Experiments towards the Synthesis of Corrins. Part XII.[1] Synthesis and Some Reactions of β-Oxo-Δ^1-pyrroline 1-Oxides

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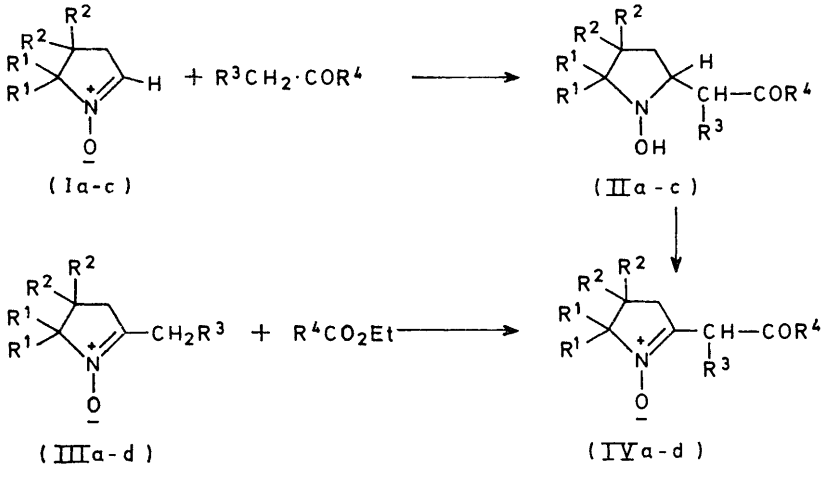
β-Oxo-Δ^1-pyrroline 1-oxides have been synthesised in two ways: (i) by oxidation of the corresponding γ-oxo-*N*-hydroxypyrrolidine formed by the base-catalysed aldol-type reaction of a nitrone and a methylene ketone, (ii) by the Claisen-type reaction of a 2-alkyl-Δ^1-pyrroline 1-oxide with a carboxylic ester. β-Oxo-nitrones can, in some cases, be reduced to the corresponding β-amino-αβ-unsaturated ketones, which are potential precursors of the AB component of the corrin ring system. Under oxidative conditions β-oxo-nitrones yield dimers in a manner similar to β-dinitrones.

BASE-CATALYSED aldol-type reactions of Δ^1-pyrroline 1-oxides have already been described,[2] and the carbonyl-like properties of these cyclic nitrones have been demonstrated. We now report the synthesis of β-oxo-Δ^1-pyrroline 1-oxides by two routes, each of which makes use of these properties. The first involves reaction of the nitrone (I) with a methylene ketone to produce the γ-oxo-hydroxylamine (II), which can then be oxidised to the corresponding β-oxo-nitrone (IV). In the second route the β-oxo-nitrones (IV) are formed, without an oxidative step, by the Claisen-type condensation of the 2-alkyl nitrone (III) and a carboxylic ester.



a; $R^1 = Me, R^2 = R^3 = H, R^4 = Ph$
b; $R^1 = R^3 = Me, R^2 = H, R^4 = Ph$
c; $R^1 = Me, R^2 = R^3 = H, R^4 = CMe_3$
d; $R^1 = R^3 = H, R^2 = Me, R^4 = Ph$

Acyclic examples of γ-oxo-hydroxylamines were first reported by Thesing[3] who treated the methiodides and methosulphates of Mannich bases with phenylhydroxylamine. Oxidation of these with 2 mol. equiv. of alkaline potassium hexacyanoferrate(III) gave the corresponding β-oxo-nitrones. Products of further oxidation were obtained but not identified. This preparative method is not readily applicable to the Δ^1-pyrroline series.

Condensations of acetophenone, propiophenone, and pinacolone with 5,5-dimethyl-Δ^1-pyrroline 1-oxide (Ia), by use of sodamide in liquid ammonia, gave high yields of the γ-oxo-hydroxylamines (11a—c), respectively. Their structures were confirmed by the presence of hydroxy and carbonyl i.r. absorptions. Compounds (IIa and c) were obtained as viscous oils. The propiophenone product (IIb), initially also a viscous oil, crystallised as prisms, whose i.r. spectrum (Nujol) lacked a carbonyl stretching band and contained a broad hydroxy-absorption. On attempted sublimation, a viscous oil distilled over and this, unlike the initial product, showed carbonyl i.r. absorption. It appears that the adduct (IIb) exists in the solid phase as the cyclol isomer (V). The ^1H n.m.r. spectrum indicated that the ketonic form was

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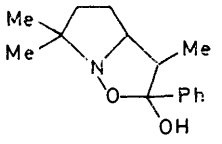
[1] Part XI, D. St. C. Black, V. M. Clark, B. G. Odell, I. O. Sutherland, and Lord Todd, preceding paper.

[2] R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and Sir Alexander Todd, *J. Chem. Soc.*, 1959, 2094.

[3] J. Thesing, A. Muller, and G. Michel, *Chem. Ber.*, 1955, **8**, 1027.

present in carbon tetrachloride solution, the CH·CO resonance appearing as a multiplet at τ 6.6.

Oxidation of the hydroxylamine (IIa) with 2 mol. equiv. of alkaline potassium hexacyanoferrate(III) afforded the yellow, crystalline β-oxo-nitrone (IVa), which was also the product of copper-catalysed aerial oxidation. The spectral data of (IVa) are discussed in detail below.



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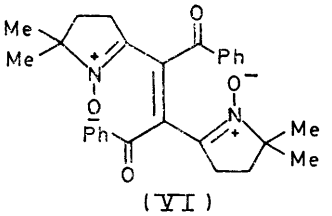

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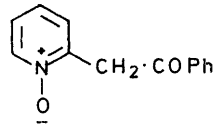

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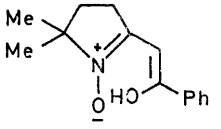

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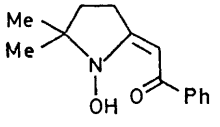


(IX)

Prolonged aerial oxidation, or use of more than 2 mol. equiv. of hexacyanoferrate gave the tetrasubstituted dimer (VI), $\nu_{max.}$ 1 530 (conjugated nitrone) and 1 578 cm^{-1} (conjugated carbonyl), $\lambda_{max.}$ 250 and 300 nm, and no vinyl proton n.m.r. signals.

Oxidation of the hydroxylamine (IIb) with 2 mol. equiv. of hexacyanoferrate gave the corresponding β-oxo-nitrone (IVb), which decomposed when recrystallisation or sublimation was attempted.

The Claisen-type condensation of 2-alkyl-Δ^1-pyrroline 1-oxides with carboxylic esters proceeds smoothly with either sodium hydride in ether or potassium t-butoxide in t-butyl alcohol, to yield β-oxo-nitrones. Because of the ready oxidation of these species, as discussed above, this non-oxidative synthesis is, in general, more reliable. Claisen condensation of the nitrone (IIIa or b) with ethyl benzoate yielded the corresponding β-oxo-nitrone (IVa or b), identical with that obtained by the oxidative route. Again, the nitrone (IVb) could not be satisfactorily purified. This condensation also led to the β-oxo-nitrones (IVc and d).

In view of these results for β-oxo-nitrones, a formally similar derivative was prepared in the pyridine 1-oxide series. The reaction of 2-methylpyridine 1-oxide with ethyl benzoate in benzene, with sodium hydride as catalyst, gave the colourless crystalline oxo-*N*-oxide (VII). Spectral data indicated that this product was not enolised, but in alkali an intense u.v. absorption arising from the enolate anion was observed at 399 nm. In contrast, the condensation product [4] of 2-methylpyridine 1-oxide with diethyl oxalate was a yellow solid, whose colour pointed to enolisation. In our hands esters did not react with 2-ethylpyridine 1-oxide.

The Structure of β-Oxo-Δ^1-pyrroline 1-Oxides.—The ^1H n.m.r. spectrum of the β-oxo-nitrone (IVa) showed a singlet resonance at τ 4.8 (vinyl proton) and a broad singlet at τ 5.2 (chelated OH). Such a spectrum could be attributed to the enolic β-oxo-nitrone (VIII) or the vinylogous hydroxamic acid (IX).

The u.v. maxima at 237 (ε 12 100) and 331 nm (12 100) correspond to the enol (VIII). The acidic properties of β-oxo-nitrones closely parallel those of β-diketones,[5,6] and are lowered by methylation of the active methylene group: compound (IVa) had an apparent pK_a value of 9.3, whereas (IVb) gave an anion only in strong alkali. The i.r. spectrum of (IVa) (in Nujol or carbon tetrachloride) shows very broad absorptions at 1 625 and 1 590 cm^{-1}, but no sharp band attributable to O–H stretching. The spectrum does not resemble that of a simple nitrone [7] but rather that of dibenzoylmethane, which has a hydrogen-bonded enol structure both in the solid state and in solution, with a broad band centred near 1 540 cm^{-1} and no obvious O–H stretching band.[8] A hydrogen-bonded structure for (IVa) would closely resemble the hydrogen maleate anion, the proton being part of a seven-membered ring. The i.r. spectrum of potassium hydrogen maleate shows [9] broad bands in the double-bond region, the one of highest frequency appearing at 1 575 cm^{-1}. Comparison of the above i.r. data leads us to suggest a hydrogen-bonded structure (VIII) or (IX) for the β-oxo-Δ^1-pyrroline 1-oxide in the solid state and in solution in carbon tetrachloride.

In the hydrolysis of asymmetric β-diketones the predominant acidic product is usually that derived from the portion of the molecule for which the enol is less stabilised.[10] However, hydrolysis of the β-oxo-nitrone (IVa) with dilute acid yielded benzoic acid and the 2,5,5-trimethyl-Δ^1-pyrroline 1-oxide (IIIa) (identified as its picrate). Alkaline hydrolysis of (IVa) was slow, but after 24 h a trace of benzoic acid was observed. Thesing [3] reported that hydrolysis of his acyclic β-oxo-nitrones to α-formyl ketones was effected in acidic solutions: the above results underline the stability of Δ^1-pyrroline 1-oxides to acidic hydrolysis.

A Model for the AB *Component of the Corrin Ring System.*—The β-oxo-nitrone approach to a corrin AB intermediate

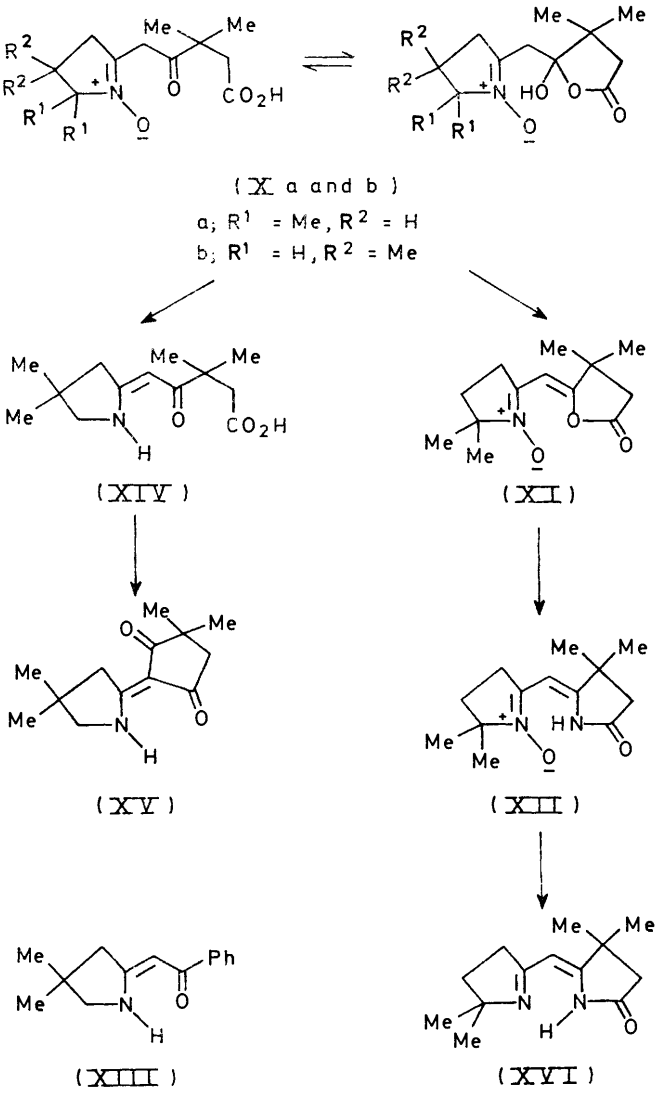
[4] R. Adams and S. Miyano, *J. Amer. Chem. Soc.*, 1954, **76**, 3168.
[5] M. L. Eidinoff, *J. Amer. Chem. Soc.*, 1945, **67**, 2072.
[6] G. W. Wheland, 'Advanced Organic Chemistry,' Wiley, New York, 1960, p. 681 and references cited therein.
[7] J. Hamer and A. Macaluso, *Chem. Rev.*, 1964, **64**, 473.
[8] R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1068.
[9] H. M. E. Cardwell, J. D. Dunitz, and L. E. Orgel, *J. Chem. Soc.*, 1953, 3740.
[10] E. S. Gould, ' Mechanism and Structure in Organic Chemistry,' Holt, Rinehart, and Wilson, New York, 1959, p. 337.

requires condensation of a succinic ester with a Δ^1-pyrroline 1-oxide, followed by cyclisation of the oxo-acid side chain to give the second ring. The methyl half ester [11] of 2,2-dimethylsuccinic acid [12] was condensed with the nitrones (IIIa and d), by using sodium hydride in boiling dioxan, to give the carboxylic acids (Xa and b), respectively. These appear to exist in the solid state as the oxo-acids, since the i.r. spectrum (Nujol) contains no high frequency carbonyl stretching band. In solution, however, a tautomeric equilibrium is established and ^{1}H n.m.r. spectra showed broad peaks in $CDCl_3$ but sharp ones in D_2O: in the former, solvent interconversion of the tautomers is slow, whereas in the latter it is rapid or one form is stabilised. This phenomenon is well known [13] for γ-oxo-acids.

The large percentage of enol found for simple β-oxo-nitrones was not present in the acids (Xa and b). For example, (Xb) showed u.v. absorption in ethanol at 233 (ε 9 000) and 312 nm (1 500), the second peak being attributable to a trace of enol. On addition of alkali, intense absorption at 326 nm (ε 30 200), arising from the enolate anion, was observed.

The oxo-acid (Xa) was cyclised to the presumed enol-lactone (XI) by treatment with dicyclohexylcarbodi-imide in methylene chloride. The i.r. spectrum of (XI) showed absorption at 1 808, 1 660, and 1 540 cm^{-1} and the u.v. spectrum absorption at 233 and 297 nm. Compound (XI) was converted into the corresponding lactam (XII) by reaction with liquid ammonia, followed by thermal dehydration of the intermediate hydroxy-lactam. The lactam (XII) was preferably prepared by refluxing the acid (Xa) in anhydrous benzene while a stream of dry ammonia was passed through the solution: the water formed in the reaction was removed by use of a Dean–Stark head. The ^{1}H n.m.r. spectrum of (XII) showed a broad signal at τ −1.75 indicating the N–H proton to be hydrogen-bonded. This view is supported by the presence of a broad NH stretching absorption in the i.r. spectrum. Values for lactam carbonyl absorption (1 710 and 1 715sh cm^{-1}) are consistent with those for a simple model.[14] The u.v. absorption in ethanol at 314 (ε 14 000) and 233 nm (7 800) moved to 310 nm (32 200) in acid and to 340 (35 400) and 255 nm (3 900) in alkali.

A nitrone route to the corrin nucleus requires removal of an oxygen atom from each nitrone and dehydration of each hydroxylamine. Deoxygenation of nitrones has been achieved by a variety of methods,[7] but none is consistently reliable. Hydrogenation over freshly prepared Raney nickel W4 has been used [15] for this type of process, and in the present work proved valuable for the deoxygenation of Δ^1-pyrroline 1-oxides, provided that the 5-position was unsubstituted. Thus, the simple 2,4,4-trimethyl nitrone (IIId) was converted into the corresponding pyrroline, whereas the 2,5,5-trimethyl isomer was unaffected; the β-oxo-nitrone (IVd) was readily deoxygenated to the vinylogous amide (XIII), whereas



the isomer (IVa) was not; and the nitrone oxo-acid (Xb) was converted into the related (XIV), whereas (Xa) proved unreactive.

The β-oxo-imine (XIV) is potentially susceptible to *N*-, *O*-, and *C*-alkylation: [16,17] when (XIV) was heated alone or dehydrated with dicyclohexylcarbodi-imide, the product (XV) was that of *C*-acylation.

Hydrogenation over Raney nickel did not deoxygenate the conjugated enol lactam (XII), and treatment with

[11] P. A. S. Smith and J. P. Horwitz, *J. Amer. Chem. Soc.*, 1949, **71**, 3418.
[12] C. K. Warren and B. C. L. Weedon, *J. Chem. Soc.*, 1958, 3972.
[13] C. Pascual, D. Wegmann, U. Graf, R. Scheffold, P. F. Sommer, and W. Simon, *Helv. Chim. Acta*, 1964, **47**, 213.
[14] E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwend, E. F. Meyer, M. Pesaro, and R. Scheffold, *Angew. Chem. Internat. Edn.*, 1964, **3**, 490.
[15] A. C. Cope and A. C. Haven, *J. Amer. Chem. Soc.*, 1950, **72**, 4896.
[16] N. J. Leonard and J. A. Adamcik, *J. Amer. Chem. Soc.*, 1959, **81**, 595.
[17] N. K. Kochetkov, *Izvest. Akad. Nauk. S.S.S.R., Otdel. khim. Nauk.*, 1954, 47 (*Chem. Abs.*, 1955, **49**, 6090).

triphenylphosphine at 120 °C also led to no reaction. However, an acid-soluble, crystalline solid, whose spectroscopic data are consistent with the structure of the required acyl vinylogous amidine (XVI), was isolated in 15% yield when (XII) was heated at 120 °C in triphenyl phosphite.[18] The specimen was not obtained analytically pure, but its mass spectrum had a molecular ion at *m/e* 220. This product was a strong base which dissolved in water to give an alkaline solution.

Vinylogous amides and amidines have been prepared by Eschenmoser and his co-workers using their sulphide-contraction process.[19] Their examples include dimethyl analogues of compounds (XIII),[19] (XIV),[19] (XV),[20] and (XVI);[20] the spectroscopic data of the two series are in good agreement.

EXPERIMENTAL

General information is the same as for Part XI.[1]

Preparation of γ-Oxo-hydroxylamines (II).—(a) *Reaction of acetophenone with 5,5-dimethyl-Δ¹-pyrroline 1-oxide.* Acetophenone (1.2 g) was added to sodamide [from sodium (9.25 g)] in liquid ammonia (30 ml). After 2 h, the nitrone (1.1 g) was added, and the mixture was shaken occasionally for a further 3 h, until all the ammonia had evaporated. Ammonium chloride and dilute hydrochloric acid were added and the mixture was extracted with chloroform, concentrated, dissolved in dilute hydrochloric acid, and extracted with ether to remove unchanged acetophenone. The aqueous solution was made alkaline and extracted with ether; the extract was dried (Na_2SO_4) and concentrated to yield 2-(1-*hydroxy-5,5-dimethylpyrrolidin-2-yl*)*acetophenone* (IIa) (1.9 g, 83%), which was distilled at 0.1 mmHg to give a viscous pale yellow oil, $\nu_{max.}$ (liquid) 3 400, 3 100, 1 680, 1 590, 1 380, 1 360, 1 300, 1 275, 1 210, 1 160, 1 130, and 1 000 cm^{-1}, $\lambda_{max.}$(EtOH) 242 nm, τ 9.00 (3 H, s), 8.80 (3 H, s), 8.7—7.6 (4 H, m), 6.80 (2 H, m), 2.65 (m) and 2.20 (m) (5 H), pK_a (aqueous methanol) 5.4, equiv. 277 (calc. 233) (Found: C, 72.4; H, 8.6; N, 6.2. $C_{14}H_{19}NO_2$ requires C, 72.1; H, 8.2; N, 6.0%). The *hydrogen oxalate* (from ethyl acetate) had m.p. 130° (Found: C, 59.0; H, 6.2; N, 4.3. $C_{16}H_{21}NO_6$ requires C, 59.4; H, 6.5, N, 4.3%).

(b) *Reaction of propiophenone with 5,5-dimethyl-Δ¹-pyrroline 1-oxide.* Propiophenone and 5,5-dimethyl-Δ¹-pyrroline 1-oxide were condensed in liquid ammonia by a procedure similar to that described above. A solution of the crude product in light petroleum deposited large prisms (61%) when refrigerated, and these were recrystallised from ethyl acetate to yield 2-(1-*hydroxy-5,5-dimethylpyrrolidin-2-yl*)*propiophenone* (IIb), m.p. 104°. Attempted sublimation, at 10^{-4} mmHg, of the crystalline material led to a viscous oil, $\nu_{max.}$ ($CHCl_3$) (oil) 3 100br, 1 680, 1 600, 1 585, and 1 500 cm^{-1}, $\nu_{max.}$ (Nujol) 3 000br, 1 500, 1 300, 1 250, 1 238, 1 190, 1 130, 1 100, 1 013, 970, 940, 762, and 700 cm^{-1}, $\lambda_{max.}$ (EtOH) 244 and 280sh nm, τ ($CDCl_3$) 9.00 (3 H, s), 8.91 (3 H, s), 8.68 (3 H, d, *J* 7.2 Hz), 8.6—8.0 (4 H, m), 6.6 (1 H, m), 6.1 (1 H, m), 5.4br (1 H), and 2.50 (m) and 2.05 (m) (5 H) (Found: C, 72.5; H, 8.3; N, 6.0. $C_{15}H_{21}NO_2$ requires C, 72.8; H, 8.6; N, 5.7%).

(c) *Reaction of pinacolone with 5,5-dimethyl-Δ¹-pyrroline 1-oxide.* Pinacolone (2.0 g) and the nitrone (2.2 g) were treated in liquid ammonia by the above procedure to yield a viscous yellow oil, 1-(1-hydroxy-5,5-dimethylpyrrolidin-2-yl)-3,3-dimethylbutan-2-one (IIc), b.p. (bath) 140° at 3 mmHg (3.6 g, 85%), $\nu_{max.}$ (liquid) 3 150, 1 700, 1 360, and 1 310 cm^{-1}. The *oxalate* (from ethanol–ethyl acetate) had m.p. 204° (Found: C, 60.3; H, 9.8; N, 5.3. $C_{26}H_{48}N_2O_8$ requires C, 60.4; H, 9.4; N, 5.4%)

Oxidation of 2-(1-Hydroxy-5,5-dimethylpyrrolidin-2-yl)-acetophenone (IIa).—(a) *With potassium hexacyanoferrate*(III) (*2 mol. equiv.*). A solution of (IIa) (1.16 g) in chloroform (40 ml) was shaken for 3 h with a solution of potassium hexacyanoferrate (3.3 g) and sodium hydrogen carbonate (0.84 g) in water (40 ml). The chloroform layer was separated and evaporated. The residual yellow oil was dissolved in N-sodium hydroxide and extracted with chloroform to remove alkali-insoluble material. The aqueous layer was then carefully acidified and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to yield a yellow crystalline mass. Recrystallisation from petroleum gave yellow prisms (0.40 g, 38%), of *5,5-dimethyl-2-phenacyl-Δ¹-pyrroline 1-oxide* (IVa). It was sublimed (70° and 10^{-4} mmHg) to yield yellow crystals, m.p. 92—93°, $\lambda_{max.}$ (EtOH–HCl) 237 (ε 12 000) and 331 nm (12 100), $\lambda_{max.}$ (EtOH–NaOH) 234 (12 300), 264 (9 200), and 368 nm (21 500), $\nu_{max.}$ (Nujol) 1 625br, 1 570br, 1 345, 1 245, 1 140, 762, and 695 cm^{-1}, τ (CCl_4) 8.62 (6 H, s), 8.02 (2 H, t), 7.41 (2 H, t), 4.80 (1 H, s), 2.75 (m) and 2.30 (m) (5 H), and −5.2br (1 H), pK_a 9.3 (Found: C, 72.8; H, 7.1; N, 5.8. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.1%).

(b) *With potassium hexacyanoferrate*(III) (*4 mol. equiv.*). This was performed similarly to that described above, but with potassium hexacyanoferrate (6.6 g) and potassium hydrogen carbonate (1.68 g). After initial evaporation of chloroform, the residual oil was insoluble in sodium hydroxide solution. It crystallised when treated with light petroleum. Recrystallisation from carbon tetrachloride gave yellow needles of *2,3-bis-(5,5-dimethyl-Δ¹-pyrrolin-2-yl)-1,4-diphenylbut-2-ene-1,4-dione di-N-oxide* (VI) (0.4 g, 38%), m.p. 161—163°, $\lambda_{max.}$ (EtOH) 250 (ε 15 000) and 300 nm (7 000), $\nu_{max.}$ (Nujol) 1 600, 1 578, 1 530, 1 525, 1 270, 1 248, 710, and 700 cm^{-1}, τ($CDCl_3$) 8.98 (6 H, s), 8.36 (t) and 7.60 (t) (4 H), and 2.55 (m) and 2.15 (m) (5 H) [Found: C, 73.6; H, 6.7; N, 6.0%; *M* (electrometric titration), 450. $C_{28}H_{30}N_2O_4$ requires C, 73.3; H, 6.6; N, 6.1%; *M*, 458].

(c) *Aerial oxidation in the presence of cuprammonium acetate.* Air was passed through a solution of (IIa) in aqueous ethanol containing cuprammonium acetate until a blue colouration was restored (15 min). Work-up at this point led to the isolation of (IVa) in 20% yield. When the oxidation was prolonged to 5 h, no (IVa) was produced, but a 25% yield of (VI) was obtained.

Oxidation of 2-(1-Hydroxy-5,5-dimethylpyrrolidin-2-yl)-propiophenone (IIb).—Oxidation of (IIb) with 2 mol. equiv. of alkaline potassium hexocyanoferrate(III) was performed as described for the lower homologue (IIa). The product, which was not readily soluble in dilute aqueous alkali, crystallised on cooling in light petroleum containing a little diethyl ether; m.p. 50—60° (decomp.). Recrystallisation and attempted sublimation caused extensive decomposition. The product, probably 2-(5,5-dimethyl-Δ¹-pyrrolin-2-yl)-propiophenone *N*-oxide (IVb), had $\nu_{max.}$ (Nujol) 1 680,

[18] F. Ramirez and A. Aguiar, Amer. Chem. Soc., Abstracts 134th Meeting, 1958, p. 42-N; A. Aguiar, *Diss. Abs.*, 1960, **21**, 457.

[19] M. Roth, P. Dubs, E. Götschi, and A. Eschenmoser, *Helv. Chim. Acta*, 1971, **54**, 710.

[20] E. Götschi, Dissertation E.T.H., Zürich, 1973.

1 600sh, 1 580, 1 500, 1 260, 975, 950, 763, 750, 720, and 697 cm^{-1}, $\lambda_{max.}$ (EtOH) 240 nm, $\lambda_{max.}$ (2M-NaOH–EtOH) 339 nm, τ (CCl_4) 8.84 (3 H, d, *J* 7 Hz), 8.75 (6 H, s), 8.1 (2 H, m), 7.6 (2 H, m), 5.07 (1 H, q, *J* 7 Hz), and 2.5 (m) and 1.95 (m) (5 H).

Claisen Condensation of 2,5,5-Trimethyl-Δ¹-pyrroline 1-Oxide and Ethyl Benzoate.—Freshly distilled ethyl benzoate (12 g) in dry ether (80 ml) was introduced into a three-necked, round-bottomed flask equipped with stirrer, an inlet for dry nitrogen, and a reflux condenser. Sodium hydride (50% dispersion in oil; 3.84 g) was added and the mixture heated to reflux. 2,5,5-Trimethyl-Δ¹-pyrroline 1-oxide (5.0 g) in dry ether (25 ml) was introduced over 1 h. Hydrogen was evolved steadily, and the contents of the flask became bright yellow. The mixture was heated under reflux for 2 h, more ether being added, as required, to keep the suspension mobile. The flask, under dry nitrogen, was set aside overnight, after which methanol (10 ml) was added carefully to destroy unchanged sodium hydride. The product was extracted with water (100 ml) to give an intensely yellow aqueous solution. This was shaken with ether (40 ml) and with chloroform (40 ml) to remove unchanged ester, nitrone, and also the oil in which the sodium hydride had been suspended. It was then acidified with dilute hydrochloric acid and the product was extracted with chloroform. The extract was washed with sodium carbonate solution and with water and then dried and evaporated to yield crystals of 5,5-dimethyl-2-phenacyl-Δ¹-pyrroline 1-oxide (IVa), which was recrystallised from petroleum (yield 4.2 g, 45%; m.p. 92—93°) and was identical with the product of the oxidation of the corresponding hydroxylamine reported above. The same compound was obtained in 52% yield when the condensation was performed in t-butyl alcohol, with potassium butoxide as catalyst.

Claisen Condensation of 2-Ethyl-5,5-dimethyl-Δ¹-pyrroline 1-Oxide and Ethyl Benzoate.—The pyrroline oxide (0.01 mol) was treated with ethyl benzoate (0.02 mol) in the presence of sodium hydride (0.01 mol) as described for the 2-methyl nitrone. There being no alkali-soluble product, the initial chloroform extract was dried and evaporated and the residue rapidly chromatographed, in methylene chloride, on silicic acid. Starting material and oil were eluted with methylene chloride. Methylene chloride–2% methanol eluted a small amount of pale yellow oil, spectrally identical with 2-(5,5-dimethyl-Δ¹-pyrrolin-2-yl)propiophenone·*N*-oxide (IVb), prepared by oxidation of the corresponding hydroxylamine.

Claisen Condensation of Ethyl Pivalate and 2,5,5-Trimethyl-Δ¹-pyrroline 1-Oxide.—Ethyl pivalate was prepared (46%) by ethanolysis of pivaloyl chloride, in turn prepared from the parent acid.[21] It boiled at 117° (lit.,[22] 117°).

The condensation was carried out, with nitrone (0.04 mol) and ester (0.08 mol), in a manner similar to that described for the reaction with ethyl benzoate. The yellow product, *2-(3,3-dimethyl-2-oxobutyl)-5,5-dimethyl-Δ¹-pyrroline 1-oxide* (IVc) (25%) was purified by sublimation (10^{-4} mmHg and 50 °C); m.p. 53—55°, $\nu_{max.}$ (Nujol) 1 630br, 1 585, 1 245, 1 220, 1 170, 900, and 775 cm^{-1}, $\lambda_{max.}$ (EtOH–HCl) 233 (ε 7 200) and 308 nm (2 200), $\lambda_{max.}$ (EtOH–NaOH) 326 nm (ε 24 600), τ (CCl_4) 8.90 (9 H, s), 8.65 (6 H, s), 8.04 (2 H, t), 7.43 (2 H, t), 5.41 (1 H, s), and −5.5br (1 H) (Found: C, 68.6; H, 10.2; N, 6.6. $C_{12}H_{21}NO_2$ requires C, 68.2; H, 10.0; N, 6.6%).

Claisen Condensation of Ethyl Benzoate and 2,4,4-Trimethyl-Δ¹-pyrroline 1-Oxide.—The ester and nitrone were treated according to the procedure already described to give *4,4-dimethyl-2-phenacyl-Δ¹-pyrroline 1-oxide* (62%), m.p. (after sublimation) 103.5—104.5°, $\nu_{max.}$ (Nujol) 1 625br, 1 590, 1 570br, 1 270, 1 250, 860, 760, and 693 cm^{-1}, $\nu_{max.}$ (CCl_4) 1 620br, 1 590, 1 570br, 1 460, 1 390, 1 370, 1 270, 1 250, 860, and 690 cm^{-1}, $\lambda_{max.}$ (EtOH–HCl) 240 and 331 nm, $\lambda_{max.}$ (EtOH–NaOH) 375 nm, τ (CCl_4) 8.81 (6 H, s), 7.54 (2 H, s), 6.42 (2 H, s), 4.82 (1 H, s), 2.8 (m) and 2.3 (m) (5 H), and −5.45br (1 H) (Found: C, 73.0; H, 7.3; N, 5.8. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.1%).

Oxidation of 5,5-Dimethyl-2-phenacyl-Δ¹-pyrroline 1-Oxide (IVa). Compound (IVa) (0.23 g) in chloroform (10 ml) was shaken for 2 h with potassium hexacyanoferrate(III) (0.66 g), and sodium hydrogen carbonate (0.15 g) in water (10 ml). The chloroform layer was separated, dried, and evaporated to yield 2,3-bis-(5,5-dimethyl-Δ¹-pyrrolin-2-yl)-1,4-diphenylbut-2-ene-1,4-dione di-*N*-oxide (VI) (0.13 g, 54%), identical with the product described previously.

2-Phenacylpyridine 1-Oxide (VII).—(a) *By Claisen condensation.* 2-Methylpyridine 1-oxide was redistilled (b.p. 128° at 15 mmHg) to give a hygroscopic oil which crystallised at 0 °C.

Sodium hydride (50% suspension in oil; 3.84 g) was suspended in anhydrous benzene (100 ml) containing freshly redistilled ethyl benzoate (12 g). 2-Methylpyridine 1-oxide (4.4 g) in anhydrous benzene (25 ml) was added during 1 h to the suspension heated under reflux. Throughout the experiment a stream of dry nitrogen was passed through the apparatus. Hydrogen was evolved and the solution became yellow. Heating was continued for 5 h, after which methanol (15 ml) was added to destroy the excess of sodium hydride. The product was extracted into water (150 ml). The aqueous solution was shaken with chloroform (2 × 40 ml) and then acidified with dilute hydrochloric acid to precipitate the product, which was extracted into chloroform. The extract was washed with sodium carbonate solution and water, dried, and evaporated under reduced pressure to give a crystalline mass of *2-phenacylpyridine 1-oxide* (5.9 g, 69%), m.p. 156—160° (from benzene), $\nu_{max.}$ (Nujol) 1 680, 1 600w, 1 480, 1 340, 1 250, 1 220, 1 205, 1 105, 980, 773, and 763 cm^{-1}, $\lambda_{max.}$ (EtOH) 245 nm (ε 18 200), $\lambda_{max.}$ (EtOH–NaOH) 243 (ε 13 800), 260—268sh (11 100), and 399 nm (21 800), τ ($CDCl_3$) 5.42 (2 H, s), and 2.6 (m) and 1.8 (m) (9 H) (Found: C, 73.6; H, 5.6; N, 6.5. $C_{13}H_{11}NO_2$ requires C, 73.2; H, 5.2; N, 6.6%).

(b) *From 2-bromopyridine 1-oxide.* 2-Bromopyridine 1-oxide, prepared[23] from 2-bromopyridine, was condensed with ethyl benzoylacetate (from ethyl benzoate and ethyl acetoacetate).[24]

Sodium hydride (50% suspension in oil; 0.24 g) was washed with anhydrous benzene (to remove the oil) and suspended in benzene (10 ml). Ethyl benzoylacetate (0.96 g) in benzene (1 ml) was added, followed by 2-bromopyridine 1-oxide (0.87 g) in benzene (1 ml). The mixture was heated under reflux (under nitrogen) for 24 h, cooled, and evaporated under reduced pressure to leave a solid. This was washed with a little aqueous ethanol and the boiled under

[21] H. C. Brown, *J. Amer. Chem. Soc.*, 1938, **60**, 1325.
[22] B. E. Hudson and C. R. Hauser, *J. Amer. Chem. Soc.*, 1940, **62**, 2457.
[23] R. Adams and W. Reifschneider, *J. Amer. Chem. Soc.*, 1957, **79**, 2236.
[24] J. M. Straley and A. C. Adams, *Org. Synth.*, Coll. Vol. IV, 1963, 415.

reflux for 2 h with N-sodium hydroxide (5 ml). The solution was acidified with dilute hydrochloric acid and extracted with chloroform. Washing (Na_2CO_3 solution and water), drying, and evaporation gave a crystalline solid (0.11 g, 10%), identical (i.r. spectrum, m.p. and mixed m.p.) with the product prepared in (a).

Hydrolysis of 5,5-*Dimethyl*-2 *phenacyl*-Δ^1-*pyrroline* 1-*Oxide* (IVa).—(a) *With sodium hydroxide.* (i) Compound (IVa) (0.23 g) was dissolved in water (20 ml) containing sodium hydroxide (0.08 g). The yellow solution was refluxed for 3 h, under nitrogen (to prevent oxidation to a dimer), and then cooled and acidified. Starting material (0.20 g, 90%) was recovered.

(ii) Compound (IVa) (0.23 g) was dissolved in water (20 ml) containing sodium hydroxide (0.4 g, 20 mol.) equiv. and the solution was refluxed for 24 h under nitrogen. Work-up gave starting material (0.11 g, 55%) and benzoic acid (22 mg), identified by m.p. (121°), mixed m.p., and i.r. spectrum.

(b) *With hydrochloric acid.* Compound (IVa) (0.46 g) was refluxed for 3 h in 2N-hydrochloric acid. The solution was cooled and treated with sodium carbonate. After extraction with chloroform in the usual manner, an oil (0.11 g) was obtained which was identified as 2,5,5-trimethyl-Δ^1-pyrroline 1-oxide, by comparison of its picrate (m.p. 98°) with an authentic sample.[2] Acidification of the aqueous solution gave benzoic acid (0.16 g).

1-*Methyl Hydrogen* 2,2-*Dimethylsuccinate.*—2,2-Dimethylsuccinic acid was prepared from acetone, ethyl cyanoacetate ester, and potassium cyanide.[11] The half methyl ester was prepared by partial hydrolysis of the diester.[12]

Claisen Condensation of 2,4,4-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide with* 1-*Methyl Hydrogen* 2,2-*Dimethylsuccinate.*—Sodium hydride (50% suspension in oil; 5.76 g) was suspended in dry dioxan (50 ml) in a flask with a stirrer and an inlet for dry nitrogen. The half methyl ester (5.9 g) in dioxan (20 ml) was slowly added, hydrogen being evolved. Freshly distilled 2,4,4-trimethyl-Δ^1-pyrroline 1-oxide (5.0 g, 0.04 mol) in dioxan was added to the mixture, which was maintained at reflux temperature for 6 h. After cooling, the excess of sodium hydride was destroyed with methanol (15 ml). The resulting mixture was diluted with water (200 ml), and the alkali-insoluble material extracted with chloroform (4 × 75 ml). Acidification of the aqueous layer with hydrochloric acid (ice being added to keep the temperature below 40 °C) precipitated the product, which was extracted into chloroform (4 × 75 ml). The extract was dried and evaporated to yield an oil (3.1 g, 30%), which crystallised when triturated with light petroleum. More product was obtained by chromatography of the residue from evaporation of the mother liquor on silicic acid in chloroform. After washing the column with further chloroform, the product (0.9 g, 9%) was eluted with chloroform–4% methanol. Recrystallisation from benzene–petroleum gave needles of 5-(4,4-*dimethyl*-Δ^1-*pyrrolin*-2-*yl*)-2,2-*dimethyl*-3-*oxopentanoic acid* N-*oxide* (Xb), m.p. 145—147°, $\nu_{max.}$ (Nujol) 2 500br, 1 900br, 1 710, 1 630, 1 335, 1 230, 1 145, 1 045, 770, and 705 cm^{-1}, $\lambda_{max.}$ (EtOH) 233 (ε 9 000) and 312 nm (1 500), $\lambda_{max.}$ (EtOH–HCl) 228 (ε 5 300) and 295 nm (1 900), $\lambda_{max.}$ (EtOH–NaOH) 326 nm (ε 30 200), τ ($CDCl_3$) 8.76br (12 H, s), 7.16br (4 H), 6.20br (4 H), and —1.84br (1 H), τ (D_2O) 8.28 (6 H, s), 8.76 (6 H, s), 7.36 (2 H, t, *J* 1 Hz), 7.26 (2 H, s), and 6.19 (2 H, t, *J* 1 Hz), [Found: C, 61.6; H, 8.2; N, 5.4%; *M* (electrometric titration), 275. $C_{13}H_{21}NO_4$ requires C, 61.2; H, 8.3; N, 5.5%; *M*, 255].

Claisen Condensation of 2,5,5-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide with* 1-*Methyl Hydrogen* 2,2-*Dimethylsuccinate.*—5-(5,5-*Dimethyl*-Δ^1-*pyrrolin*-2-*yl*)-2,2-*dimethyl*-3-*oxopentanoic acid* N-*oxide* (Xa) was prepared by the procedure described above (31%); m.p. 110—111° (from ether), $\nu_{max.}$ (Nujol) 2 500br, 1 930br, 1 710, 1 620, 1 220, 1 136, 1 060, 880, and 725 cm^{-1}, $\lambda_{max.}$ (EtOH) 239 (ε 9 000), and 312 nm (2 000), $\lambda_{max.}$ (EtOH–NaOH) 331 nm (ε 30 000), τ ($CHCl_3$) 8.76 (6 H, s), 8.68 (6 H, s), 7.94 (2 H, m), 7.30br (4 H), and 6.3br (2 H), τ (D_2O) 8.74 (6 H, s), 8.65 (6 H, s), 7.92 (2 H, t), 7.26 (2 H, t), and 7.2br (2 H) (Found: C, 61.0; H, 8.1; N, 5.3. $C_{13}H_{21}NO_4$ requires C, 61.2; H, 8.3; N, 5.5%).

2-(3,3-*Dimethyl*-5-*oxopyrrolidin*-2-*ylidenemethyl*)-5,5-*dimethyl*-Δ^1-*pyrroline* 1-*Oxide* (XII).—(a) Compound (Xa) (0.26 g) in methylene chloride (20 ml) was treated with dicyclohexylcarbodi-imide (0.22 g) at room temperature. *NN'*-Dicyclohexylurea was filtered off after 24 h, and the filtrate evaporated to dryness. The residual solid was washed with pentane and then recrystallised from ether to yield the presumed enol lactone (XI) (0.15 g, 63%), m.p. 134—145° (decomp.), $\nu_{max.}$ (Nujol mull) 1 808, 1 660, 1 540, 1 210, 1 160, 1 053, and 792 cm^{-1}, $\lambda_{max.}$ (EtOH) 233 and 297 nm, τ ($CHCl_3$) 8.60 (12 H, s), 8.0 (2 H, t), 7.0 (2 H, t), 7.43 (2 H, s), and 3.90 (1 H, s).

Compound (XI) (0.24 g) was shaken with liquid ammonia (20 ml) and set aside at room temperature. A solid (0.26 g) [$\nu_{max.}$ (Nujol) 3 300br, 3 150, 1 700, 1 630, and 1 600 cm^{-1}, $\lambda_{max.}$ (EtOH) 240 nm, $\lambda_{max.}$ (EtOH–NaOH) 328 nm] was obtained, and was suspended in anhydrous benzene (100 ml). The solution obtained on warming this suspension was refluxed in a Dean–Stark apparatus for 2 h, cooled, filtered, and evaporated to yield an oil which was chromatographed on silicic acid (10 g) in methylene chloride. The product was eluted with methylene chloride–4% methanol; the eluate was evaporated and the residue crystallised by stirring with petroleum (yield 0.14 g, 58%). It was sublimed for analysis (90 °C and 10^{-4} mmHg); m.p. 120° (sealed tube), $\nu_{max.}$ (KBr) 3 420br, 1 710, 1 638, 1 562, 1 375, 1 245, 1 150, 810, and 800 cm^{-1}, $\lambda_{max.}$ (EtOH) 233 (ε 7 800) and 314 nm (14 000), $\lambda_{max.}$ (EtOH–NaOH) 255 (ε 3 900) and 340 nm (35 400), $\lambda_{max.}$ (EtOH–HCl) 310 nm (ε 32 200), τ ($CHCl_3$) 8.69 (6 H, s), 8.59 (6 H, s), 8.0 (2 H, t) and 7.35 (2 H, t), 7.64 (2H, s), 5.30 (1 H, s), and —1.75br (1 H), *m/e* 236 [Found: C, 65.9; H, 8.4; N, 12.1%; *M* (electrometric titration), 226. $C_{13}H_{20}N_2O_2$ requires C, 66.1; H, 8.5; N, 11.9%; *M*, 236].

(*b*) Compound (Xa) (0.51 g) in benzene (70 ml) was refluxed for 18 h in a Dean–Stark apparatus while a slow stream of dry ammonia was passed through the solution. The solvent was evaporated off and the brown oil extracted with methylene chloride (50 ml). The extract was evaporated to one quarter of its volume and chromatographed on silicic acid. Elution with methylene chloride–4% methanol gave two products. The second fraction contained the enol lactam (XII) (0.28 g, 60%), m.p. 119° (sealed tube).

Ozonolysis of 2-(3,3-*Dimethyl*-5-*oxopyrrolidin*-2-*ylidinemethyl*)-5,5-*dimethyl*-Δ^1-*pyrroline* 1-*Oxide* (XII).—The enol lactam (50 mg) was dissolved in ethyl acetate (30 ml) and ozone was passed through the solution for 30 min, at room temperature. The solution was hydrogenated over 5% palladium–barium sulphate, filtered, and evaporated to give an oil. Sublimation yielded crystals, m.p. 85—95°, whose i.r. spectrum was identical with that of authentic 2,2-dimethylsuccinimide.[25]

Deoxygenation of 2,4,4-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide.*—

[25] S. S. G. Sircar, *J. Chem. Soc.*, 1927, 1252.

The nitrone (1.3 g) in absolute ethanol (50 ml) was hydrogenated over Raney nickel W4 (*ca.* 1 g) at atmospheric pressure and room temperature. Uptake became slow after 1 mol. equiv. had been absorbed (6 h). The catalyst was filtered off and washed with absolute ethanol. The combined filtrate and washings were evaporated to leave 5 ml of solution, which was distilled to give 2,4,4-*trimethyl*-Δ^1-*pyrroline*, b.p. 126—130°, identified by comparison of its i.r. spectrum with that of an authentic sample.

The ethanolic solution from a parallel preparation was evaporated and the residue diluted with water and treated with saturated aqueous picric acid to yield 2,4,4-trimethyl-Δ^1-pyrrolinium picrate [26] (2.18 g, 64%), m.p. and mixed m.p. 195°.

Deoxygenation of 4,4-*Dimethyl*-2-*phenacyl*-Δ^1-*pyrroline* 1-*Oxide* (IVd).—The β-oxo-nitrone (0.46 g) in absolute ethanol (20 ml) was hydrogenated over Raney nickel W4 (*ca.* 0.5 g) at atmospheric pressure and room temperature. Uptake became slow after 6 h, when 1 mol. equiv. had been absorbed. Filtration and evaporation yielded an oil which solidified on being stirred with a little light petroleum. This solid was recrystallised from petroleum to give needles of 2-(4,4-*dimethylpyrrolidin*-2-*ylidene*)*acetophenone* (XIII) (0.28 g, 65%), m.p. 97°, $\nu_{max.}$ (Nujol) 3 270, 1 620, 1 585w, 1 540, 1 380, 1 285, 1 240, 1 190, 1 020, 858, 755, 730, and 687 cm^{-1}, $\lambda_{max.}$ (EtOH) 242 (ε 10 700) and 336 nm (21 500), τ (CCl_4) 8.88 (6 H, s), 7.60 (2 H, s), 6.70 (2 H, s), 4.33 (1 H, s), 2.65 (m) and 2.1 (m) (5 H), and —0.15br (1 H) (Found: C, 77.9; H, 8.0; N, 6.3. $C_{14}H_{17}NO$ requires C, 78.1; H, 8.0; N, 6.5%).

Deoxygenation of 5-(4,4-*Dimethyl*-Δ^1-*pyrrolin*-2-*yl*)-2,2-*dimethyl*-3-*oxopentanoic Acid* N-*Oxide* (Xb).—The nitrone γ-oxo-acid (Xb) (0.51 g) in absolute ethanol (30 ml) was hydrogenated over Raney nickel W4 (0.5 g) at atmospheric pressure and room temperature. When uptake had become slow (6 h), filtration and evaporation gave crystals of 5-(4,4-*dimethylpyrrolidin*-2-*ylidene*)-2,2-*dimethyl*-5-*oxopentanoic acid* (XIV) (0.37 g, 77%), m.p. 112° (from benzene–petroleum), $\nu_{max.}$ (Nujol) 3 230, 1 690, 1 595, 1 520, 1 280, 1 245, 1 220, 1 020, 890, 810, 749, and 690 cm^{-1}, $\lambda_{max.}$ (EtOH) 306 nm (ε 27 500), τ ($CDCl_3$) 8.81 (6 H, s), 8.72 (6 H, s), 7.47 (2 H, s), 7.39 (2 H, s), 6.56 (2 H, s), 4.73 (1 H, s), 0.06br (1 H), and —3.19br (1 H) (Found: C, 65.9; H, 8.5; N, 6.0. $C_{13}H_{21}NO_3$ requires C, 65.2; H, 8.8; N, 5.9%).

2-(4,4-*Dimethylpyrrolidin*-2-*ylidene*)-4,4-*dimethylcyclopentane*-1,3-*dione* (XV).—(a) *With dicyclohexylcarbodi-imide* (*DDC*). The enamino-oxo-acid (XIV) (0.24 g) in methylene chloride (20 ml) was treated with DCC (0.22 g) at room temperature. After 24 h, crystalline *NN'*-dicyclohexylurea was filtered off and the solution evaporated to dryness. The product was extracted with pentane and then recrystallised from benzene–petroleum to give *needles* (0.18 g, 81%), subl. 120°. A sample was purified by sublimation at 50 °C and 10^{-1} mmHg; $\lambda_{max.}$ (EtOH) 238 (ε 12 000) and 295 nm (17 000), τ ($CDCl_3$) 8.79 (6 H, s), 8.78 (6 H, s), 7.60 (2 H, s), 6.88 (2 H, s), 6.50 (2 H, s), and —0.39br (1 H) (Found: C, 70.6; H, 8.8; N, 6.4. $C_{13}H_{19}NO_2$ requires C, 70.6; H, 8.7; N, 6.3%).

(b) *By heat.* The dione (XV) was obtained in 58% yield by sublimation after heating (XIV) in an oil-bath at 150 °C for 5 min.

(*c*) When ammonia was passed through a refluxing solution of (XIV) in benzene in a Dean–Stark apparatus, the only product isolated was the dione (XV); no enol lactam was found.

Deoxygenation of the Enol Lactam (XII) *with Triphenyl Phosphite.*—Crystals of the enol lactam (0.95 g) were dissolved in freshly distilled triphenyl phosphite (b.p. 220 °C at 11 mmHg) (1.9 g) and heated at 120 °C for 20 min. The mixture was shaken with diethyl ether and dilute hydrochloric acid. The aqueous acidic layer was further extracted with ether and then basified (NaOH). Extraction with ether, followed by drying and evaporation in the usual way, led to an oil which gave oily crystals on sublimation (50 °C and 10^{-1} mmHg) (0.13 g 15%). Resublimation followed by recrystallisation from a small volume of petroleum (b.p. 40—60°) gave prisms of 2-(3,3-*dimethyl*-5-*oxopyrrolidin*-2-*ylidenemethyl*)-5,5-*dimethyl*-Δ^1-*pyrroline* (XVI), m.p. 55—57°, *m/e* 220, $\nu_{max.}$ (Nujol) 3 340br, 3 200br, 1 735, 1 720sh, 1 645, 1 585sh, 1 575, 1 320, 1 250, 1 160, 1 135, 945, and 780 cm^{-1}, $\lambda_{max.}$ (EtOH) 284 (ε 6 200) and 349 nm (13 700), $\lambda_{max.}$ (EtOH–HCl) 310 nm (ε 25 100), $\lambda_{max.}$ (EtOH–NaOH) 290 (ε 7 100) and 350 nm (15 300), τ (CCl_4) 8.76 (6 H, s), 8.71 (6 H, s), 8.37 (2 H, t), 7.77 (2 H, s), 7.37 (2 H, t), 5.14 (1 H, s), and 0.09br (1 H).

Ozonolysis of a small sample of the product in ethyl acetate, as described for (XII), gave 2,2-dimethylsuccinimide, identical with an authentic sample.[25]

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[26] R. Bonnett, V. M. Clark, A. Giddey, and Sir Alexander Todd, *J. Chem. Soc.*, 1959, 2087.