In the examples studied the direction of elimination followed the Saytzeff rule. Reduction of (I; $R^1 = R^2 = H$; $R^3 = R^4 = R^5 = Me$) by zinc and acetic acid gave the pyrroline, but tin and hydrochloric acid brought about further reduction to the pyrrolidine. Treating a Δ^1-pyrroline 1-oxide with a solution of sulphur dioxide in chloroform also gave a small yield of the pyrroline.

[6] Brown, Clark, and Todd, *Proc. Chem. Soc.*, 1957, 97.
[7] Buckley and Elliott, *J.*, 1947, 1508.
[8] Thesing and Mayer, *Chem. Ber.*, 1956, **89**, 2159.
[9] Banfield and Kenyon, *J.*, 1926, 1612.
[10] Utzinger and Regenass, *Helv. Chim. Acta*, 1954, **37**, 1892.
[11] Bamberger, *Ber.*, 1900, **33**, 941; Hellmann and Teichmann, *Chem. Ber.*, 1956, **89**, 1134.
[12] Staudinger and Miescher, *Helv. Chim. Acta*, 1919, **2**, 554; Kröhnke and Börner, *Ber.*, 1936, **69**, 2006.
[13] Schöpf, Komak, Braun, and Jacobi, *Annalen*, 1948, **559**, 1.

Addition of Grignard reagents to nitrones [14] proceeds smoothly with the dimeric tetrahydropyridine 1-oxide (IX), and the Δ^1-pyrroline 1-oxides (I; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$; and $R^1 = R^2 = Me$, $R^3 = R^4 = R^5 = H$) behaved similarly, giving the 2-alkyl cyclic hydroxylamines in high yield. Copper-catalysed aerial oxidation in alkaline solution [15] converted these 1-hydroxypyrrolidines into Δ^1-pyrroline 1-oxides once again. Re-oxidation, under these conditions, of the cyclic hydroxylamine (II; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$) gave the pyrroline oxide (I; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$), *i.e.*, the product with the more highly substituted nitrone grouping was formed.

Those Δ^1-pyrroline 1-oxides unsubstituted at position 2, *i.e.*, where $R^5 = H$, with hydrogen cyanide in aqueous solution gave 2-cyano-1-hydroxypyrrolidines, analogous to cyanohydrins. The cyano-hydroxypyrrolidines (II; $R^1 = R^2 = Me$, $R^3 = R^4 = H$, $R^5 = CN$; and $R^1 = R^2 = R^3 = Me$, $R^4 = H$, $R^5 = CN$) underwent copper-catalysed aerial oxidation in alkaline solution to the 2-cyano-Δ^1-pyrroline 1-oxides which, on alkaline hydrolysis, gave the expected 2-carboxylic acids together with the cyclic hydroxamic acids (XI). The latter presumably arise through replacement of cyanide by hydroxyl as in the alkaline hydrolysis of acyl cyanides. The structure of the cyclic hydroxamic acid (XI; $R^1 = R^2 = Me$, $R^3 = H$) was confirmed by its synthesis from methyl 4-methyl-4-nitropentanoate by reduction with zinc in ammonium chloride solution.



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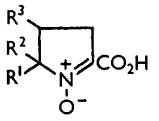

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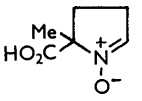
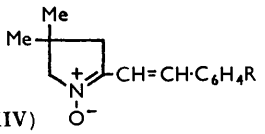


(XIII)

The 2-carboxy-Δ^1-pyrroline 1-oxides (XII; $R^1 = R^2 = Me$, $R^3 = H$; and $R^1 = R^2 = R^3 = Me$) were decarboxylated above 140° to the pyrroline oxides; the 5-carboxylic acid (XIII) decomposed at the same temperature but gave no identifiable product.

Base-catalysed addition of nitroalkanes to a carbonyl group yields β-nitro-alcohols: as expected, addition of nitromethane and nitroethane to a Δ^1-pyrroline 1-oxide gave the β-nitro-hydroxylamines. However, the pyrroline oxides themselves can yield carbanions in the presence of bases (cf. ref. 10), and the oxide (I; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$) underwent base-catalysed condensation with benzaldehyde and *p*-nitrobenzaldehyde to give crystalline monobenzylidene derivatives. Of the possible structures (XIV) and (XV), formulation (XIV) is preferred since the infrared spectrum of the benzylidene



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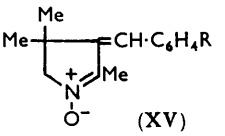


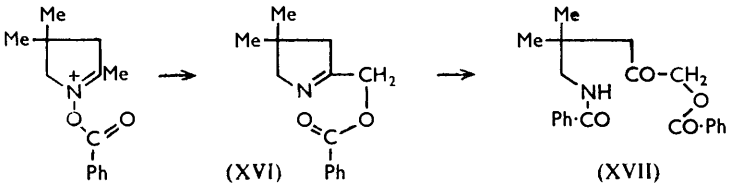
(XV)

derivative (R = H) showed a strong band at 977 $cm.^{-1}$ indicative of a *trans*-disubstituted ethylene rather than a trisubstituted ethylene.[16] Furthermore, Δ^1-pyrroline 1-oxides having no 2-methyl group failed to condense with *p*-nitrobenzaldehyde under the same conditions; and so did the ethyl analogue (I; $R^1 = R^2 = Me$, $R^3 = R^4 = H$, $R^5 = Et$).

Although nitrones give addition products with phenyl *iso*cyanate [12,17] and are weakly basic, attempted acylation of the Δ^1-pyrroline 1-oxides leads to rearrangement. Benzoylation of the oxide (I; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$) under Schotten–Baumann conditions gave a crystalline product, $C_{21}H_{23}O_4N$, containing two benzoyl residues and a

[14] Angeli, Alessandri, and Aiazzi-Mancini, *Atti R. Accad. Lincei*, 1911, **20**, i, 546.
[15] Johnson, Rogers, and Trappe, *J.*, 1956, 1093.
[16] Bellamy, " The Infrared Spectra of Complex Molecules," Methuen, London, Second Edition, 1958, p. 45.
[17] Goldschmidt and Kjellin, *Ber.*, 1891, **24**, 2808.

carbonyl group which readily gave rise to a 2 : 4-dinitrophenylhydrazone. The presence of strong bands at 3360, 1637, and 1547 cm.$^{-1}$ in the infrared spectrum showed that one benzoyl group was present in a secondary amide, and a strong band at 1718 cm.$^{-1}$ could be assigned to the carbonyl group of a benzoate or an aliphatic carbonyl group or both. On this evidence we assign structure (XVII) to the compound. Its formation involves an



acyl migration formally analogous to that in the formation of 2-benzoyloxymethylquinoline on benzoylation of quinaldine *N*-oxide.[18] In the present case the rearrangement probably proceeds through a cyclic transition state to give the intermediate pyrroline (XVI) which then undergoes ring-fission and benzoylation.

Experimental

2 : 4 : 4-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide*.—4 : 4-Dimethyl-5-nitropentan-2-one [5] (33·0 g.) and ammonium chloride (9 g.) in water (250 ml.) were stirred vigorously with ice-cooling whilst zinc dust (45 g.) was added during 2 hr. Stirring was continued for a further 2 hr., the mixture filtered, and the filter cake washed with warm water (4 × 50 ml.). The filtrate and washings were combined and evaporated below 60° to a thick syrup which was dissolved in chloroform (75 ml.). This solution was dried (Na_2SO_4) and evaporated and the residue distilled to give 2 : 4 : 4-*trimethyl*-Δ^1-*pyrroline* 1-*oxide* (19·8 g., 75%) as a colourless hygroscopic oil, b. p. 72°/0·4 mm. (Found: C, 64·8; H, 10·6. $C_7H_{13}ON$ requires C, 66·1; H, 10·3%), $\nu_{max.}$ (liquid film) 1613 cm.$^{-1}$, $\lambda_{max.}$ (in 95% ethanol) 229 mμ (ε 9000). The *picrate* formed lemon-yellow needles, m. p. 111°, from ethanol (Found: C, 44·0; H, 4·5; N, 15·3. $C_{13}H_{16}O_8N_4$ requires C, 43·8; H, 4·5; N, 15·7%). Dissolution of the nitrone in excess of methyl iodide gave, overnight, the *methiodide* as off-white, light-sensitive prisms, having m. p. 106° (decomp.) on recrystallisation from ethanol–ether (Found: C, 35·6; H, 5·8; N, 5·2. $C_8H_{16}ONI$ requires C, 35·7; H, 6·0; N, 5·2%).

4 : 5 : 5-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide*.—Freshly distilled crotonaldehyde (17·5 g.) in anhydrous methanol (25 ml.) was added dropwise to a solution of 2-nitropropane (25 g.) in anhydrous methanol (40 ml.) containing sodium methoxide (from 1 g. of sodium), the temperature being kept at 60°. After being stirred for 3 hr. the solution was left overnight. Acetic acid (3 ml.) was added, the methanol evaporated, and the residue poured into water. The product was extracted with ether, the extract washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated, and the residue distilled, yielding 3 : 4-*dimethyl*-4-*nitropentanal* (20·4 g., 51%), b. p. 80°/0·5 mm. (Found: C, 53·2; H, 8·2; N, 8·4. $C_7H_{13}O_3N$ requires C, 52·8; H, 8·2; N, 8·8%). Its *semicarbazone* formed leaflets, m. p. 150—151°, from aqueous ethanol (Found: C, 44·7; H, 7·3. $C_8H_{16}O_3N_4$ requires C, 44·4; H, 7·5%).

Reduction of this pentanal (60 g.) with zinc dust (74 g.) and ammonium chloride (15 g.) in water (400 ml.) gave 4 : 5 : 5-trimethyl-Δ^1-pyrroline 1-oxide (24·3 g., 51%), b. p. 85°/1 mm., $\lambda_{max.}$ 234 mμ (ε 8800) in 95% ethanol, $\nu_{max.}$ (liquid film) 1572 cm.$^{-1}$. The *picrate* formed lemon-yellow laths, m. p. 112°, from ethanol (Found: C, 44·1; H, 4·7; N, 15·4. $C_{13}H_{16}O_8N_4$ requires C, 43·8; H, 4·5; N, 15·7%).

5 : 5-*Dimethyl*-Δ^1-*pyrroline* 1-*Oxide*.—2-(3-Methyl-3-nitrobutyl)-1 : 3-dioxolan [19] (50 g.) and ammonium chloride (15 g.) in water (300 ml.) at 10° were rapidly stirred whilst zinc dust (70 g.) was added during 20 min., ice being introduced to keep the temperature below 15°. The mixture was stirred for 15 min., then filtered, and the filter cake washed with hot water (70°) (5 × 35 ml.). The combined filtrate and washings were acidified with concentrated hydrochloric acid (40 ml.), left overnight, and then heated to 75° for 1 hr. before being evaporated at >60° to 150 ml., made alkaline, and reduced in bulk to 100 ml. After saturation with borax

[18] Pachter, *J. Amer. Chem. Soc.*, 1953, **75**, 3026.
[19] Bonnett, Clark, Giddey, and Todd, preceding paper.

the solution was extracted with chloroform (6 × 75 ml.), and the extract dried (Na_2SO_4) and fractionated to yield 5 : 5-dimethyl-Δ^1-pyrroline 1-oxide (23·6 g., 79%), b. p. 66—67°/0·6 mm., hygroscopic, $\lambda_{max.}$ 234 mμ (ε 7700) in 95% ethanol, $\nu_{max.}$ (liquid film) 1573 cm.$^{-1}$. The *picrate* crystallised from ethanol in yellow needles, m. p. 81° (Found: C, 41·7; H, 4·2; N, 16·1%; equiv. of base, 115. $C_{12}H_{14}O_8N_4$ requires C, 42·1; H, 4·1; N, 16·4%; equiv. of base, 113). Reduction of 4-methyl-4-nitropentanal with zinc dust and ammonium chloride gave the pyrroline 1-oxide (27%) and a high-boiling residue.

4-(3 : 4-*Methylenedioxyphenyl*)-2-*phenyl*-Δ^1-*pyrroline* 1-*Oxide*.—3-(3 : 4-Methylenedioxyphenyl)-4-nitro-1-phenylbutan-1-one [3] (V) (3·13 g.) and ammonium chloride (0·50 g.) in 1 : 3 v/v aqueous tetrahydrofuran (40 ml.) were stirred vigorously whilst zinc dust (3·9 g., 6 g.-atoms) was added during 1 hr. at ≯5—10°. After filtration and washing with hot methanol (50 ml.) the combined filtrate and washings were evaporated to a gum which was distributed between 5N-hydrochloric acid and ether. The aqueous acid layer was made alkaline and extracted with methylene chloride (4 × 10 ml.). Adding ether to the extract afforded 4-(3 : 4-*methylenedioxyphenyl*)-2-*phenyl*-Δ^1-*pyrroline* 1-*oxide* as needles (1·12 g., 40%), m. p. 145° (corr.) after recrystallisation from methylene chloride–ether (Found: C, 73·6; H, 5·4; N, 5·1. $C_{17}H_{15}O_3N$ requires C, 72·6; H, 5·4; N, 5·0%), $\nu_{max.}$ (mull) 1613 cm.$^{-1}$ (aryl-conjugated nitrone).

Reduction of the pyrroline 1-oxide (300 mg.) with zinc dust (1·2 g.) and ammonium chloride (0·3 g.) in 60% aqueous methanol (30 ml.) at room temperature for 8 hr. gave 4-(3 : 4-methylenedioxyphenyl)-2-phenyl-Δ^1-pyrroline,[4] isolated as the hydrochloride (200 mg., 62%), m. p. 235—240° (decomp.). The $\rangle C{=}^{+}N-$ group in this product provided an infrared maximum at 1660 cm.$^{-1}$.

Ethyl 2-*Methyl*-2-*nitro*-5-*oxopentanoate*.—Acraldehyde (14 ml.) was added to a stirred solution of ethyl α-nitropropionate [20] (36 g.) in ethanol (200 ml.) containing sodium ethoxide (from 0·3 g. of sodium), and the mixture maintained at 40—50° for 3 hr. Acetic acid (1 ml.) was added, the solvent evaporated, and the product isolated by extraction with benzene. Distillation gave the *aldehydo-ester* (31·5 g., 65%), b. p. 107°/0·5 mm. (Found: C, 47·2; H, 6·5; N, 7·2. $C_8H_{13}O_5N$ requires C, 47·3; H, 6·5; N, 6·9%). The 2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 75—76°, from ethanol (Found: C, 43·7; H, 4·5; N, 18·3. $C_{14}H_{17}O_8N_5$ requires C, 43·9; H, 4·5; N, 18·3%). The 1 : 3-*dioxolan* was prepared in 78% yield from the nitro-aldehyde and ethylene glycol in the presence of toluene-*p*-sulphonic acid. Fractionation gave an oil, b. p. 121—125°/0·5 mm. (Found: C, 48·6; H, 6·7; N, 5·9. $C_{10}H_{17}O_6N$ requires C, 48·6; H, 6·9; N, 5·7%).

5-*Carboxy*-5-*methyl*-Δ^1-*pyrroline* 1-*Oxide*.—The above dioxolan (28·5 g.) was reduced with zinc dust (41·5 g.) in 50% aqueous ethanol (200 ml.) containing ammonium chloride (5·5 g.). After removal of the excess of zinc and zinc oxide, the solution was concentrated to 50 ml. and extracted with chloroform (4 × 50 ml.). Evaporation of the dried (Na_2SO_4) chloroform solution gave the crude *hydroxylamine* (26 g.); molecular distillation (140—155°/0·3 mm.) of a small sample gave a viscous oil (Found: C, 51·2; H, 8·2; N, 6·0. $C_{10}H_{19}O_5N$ requires C, 51·5; H, 8·2; N, 6·0%). The hydroxylamine (25·5 g.) was dissolved in 0·3N-hydrochloric acid (400 ml.) and left overnight at room temperature. After neutralisation with ammonia the aqueous solution was evaporated below 60° and the residue extracted with chloroform. Fractionation of the dried (Na_2SO_4) extract gave 5-*ethoxycarbonyl*-5-*methyl*-Δ^1-*pyrroline* 1-*oxide* (11·6 g., 60%), b. p. 120°/0·3 mm. (Found: C, 53·6; H, 8·2; N, 7·5. Calc. for $C_8H_{13}O_3N$: C, 56·1; H, 7·7; N, 8·2. $C_8H_{13}O_3N,\frac{1}{2}H_2O$ requires C, 53·3; H, 7·8; N, 7·8%), $\nu_{max.}$ (liquid film) 1740 and 1585 cm.$^{-1}$. Treatment of the pyrroline 1-oxide ester (2·13 g.) with 2·5% aqueous sodium hydroxide (20 ml.) at 100° for 1 hr. followed by passage of the solution through a column of Dowex 50 (H^+ form) and evaporation of the acidic eluate gave 5-*carboxy*-5-*methyl*-Δ^1-*pyrroline* 1-*oxide* (1·37 g., 77%) as needles, m. p. 135—136° (decomp.) (from chloroform) (Found: C, 50·4; H, 6·5; N, 10·0%; equiv., 141. $C_6H_9O_3N$ requires C, 50·3; H, 6·3; N, 9·8%; equiv., 143). Titration in aqueous solution indicated an apparent pK_a 2·95. $\lambda_{max.}$ in 95% ethanol was at 235—236 mμ (ε 7700).

Reduction of Δ^1-*Pyrroline* 1-*Oxides with Potassium Borohydride*.—(i) 1-*Hydroxy*-2 : 4 : 4-*trimethylpyrrolidine*. Potassium borohydride (0·4 g.) and 2 : 4 : 4-trimethyl-Δ^1-pyrroline 1-oxide (2·5 g.) in water (10 ml.) were kept at room temperature for 2 days, then saturated with potassium carbonate, and the product was extracted with ether. The dried (K_2CO_3) extract was evaporated and the residue fractionated to give the crude *hydroxylamine* (0·86 g.), b. p.

[20] Kornblum, Blackwood, and Powers, *J. Amer. Chem. Soc.*, 1957, **79**, 2507.

95—100°/25 mm. Addition of anhydrous oxalic acid in acetone gave the *hydrogen oxalate*, needles, m. p. 88° (from acetone–ether) (Found: C, 49·2; H, 7·5; N, 6·5. $C_9H_{17}O_5N$ requires C, 49·3; H, 7·8; N, 6·4%). Both the free base and the salt readily reduced aqueous alkaline triphenyltetrazolium chloride to the red formazan.[21]

The base (0·5 g.) in water (10 ml.) containing ammonia (1 ml.; *d* 0·880) and copper sulphate (5 mg.) was re-oxidised to the pyrroline 1-oxide by bubbling air through the solution for 2 hr. The nitrone, isolated as previously described, was treated with an excess of ethanolic picric acid to yield the picrate of 2 : 4 : 4-trimethyl-Δ^1-pyrroline 1-oxide as lemon-yellow needles, m. p. and mixed m. p. 111°.

(ii) 1-*Hydroxy*-2 : 2 : 3-*trimethylpyrrolidine*. Reduction of 4 : 5 : 5-trimethyl-Δ^1-pyrroline 1-oxide (0·63 g.) with potassium borohydride (0·2 g.) in water (10 ml.) followed by isolation of the cyclic hydroxylamine as described above gave the crude base; addition of ethanolic hydrogen chloride gave 1-*hydroxy*-2 : 2 : 3-*trimethylpyrrolidine hydrochloride* as prisms, m. p. 163° (from thanol–ether) (Found: C, 50·7; H, 9·6; N, 8·6%; equiv., 169. $C_7H_{16}ONCl$ requires C, 50·8; H, 9·7; N, 8·5%; equiv., 166). Titration in aqueous solution indicated an apparent pK_a 5·9. The base readily reduced aqueous alkaline triphenyltetrazolium chloride.

Other Reductions of Δ^1-*Pyrroline* 1-*Oxides*.—(a) *With zinc and acetic acid*. 2 : 4 : 4-Trimethyl-Δ^1-pyrroline 1-oxide (0·5 g.), zinc dust (5 g.), acetic acid (2 ml.), and water 8 ml.) were heated under reflux for 5 hr. after which more acetic acid (2 ml.) was added and heating continued for a further 20 hr. The solution was made alkaline with aqueous sodium hydroxide and steam-distilled. Neutralisation of the distillate with picric acid, evaporation to dryness below 60°, and recrystallisation of the residue from ethanol gave 2 : 4 : 4-trimethyl-Δ^1-pyrrolinium picrate (0·88 g., 66%) as yellow needles, m. p. 192—193°, undepressed in admixture with an authentic specimen.[19]

(b) *With sulphur dioxide*. In 12 hr. at room temperature in chloroform saturated with sulphur dioxide, 2 : 4 : 4-trimethyl-Δ^1-pyrroline 1-oxide was reduced to the corresponding pyrroline, isolated as its picrate, in 15% yield.

(c) *With tin and hydrochloric acid*. 2 : 4 : 4-Trimethyl-Δ^1-pyrroline 1-oxide (0·5 g.), granulated tin (4 g.), concentrated hydrochloric acid (5 ml.), and water (5 ml.) were heated under reflux for 20 hr. after which working up as in (a) gave 2 : 4 : 4-trimethyl-Δ^1-pyrrolinium picrate (0·13 g.), needles, m. p. 192° undepressed on admixture with an authentic specimen.[19] The picrate mother-liquors were treated with charcoal, filtered, and concentrated. On cooling, clusters of yellow needles of 2 : 4 : 4-trimethylpyrrolidinium picrate appeared (0·32 g.), m. p. 162° undepressed in admixture with an authentic specimen [19] (Found: C, 45·8; H, 5·7; N, 16·6. Calc. for $C_{13}H_{18}O_7N_4$: C, 45·6; H, 5·3; N, 16·4%).

Dehydration of 1-*Hydroxypyrrolidines by Toluene*-p-*sulphonyl Chloride and Triethylamine*.—(a) 2 : 4 : 4-*Trimethyl*-Δ^1-*pyrroline*. 1-Hydroxy-2 : 4 : 4-trimethylpyrrolidine (0·63 g.) and toluene-*p*-sulphonyl chloride (0·92 g., 1 mol.) in anhydrous ether (10 ml.) were treated with triethylamine (0·98 g., 2 mols.) in ether (5 ml.) whereupon a white precipitate was formed. After being left overnight at room temperature the triethylammonium salts (1·7 g.) were filtered off and the filtrate was extracted with dilute hydrochloric acid. The acid extract was made alkaline with aqueous sodium hydroxide and saturated with potassium carbonate, and the amines were extracted with ether. Gas chromatography (cf. ref. 19) of a sample of this ethereal solution indicated that the main product was 2 : 4 : 4-trimethyl-Δ^1-pyrroline contaminated with a little triethylamine. Addition of excess of ethanolic picric acid gave the pyrrolinium picrate (0·55 g., 33%) as yellow needles, m. p. and mixed m. p. 192°.

(b) 4 : 5 : 5-*Trimethyl*-Δ^1-*pyrroline*. 1-Hydroxy-2 : 2 : 3-trimethylpyrrolidine (1·10 g.) and toluene-*p*-sulphonyl chloride (1·55 g., 1 mol.) in anhydrous ether (15 ml.) were treated with triethylamine (1·64 g., 2 mols.) in ether (5 ml.), kept overnight, and worked up as in the preceding experiment, to give an ethereal solution of the crude bases. These were transferred to water by using dilute sulphuric acid followed by addition of barium carbonate and filtration. The aqueous solution (30 ml.) was applied to a column (10 cm. × 3 cm.^{2}) of Amberlite IRC-50 resin (ammonium form) and eluted with water (200 ml.). Neutralisation of the eluate with hydrochloric acid, evaporation to dryness, dissolution in aqueous sodium hydroxide, extraction with ether, and addition of ethanolic picric acid led to 4 : 5 : 5-trimethyl-Δ^1-pyrrolinium picrate (1·08 g., 31%), yellow prisms (from acetone–ether), m. p. and mixed m. p. 172° (cf. ref. 19) (Found: C, 45·9; H, 4·7. Calc. for $C_{13}H_{16}O_7N_4$: C, 45·9; H, 4·7%).

[21] Cf. Snow, *J.*, 1954, 2588.

Addition of Hydrogen Cyanide to Δ^1*-Pyrroline* 1*-Oxides.*—(a) 5*-Cyano*-1*-hydroxy*-2 : 2*-dimethylpyrrolidine.* 2N-Hydrochloric acid (25 ml.) was added during 1½ hr. to a stirred solution of 5 : 5-dimethyl-Δ^1-pyrroline 1-oxide (5·0 g.) and potassium cyanide (3·9 g.) in water (20 ml.) at 0°. A white solid was precipitated. After a further 2 hr. the mixture was brought to pH 11 and continuously extracted with ether. Addition of light petroleum (b. p. 40—60°) to the extract gave 2*-cyano*-1*-hydroxy*-5 : 5*-dimethylpyrrolidine* (4·8 g., 78%), prisms, m. p. 92° (from ether–light petroleum) (Found: C, 60·2; H, 8·9; N, 20·0. $C_7H_{12}ON_2$ requires C, 60·0; H, 8·6; N, 20·0%), $\nu_{max.}$ (mull) 3230 and 2240 cm.$^{-1}$.

The above cyano-hydroxylamine (8·1 g.) and copper acetate (1·5 g.) in 60% aqueous ethanol (100 ml.) containing ammonia (5 ml.; *d* 0·880) were aerated until a permanent blue colour was restored. Concentration to 30 ml., extraction with chloroform, and fractionation of the extract gave 2*-cyano*-5 : 5*-dimethyl*-Δ^1*-pyrroline* 1*-oxide* (5·8 g., 73%), b. p. 110°/0·5 mm. (Found: C, 60·8; H, 7·5; N, 20·1. $C_7H_{10}ON_2$ requires C, 60·9; H, 7·3; N, 20·3%), $\nu_{max.}$ (liquid film) 2220 and 1540 cm.$^{-1}$, $\lambda_{max.}$ (in 95% ethanol) 271 mμ (ε 10,700).

(b) 2*-Cyano*-1*-hydroxy*-4 : 5 : 5*-trimethylpyrrolidine.* Treatment of 4 : 5 : 5-trimethyl-Δ^1-pyrroline 1-oxide with hydrochloric acid and potassium cyanide as above yielded 2*-cyano*-1*-hydroxy*-4 : 5 : 5*-trimethylpyrrolidine* (66%), needles, m. p. 109° (from ether–light petroleum) (Found: C, 62·3; H, 9·3; N, 18·1. $C_8H_{14}ON_2$ requires C, 62·3; H, 9·1; N, 18·2%), $\nu_{max.}$ (mull) 3360, 3290, 2270, and 2240 cm.$^{-1}$. Copper-catalysed aerial oxidation gave 2*-cyano*-4 : 5 : 5*-trimethyl*-Δ^1*-pyrroline* 1*-oxide* (76%) as plates, m. p. 86—87°, from ethyl acetate–light petroleum (Found: C, 63·1; H, 7·8; N, 18·3. $C_8H_{12}ON_2$ requires C, 63·1; H, 8·0; N, 18·4%), $\nu_{max.}$ (mull) 2210 and 1528 cm.$^{-1}$, $\lambda_{max.}$ (in 95% ethanol) 273 mμ (ε 11,100).

(c) 5*-Cyano*-1*-hydroxy*-2*-methylpyrrolidine*-2*-carboxylic acid.* 5-Carboxy-5-methyl-Δ^1-pyrroline 1-oxide (0·80 g.) and potassium cyanide (0·37 g.) were dissolved in water (10 ml.) and left at room temperature for 6 hr. The solution was then passed through a column of Dowex 50 resin (H^+ form), and the acidic eluate evaporated. The *acid* product (0·75 g.) formed needles, m. p. 133—134° (decomp.), from ethyl acetate (Found: C, 49·3; H, 5·8; N, 16·4%; equiv., 175. $C_7H_{10}O_3N_2$ requires C, 49·4; H, 5·9; N, 16·5%; equiv., 170). Titration in aqueous solution gave an apparent pK_a 3·6. The infrared spectrum (mull) showed max. at 3250, 2245, and 1698 cm.$^{-1}$.

(d) 2 : 4 : 4*-Trimethyl*-Δ^1*-pyrroline* 1*-oxide.* This was recovered in 52% yield after attempted addition of hydrogen cyanide under the conditions of experiment (a); no cyano-derivative was obtained.

Alkaline Hydrolysis of 2*-Cyano*-Δ^1*-pyrroline* 1*-Oxides.*—(a) 2*-Cyano*-4 : 5 : 5*-trimethyl*-Δ^1*-pyrroline* 1*-oxide.* The nitrone-cyanide (4·1 g.) in 10% aqueous sodium hydroxide (40 ml.) was heated under reflux for 3 hr. and the solution then neutralised and extracted with chloroform. Evaporation of the extract gave 1*-hydroxy*-4 : 5 : 5*-trimethylpyrrolid*-2*-one* (1·1 g.), needles, m. p. 101—102° (from ether–light petroleum) (Found: C, 59·0; H, 9·2; N, 9·5. $C_7H_{13}O_2N$ requires C, 58·7; H, 9·2; N, 9·8%), $\nu_{max.}$ (mull) 3310, 3120, and 1680 cm.$^{-1}$. Titration in aqueous solution gave apparent pK_a 8·85. With ethanolic ferric chloric a deep reddish-purple colour developed.

The original aqueous solution was adjusted to pH 1 and again extracted with chloroform. The extract yielded 2*-carboxy*-4 : 5 : 5*-trimethyl*-Δ^1*-pyrroline* 1*-oxide* (2·4 g.), needles, m. p. 40—41° (from benzene) (Found: C, 55·9; H, 7·9; N, 8·3%; equiv., 172. $C_8H_{13}O_3N$ requires C, 56·1; H, 7·6; N, 8·2%; equiv., 171), $\lambda_{max.}$ (in 95% ethanol) 266 mμ (ε 8200). Titration in aqueous solution gave an apparent pK_a 2·85.

(b) 2*-Cyano*-5 : 5*-dimethyl*-Δ^1*-pyrroline* 1*-oxide.* The nitrone-cyanide (5·0 g.) was hydrolysed as in the previous experiment. Acidification to pH 1 and extraction with chloroform gave 2*-carboxy*-5 : 5*-dimethyl*-Δ^1*-pyrroline* 1*-oxide* (3·1 g.), needles, m. p. 86° (from ether–light petroleum) (Found: C, 53·6; H, 7·3; N, 8·9%; equiv., 160. $C_7H_{11}O_3N$ requires C, 53·5; H, 7·0; N, 8·9%; equiv., 157), apparent pK_a 2·80 in water, $\lambda_{max.}$ (in 95% ethanol) 265 mμ (ε 8600).

The mother-liquors from the crystallisation were evaporated, and an aqueous solution of the residue passed down a column of Dowex 1 × 2 (acetate form). Evaporation of the eluate gave 1*-hydroxy*-5 : 5*-dimethylpyrrolid*-2*-one* (1·0 g.), needles, m. p. 82—83° (from hexane) (Found: C, 55·9; H, 8·6; N, 10·7. $C_6H_{11}O_2N$ requires C, 55·8; H, 8·5; N, 10·9%), apparent pK_a 8·7 in water, $\nu_{max.}$ (mull) 3320, 3090, and 1678 cm.$^{-1}$.

An authentic sample of this hydroxamic acid was prepared by reduction of methyl 4-methyl-4-nitropentanoate (21 g.) with zinc dust (30 g.) and ammonium chloride (6 g.) in 50% aqueous

ethanol (150 ml.). The mixture was stirred for 4 hr., zinc and zinc oxide were removed and washed with hot 50% aqueous ethanol (3 × 50 ml.), and the filtrate and washings combined and evaporated below 60° to a syrup. This syrup was dissolved in 2N-hydrochloric acid (50 ml.) and extracted with chloroform; evaporation of the chloroform yielded the 1-hydroxy-pyrrolidone (4·8 g., 30%), m. p. 83° undepressed on admixture with a specimen from the previous experiment.

Thermal Decarboxylation of 2-*Carboxy*-Δ^1-*pyrroline* 1-*Oxides.*—(a) 2-*Carboxy*-4 : 5 : 5-*trimethyl*-Δ^1-*pyrroline* 1-*oxide.* The acid (100 mg.) was heated at 140—150° for 3 min.; carbon dioxide was evolved. The oily residue was converted into the picrate (120 mg., 58%), yellow needles, m. p. 114° (from ethanol) undepressed on admixture with the picrate of 4 : 5 : 5-trimethyl-Δ^1-pyrroline 1-oxide. The infrared spectra of the picrates were identical over the range 4000—650 cm.$^{-1}$.

(b) 2-*Carboxy*-5 : 5-*dimethyl*-Δ^1-*pyrroline* 1-*oxide.* Treated as described under (a) this acid (100 mg.) gave 5 : 5-dimethyl-Δ^1-pyrroline 1-oxide, isolated as the picrate (140 mg., 65%), m. p. and mixed m. p. 78—79°.

Addition of Grignard Reagents to Δ^1-*Pyrroline* 1-*Oxides.*—2-*Ethyl*-5 : 5-*dimethyl*-Δ^1-*pyrroline* 1-*oxide.* 5 : 5-Dimethyl-Δ^1-pyrroline 1-oxide (10·0 g., dried by distillation with benzene) in anhydrous ether (30 ml.) was added to ethereal ethylmagnesium bromide [from ethyl bromide (15 g.) and magnesium (3·4 g.)], and the mixture heated under reflux for 30 min. Excess of aqueous ammonium chloride was added, and the ether layer separated, dried (Na_2SO_4), and fractionated, to give 5-*ethyl*-1-*hydroxy*-2 : 2-*dimethylpyrrolidine* (11·2 g., 89%), b. p. 50—53°/0·7 mm. (Found: C, 66·8; H, 12·1; N, 9·9. $C_8H_{17}ON$ requires C, 67·1; H, 12·0; N, 9·8%). Aerial oxidation of this product in aqueous ethanol containing copper acetate and ammonia gave the corresponding *nitrone* (10·0 g., 90%), b. p. 54—56°/0·2 mm., $\nu_{max.}$ (liquid film) 1600 cm.$^{-1}$. The *picrate* formed yellow needles, m. p. 71—72°, from ethanol (Found: C, 45·6; H, 5·0; N, 15·3. $C_{14}H_{18}O_8N_4$ requires C, 45·4; H, 4·9; N, 15·1%).

2 : 5 : 5-*Trimethyl*-Δ^1-*pyrroline* 1-*oxide.* This was prepared from 5 : 5-dimethyl-Δ^1-pyrroline 1-oxide (2·0 g.) by the action of methylmagnesium iodide in ether followed by copper-catalysed aerial oxidation of the intermediary hydroxylamine. The *nitrone picrate* (1·9 g.) formed yellow needles, m. p. 98°, from ethanol (Found: C, 43·8 H, 4·3; N, 15·4. $C_{13}H_{16}O_8N_4$ requires C, 43·8; H, 4·5; N, 15·7%).

3 : 3 : 5 : 5-*Tetramethyl*-Δ^1-*pyrroline* 1-*oxide.* 2 : 4 : 4-Trimethyl-Δ^1-pyrroline 1-oxide (10·0 g.) was treated with ethereal methylmagnesium iodide [from methyl iodide (22·4 g.) and magnesium (3·8 g.)], to give 1-*hydroxy*-2 : 2 : 4 : 4-*tetramethylpyrrolidine* (9·0 g., 81%) which sublimed at 75°/14 mm. to colourless needles, m. p. 62° (Found: C, 66·7; H, 11·9; N, 9·9. $C_8H_{17}ON$ requires C, 67·1; H, 12·0; N, 9·8%). Copper-catalysed aerial oxidation of the hydroxylamine (8·5 g.) gave the Δ^1-*pyrroline* 1-*oxide* (6·0 g., 72%), b. p. 73°/1 mm., needles, m. p. 32—34° (from light petroleum) (Found: C, 67·7; H, 10·3; N, 9·6. $C_8H_{15}ON$ requires C, 68·0; H, 10·7; N, 9·9%). The *picrate* formed yellow needles, m. p. 137—138°, from ethanol (Found: C, 45·5; H, 4·9; N, 15·4. $C_{14}H_{18}O_8N_4$ requires C, 45·5; H, 4·9; N, 15·1%).

Addition of Nitro-alkanes to 5 : 5-*Dimethyl*-Δ^1-*pyrroline* 1-*Oxide.*—(*a*) Nitromethane (11·7 g.) in ethanol (50 ml.) was added to a stirred solution of the Δ^1-pyrroline 1-oxide (10·5 g.) and sodium ethoxide (from 1·8 g. of sodium) in ethanol (200 ml.) and left at room temperature overnight. After acidification with acetic acid (5 ml.) the ethanol was evaporated and the residue extracted with chloroform. Fractionation of the washed and dried (Na_2SO_4) extract gave 1-*hydroxy*-2 : 2-*dimethyl*-5-*nitromethylpyrrolidine* (11·8 g., 74%) as a viscous yellow oil, b. p. 98°/0·3 mm. (Found: C, 48·5; H, 8·0; N, 16·3. $C_7H_{14}O_3N_2$ requires C, 48·3; H, 8·1; N, 16·1%), $\nu_{max.}$ (liquid film) 3220 and 1552 cm.$^{-1}$.

(*b*) In a similar fashion nitroethane (12·6 g.) was added to the Δ^1-pyrroline-1-oxide (9·5 g.), to give 1-*hydroxy*-2 : 2-*dimethyl*-5-1′-*nitroethylpyrrolidine* (3·7 g.), b. p. 100—102°/0·4 mm. (Found: C, 50·8; H, 8·8; N, 15·0. $C_8H_{16}O_3N_2$ requires C, 51·1; H, 8·6; N, 14·9%), $\nu_{max.}$ (liquid film) 3480 and 1548 cm.$^{-1}$. Part of the Δ^1-pyrroline 1-oxide (5·7 g.) was recovered.

Base-catalysed Condensation of 2 : 4 : 4-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide with Aromatic Aldehydes.*—(*a*) The Δ^1-pyrroline 1-oxide (0·50 g.), benzaldehyde (0·45 g.), and potassium hydroxide (50 mg.) in ethanol (4 ml.) were heated under reflux for 30 min., then poured into water, giving 4 : 4-*dimethyl*-2-*styryl*-Δ^1-*pyrroline* 1-*oxide* (0·31 g.) as colourless needles, m. p. 113° (from benzene–light petroleum) (Found: C, 78·4; H, 8·3; N, 6·4. $C_{14}H_{17}ON$ requires C, 78·1; H, 8·0; N, 6·5%), $\nu_{max.}$ (mull) 1537, 990, 977, 756, and 691 cm.$^{-1}$, $\lambda_{max.}$ (in 95% ethanol) 236 and 329 mμ (ε 11,200 and 22,600).

(*b*) A similar condensation with *p*-nitrobenzaldehyde gave 4 : 4-*dimethyl*-2-4′-*nitrostyryl*-Δ^1-*pyrroline* 1-*oxide* as bright yellow leaflets, m. p. 233° (from ethanol) (Found: C, 64·4; H, 6·0; N, 10·9. $C_{14}H_{16}O_3N_2$ requires C, 64·6; H, 6·2; N, 10·8%).

Benzoylation of 2 : 4 : 4-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide*.—The pyrroline oxide (0·40 g.) was benzoylated with excess of benzoyl chloride and sodium hydroxide solution to give a semisolid product which was extracted with benzene. The dried (Na_2SO_4) extract was passed through a short column of alumina and concentrated: addition of light petroleum gave 5-*benzamido*-1-*benzoyloxy*-4 : 4-*dimethylpentan*-2-*one* (0·51 g.) as prisms, m. p. 117° (from 80% aqueous methanol) (Found: C, 71·2; H, 6·1; N, 4·0. $C_{21}H_{23}O_4N$ requires C, 71·4; H, 6·6; N, 4·0%), $\nu_{max.}$ (mull) 3360, 1718, 1637, and 1547 cm.$^{-1}$, $\lambda_{max.}$ (in 95% ethanol) 231 and 270 mμ (inflexion) (ε 25,700 and 1800). The product was insoluble in cold dilute acids and gave no colour with ferric chloride. Hydrolysis of this compound (113 mg.) with aqueous ethanolic potassium hydroxide gave benzoic acid (67 mg., 87%), identified by m. p. and mixed m. p. 119°. The 2 : 4-*dinitrophenylhydrazone* formed yellow prisms, m. p. 172° (from ethanol) (Found: C, 60·7; H, 4·9. $C_{27}H_{27}O_7N_5$ requires C, 60·8; H, 5·1%), $\lambda_{max.}$ (in 95% ethanol) 356—358 mμ (ε 21,900).

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