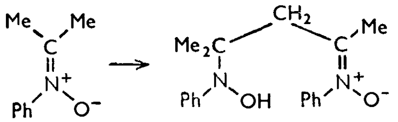
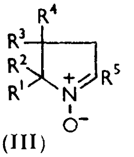
426. *Experiments towards the Synthesis of Corrins. Part V.* Base-catalysed Aldol-type Reactions of* Δ^1*-Pyrroline* 1*-Oxides.*

By R. F. C. Brown, V. M. Clark, I. O. Sutherland, and Sir Alexander Todd.

The base-catalysed formation of aldol-type products from cyclic nitrones of the Δ^1-pyrroline 1-oxide series is described; also conversion of the resulting nitrone-hydroxylamines into the bishydroxylamines and dipyrrolinylmethanes is discussed.

Banfield and Kenyon [1] in their work upon the reaction between acetone and phenylhydroxylamine showed that the nitrone (I) first formed dimerised spontaneously to the aldol-type product (II), and recently Thesing and Mayer [2] reported the condensation


(I) (II)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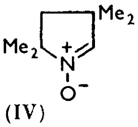
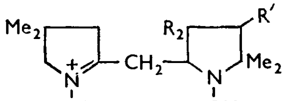
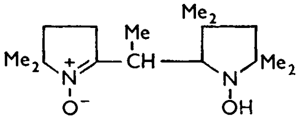

(IV)

product of butyraldehyde and phenylhydroxylamine [3] to be of the same type. The cyclic nitrones (III; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$; and $R^1 = R^2 = R^3 = Me$, $R^4 = R^5 = H$),[4] however, show little tendency to form aldolic dimers when stored at room temperature, though by basic catalysis aldol-type reactions can be brought about. Thus, the anion of the former nitrone generated by triphenylmethylsodium or sodamide in liquid ammonia has been added to the nitrones (III; $R^1 = R^2 = R^3 = Me$, $R^4 = R^5 = H$) and (IV) to yield the corresponding nitrone-hydroxylamines (Va and b) in the di-2-pyrrolidinylmethane series. The isolation of a single product (Vb) suggests that isomerism arising from a reversal of oxidation level in the two rings is absent; the formation of two isomeric products (Va) on use of triphenylmethylsodium can then be attributed to geometrical isomerism arising from the relative positions of the bridging methylene group and the isolated methyl group (R′). Use of sodamide in liquid ammonia gave only one isomer of (Va) and to this we assign the *trans*-configuration. Addition of the nitrone (III; $R^1 = R^2 = Me$, $R^3 = R^4 = H$, $R^5 = Et$) to (IV) in the presence of sodamide in liquid ammonia also gave a single product which we formulate as the nitrone-hydroxylamine (VI). As the monomeric nitrones (III; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$; and $R^1 = R^2 = R^3 = Me$, $R^4 = R^5 = H$) are isomeric it was of importance to determine whether the nitrone-hydroxylamines (Va) were derived from either compound alone or were the products of addition of one nitrone to the other. Attempted base-catalysed dimerisation of the first of this pair by triphenylmethylsodium failed whilst, under the same conditions, the second of the pair gave a dimer (VII).


(V)

a : R = H, R′ = Me

b : R = Me, R′ = H


(VI)

The infrared spectrum of the *trans*-product (Va) showed bands at 3130 (OH group)

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* Part IV, preceding paper.

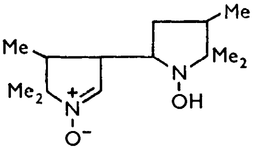
[1] Banfield and Kenyon, *J.*, 1926, 1612.

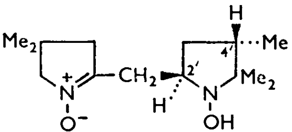
[2] Thesing and Mayer, *Chem. Ber.*, 1956, **89**, 2159.

[3] Utzinger and Regenass, *Helv. Chim. Acta*, 1954, **37**, 1892.

[4] Bonnett, Brown, Clark, Sutherland, and Todd, *J.*, 1959, 2094.

and at 1614 cm.$^{-1}$ (2-substituted nitrone [4]). The presence of the hydroxylamine group was confirmed by the colour test with triphenyltetrazolium chloride,[5] and that of the nitrone group by its ultraviolet absorption at 233 mμ. Since the 2-methyl group of the nitrone (III; $R^1 = R^2 = H, R^3 = R^4 = R^5 = Me$) had been shown to undergo condensation with aromatic aldehydes [4] whilst the 3-methylene group of the nitrone (III; $R^1 = R^2 = R^3 = Me, R^4 = R^5 = H$) did not, and since the former nitrone did not undergo dimerisation in the presence of triphenylmethylsodium, it can be concluded that addition to give products represented as (Va) had indeed taken place. The reactions of these compounds are entirely consistent with this structure. In the formation of (Va) in presence of triphenylmethylsodium the two isomers were obtained in 30% and 8% yield respectively; on oxidation they gave the same product and we suggest that these isomers are respectively the 2′ : 4′-*trans*- and 2′ : 4′-*cis*-compounds (VIII; *trans*-form shown). Aerial oxidation of either isomer in the presence of ammonia and a catalytic amount of cupric ion gave a bright yellow product, $C_{28}H_{44}O_4N_4$, evidently formed by oxidative dimerisation. The infrared spectrum of this product showed no absorption in the hydroxyl region and a single strong band in the nitrone region, at 1542 cm.$^{-1}$, which we assign to nitrone groups in conjugation with an unsaturated system. As there were no bands indicative of CH out-of-plane vibrations, it appeared that the new double bond (required by the analytical figures) was tetrasubstituted. The ultraviolet spectrum exhibited a sharp band at 256 mμ (ε 13,200) and a broad band at 380—390 mμ (ε 10,400); on this evidence we assign structure (IX) to the product and assume that it was formed by oxidative dimerisation of the anion (X) of the intermediate dinitrone, followed by a further oxidative step. In the pyrrole series analogous oxidations of dipyrrylmethanes to tetrapyrrylethanes and tetrapyrrylethylenes are well known.[6] Examination of a model of (IX) suggests that when two rings are coplanar and their nitrone groups fully conjugated, the other two rings cannot also be coplanar. In all probability the rings are inclined with respect to the plane of the central ethylenic bond and this would account for the low intensity of the long-wavelength band in the ultraviolet spectrum. A further stereochemical complication exists arising from the non-identity of the ring-substituents, *cis*- and *trans*-ethylenes being possible; that shown in (IX) is the *trans*-ethylene. The compound could not be obtained in well-formed crystals and, although it appeared to be homogeneous when subjected to paper chromatography, it may well have been a mixture of geometrical isomers.


(VII)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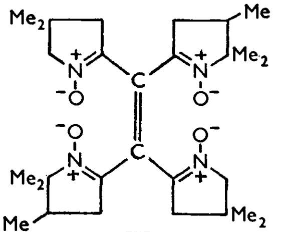
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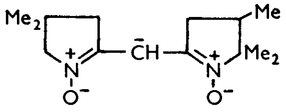
(X)

Reduction of the *trans*-compound (VIII) with aqueous potassium borohydride gave

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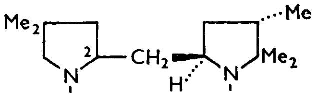
[5] Rogers, *J.*, 1955, 769; Snow, *J.*, 1954, 2588.

[6] Fischer, Baumgartner, and Plötz, *Annalen*, 1932, **493**, 9; Fischer and Beller, *ibid.*, 1925, **444**, 239.

the corresponding bishydroxylamine (XI): in consequence of the additional asymmetric centre generated at $C_{(2)}$ two diastereoisomers were obtained, although one, m. p. 156°, was formed in much greater amount than the other, m. p. 134°. Reactions expected to yield the corresponding dipyrrolinylmethanes (XII) gave, in addition, other products, the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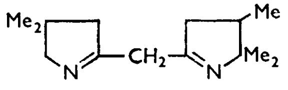
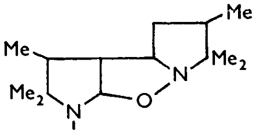

(XII)

nature of which became apparent from the detailed study of the aldonitrone dimer (VII).

The infrared spectrum of the dimer (VII), measured in Nujol mulls, showed a strong band at 3240 cm.$^{-1}$ indicative of a hydroxyl group, but no nitrone absorption in the region 1620—1570 cm.$^{-1}$. The ultraviolet spectrum, measured in ethanol, exhibited a band at 236 mμ, indicating the presence of a nitrone group; the intensity (ε 6000), however, was lower than previously observed[4] for the simple cyclic nitrones (ε *ca.* 10,000). In *cyclo*hexane solution this ultraviolet band was shifted to 249 mμ, the intensity then being normal (ε 11,800). Again, the infrared spectrum of the dimer (VII) in chloroform solution showed both hydroxyl (3680, 3560 cm.$^{-1}$) and nitrone (1583 cm.$^{-1}$) absorption. The evidence suggests an equilibrium sensitive to changes of state and of solvents, and most likely to be attributable to reversible addition of the hydroxyl group of the hydroxylamino-group to the double bond of the nitrone group to give the tricyclic system (XIII).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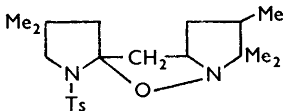
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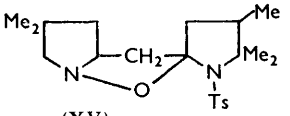
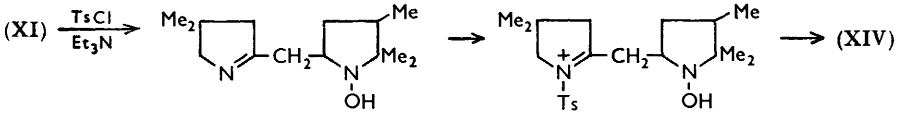

(XV)

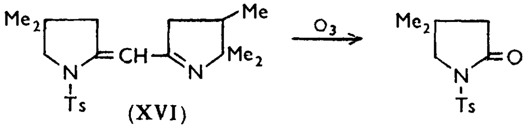
Ts = *p*-$C_6H_4Me{\cdot}SO_2$

The bishydroxylamine (XI) on treatment with three mols. of toluene-*p*-sulphonyl chloride and excess of triethylamine (cf. ref. 4) gave a mixture separable into two main fractions by chromatography on neutral alumina: each fraction yielded a crystalline base. The first product, $C_{21}H_{32}O_3N_2S$, exhibited the ultraviolet maximum at 228 mμ (ε 9900) and an inflexion at 260—265 mμ (ε 1800) to be expected of a toluene-*p*-sulphonamide. The infrared spectrum showed neither hydroxyl absorption nor strong bands in the 1700—1500 cm.$^{-1}$ region. As the toluene-*p*-sulphonyl group accounts for two of the three oxygen atoms present and there is no carbonyl or hydroxyl group, the remaining oxygen atom must be located either in a toluene-*p*-sulphonyl ester or in an ether linkage. The molecular formula requires that the heterocyclic part of the molecule should be either tricyclic and saturated, or bicyclic with a single double bond. A double bond if present would almost certainly have been detected in the infrared or ultraviolet spectrum and the introduction of an isolated 3 : 4-double bond into a pyrrolidine ring under such mild conditions is in any case unlikely. The only structures which readily accommodate the evidence are the isomeric *spiro*-structures (XIV) and (XV) of which the former is preferred since its



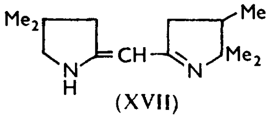
formation would involve initial attack at the less hindered hydroxylamine group of (XI). The *spiro*-compound (XIV) could arise by ordinary *O*-esterification of (XI) followed by elimination of toluene-*p*-sulphonic acid to give the pyrroline-hydroxylamine and the acylation of this to give the *spiro*-structure.

The second product of interaction of (XI) with toluene-*p*-sulphonyl chloride had a molecular formula $C_{21}H_{30}O_2N_2S$, differing from (XIV) by the elements of water. Its infrared spectrum showed the toluene-*p*-sulphonyl group to be present (C:C ring stretching at 1600 and 1495 cm.$^{-1}$; sulphone absorption at 1343 and 1164 cm.$^{-1}$); there was no hydroxyl absorption, all the oxygen atoms being accounted for by the toluene-*p*-sulphonyl group. In addition, there were two very strong bands at 1637 and 1580 cm.$^{-1}$: as the formula requires two double bonds to be present these bands may be assigned to a C=N and C=C group in conjugation. The presence of a conjugated unsaturated system in the heterocyclic portion of the molecule was confirmed by the ultraviolet spectrum of the base, which, in addition to the short-wavelength maximum at 227 mμ (ε 12,900), attributable to the toluene-*p*-sulphonyl group, showed a band of high intensity (ε 12,400) at 278 mμ. To this base we assign structure (XVI), an assignment supported by its ozonolysis



(XVI)

to 4 : 4-dimethyl-1-toluene-*p*-sulphonylpyrrolid-2-one, which on hydrolysis gave ββ-dimethyl-γ-toluene-*p*-sulphonamidobutyric acid. Treatment of the bishydroxylamine (XI) with phosphorus oxychloride and triethylamine gave a 63% yield of a dipyrrolinylmethane derivative whose high basicity (pK_a 12·1) and spectral characteristics (cf. ref. 7) showed it to exist as the vinylogous amidine (XVII); it gave the amide (XVI) on toluene-*p*-sulphonylation. Being the nitrogen analogue of a β-diketone, the product (XVII) readily formed a cobaltous and a cupric complex, both of which were soluble in light petroleum.



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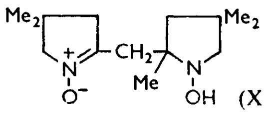

(XVIII)

From our experiments it is apparent that, under the influence of strongly basic catalysts, aldol-type products can be obtained from the Δ^1-pyrroline 1-oxides. On one occasion only did we observe spontaneous dimerisation, that of the oxide (III; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$) to a product whose properties accord with structure (XVIII): storage over alkaline catalysts seemed not to effect the dimerisation, nor did irradiation, although samples of the nitrone which had been kept for long periods reduced the triphenyltetrazolium chloride reagent,[5] a reaction characteristic of the dimer, and not of the monomer.

EXPERIMENTAL

Addition of 2 : 4 : 4-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide to* 4 : 5 : 5-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide*.—(*a*) A mixture of the pyrroline oxides (3·0 g. of each) was dried by azeotropic distillation with benzene and treated with a solution of triphenylmethylsodium (from triphenylmethyl chloride, 7·0 g., and 1·2% sodium amalgam, 120 g.) in anhydrous ether (300 ml.) in a closed evacuated apparatus which also served for the preparation of the reagent. After two days the ethereal solution was extracted with dilute hydrochloric acid. The acid extract was made alkaline with ammonia, and extracted with chloroform (4 × 20 ml.). The chloroform extract was dried (K_2CO_3), filtered through a short column of alumina, and evaporated. Recrystallisation of the solid residue from benzene–light petroleum gave clusters of large colourless needles of 2′ : 4′-trans-2-(1′-*hydroxy*-4′ : 5′ : 5′-*trimethylpyrrolidin*-2′-*ylmethyl*)-4 : 4-*dimethyl*-Δ^1-*pyrroline*

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[7] Lloyd and Marshall, *J.*, 1958, 118.

1-*oxide* (VIII) (1·80 g., 30%), m. p. 136°, $\lambda_{max.}$ (in 95% ethanol) 233 mμ (ε 11,100); $\nu_{max.}$ (mull) 3130 and 1614 cm.$^{-1}$ [Found: C, 66·2; H, 10·1; N, 10·9%; *M* (thermistor method [8]), 263. $C_{14}H_{26}O_2N_2$ requires C, 66·1; H, 10·3; N, 11·0%; *M*, 254]. It readily reduced aqueous alkaline triphenyltetrazolium chloride solution, and even in the solid state the crystals quickly became pale yellow through autoxidation to the yellow oxidation product described below.

The benzene–light petroleum mother-liquors from the crystallisation of the above product were evaporated and stirred with a little water; sticky crystals separated. The mixture was diluted with water (20 ml.) and extracted with ether (4 × 15 ml.). The ethereal extract was evaporated and the residue recrystallised from benzene–light petroleum, giving small colourless prisms of the isomeric 2′ : 4′-cis-*nitrone-hydroxylamine* (0·50 g., 8%), m. p. 171°, $\nu_{max.}$ 3190 and 1624 cm.$^{-1}$ (Found: C, 66·0; H, 10·2; N, 10·9%). It readily reduced aqueous alkaline triphenyltetrazolium chloride solution, but the crystalline substance remained colourless, even on long storage.

(*b*) (By Dr. H. Moncure, jun.) 2 : 4 : 4-Trimethyl-Δ^1-pyrroline 1-oxide (11·0 g.) which had been dried by azeotropic distillation with benzene was treated with a solution of sodamide [from sodium (3·5 g.) in liquid ammonia (500 ml.) in the presence of a trace of ferric nitrate]. After 1 hr. at room temperature, the solution was treated with 4 : 5 : 5-trimethyl-Δ^1-pyrroline 1-oxide (10·5 g., dried by azeotropic distillation with benzene). The mixture was stirred and the liquid ammonia allowed to evaporate until a slurry remained (2—3 hr.). Water (500 ml.) was added cautiously to the semi-solid residue, and the solution extracted with chloroform (5 × 100 ml.); the extract was dried (K_2CO_3) and evaporated. Recrystallisation of the crude solid from benzene–light petroleum gave colourless needles of the *trans*-nitrone-hydroxylamine (15·6 g., 74%), m. p. 136° alone or mixed with the compound prepared as in (*a*).

Extraction of the benzene–light petroleum mother-liquors as in (*a*) failed to yield any of the *cis*-isomer.

Copper-catalysed Oxidation of the Nitrone-hydroxylamines (Va).—(*a*) The above *trans*-nitrone-hydroxylamine, m. p. 136° (0·51 g.), and copper sulphate (0·01 g.) were dissolved in water (10 ml.) and ammonia (1 ml.; *d* 0·880), and air was bubbled through the solution for 2 hr. The solution was extracted with chloroform (5 × 10 ml.), and the chloroform extract evaporated to give a bright yellow gum. This was chromatographed in light petroleum on a column of magnesium carbonate (50 g.). The yellow band was eluted with benzene–light petroleum, and the eluate evaporated to give a yellow solid. Recrystallisation from light petroleum containing a little benzene gave yellow prisms (0·34 g., 68%) of 1 : 2-*di*-(4 : 4-*dimethyl*-Δ^1-*pyrrolin*-2-*yl*)-1 : 2-*di*-(4 : 5 : 5-*trimethyl*-Δ^1-*pyrrolin*-2-*yl*)*ethylene tetra*-N-*oxide* (IX), m. p. 201° (decomp.), $\lambda_{max.}$ (in 95% ethanol) 256 and 380—390 mμ (ε 13,200 and 10,400), $\nu_{max.}$ (mull) 1542 cm.$^{-1}$ [Found: C, 67·0; H, 9·0; N, 11·3%; *M* (micro-Rast), 447. $C_{28}H_{44}O_4N_4$ requires C, 67·2; H, 8·9; N, 11·2%; *M*, 501].

(*b*) The *cis*-nitrone-hydroxylamine (0·10 g.) was oxidised and the product isolated as in (*a*), to give the same yellow oxidation product (0·04 g.), identified by m. p. and mixed m. p. 201° (decomp.).

Reduction of Compound (VIII) *with Potassium Borohydride*.—The *trans*-nitrone-hydroxylamine, m. p. 136° (0·51 g.), and potassium borohydride (0·5 g.) were dissolved in water (10 ml.) and left at room temperature for 48 hr. A crystalline precipitate was then collected and, after drying, weighed 0·31 g. Extraction of the filtrate with ether yielded a colourless gum (0·11 g.). The crystals and the gum were combined and recrystallised from low-boiling light petroleum. Repeated recrystallisation, finally from ethanol, gave rosettes of small needles (0·20 g.) of 1 : 1′-*dihydroxy*-4 : 4 : 4′ : 5′ : 5′-*pentamethyl*-2 : 2′-*dipyrrolidinylmethane*, m. p. 156°, $\nu_{max.}$ 3220 cm.$^{-1}$ (Found: C, 65·6; H, 10·9; N, 11·1. $C_{14}H_{28}O_2N_2$ requires C, 65·6; H, 11·0; N, 10·9%).

The light petroleum mother-liquors from the crystallisation were concentrated, and a small quantity of crystals which separated was collected. The filtrate was evaporated, and the sticky residue recrystallised several times from aqueous methanol. The material thus obtained was sublimed *in vacuo* (bath-temperature 100°/0·5 mm.) and again recrystallised from aqueous methanol, to give a diastereoisomeric *bishydroxylamine* as small feathery needles, m. p. 134° (Found: C, 65·7; H, 11·2; N, 11·1%). The m. p. of this compound was depressed below 120° in admixture with the compound of m. p. 156°. The infrared spectra of the two isomers were similar, but showed distinct differences in the fingerprint region.

Addition of 2 : 4 : 4-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide to* 3 : 3 : 5 : 5-*Tetramethyl*-Δ^1-*pyrroline*

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[8] Iyengar, *Rec. Trav. chim.*, 1954, **73**, 789.

1-*Oxide.*—These pyrroline oxides (2·0 g. of each) were condensed in liquid ammonia (100 ml.) containing sodamide (from 0·7 g. of sodium), and the product isolated as described above. 2-(1′-*Hydroxy*-3′ : 3′ : 5′ : 5′-*tetramethylpyrrolidin*-2′-*ylmethyl*)-4 : 4-*dimethyl*-Δ^1-*pyrroline* 1-*oxide* (Vb) (1·60 g., 40%) was obtained as needles (from methylene chloride–light petroleum), m. p. 150° (Found: C, 67·2; H, 10·4; N, 10·5. $C_{15}H_{28}O_2N_2$ requires C, 67·2; H, 10·4; N, 10·4%). The infrared spectrum (mull) showed maxima at 3110, 1635, and 1617 cm.$^{-1}$.

Addition of 2-*Ethyl*-5 : 5-*dimethyl*-Δ^1-*pyrroline* 1-*Oxide to* 3 : 3 : 5 : 5-*Tetramethyl*-Δ^1-*pyrroline* 1-*Oxide.*—These pyrroline oxides (1·5 g. of each) were condensed in liquid ammonia (100 ml.) containing sodamide (from 0·5 g. of sodium). Next morning water (40 ml.) was added, and the aqueous solution was extracted with chloroform. Evaporation of the chloroform extract yielded an oily mixture of product and starting materials. The latter were removed by sublimation at 90°/15 mm., and the crystalline non-volatile residue was recrystallised from light petroleum to give 2-[1-(1′-*hydroxy*-3′ : 3′ : 5′ : 5′-*tetramethylpyrrolidin*-2′-*yl*)*ethyl*]-5 : 5-*dimethyl*-Δ^1-*pyrroline* 1-*oxide* (VI) (0·48 g., 16%) as prisms, m. p. 121—122° (Found: C, 68·1; H, 10·8; N, 9·8. $C_{16}H_{30}O_2N_2$ requires C, 68·0; H, 10·7; N, 9·9%), $\nu_{max.}$ (mull) at 3260 and 1590 cm.$^{-1}$.

The *picrate* formed needles (from ethanol), m. p. 144° (Found: C, 51·8; H, 6·8; N, 13·7. $C_{22}H_{33}O_9N_5$ requires C, 51·7; H, 6·5; N, 13·7%).

Dimerisation of 4 : 5 : 5-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide with Ethereal Triphenylmethylsodium.*—Triphenylmethylsodium (from triphenylmethyl chloride, 3·5 g., and 1·2% sodium amalgam, 50 g.) in anhydrous ether (200 ml.) was added to the pyrroline oxide (2·0 g.) in benzene (5 ml.) in a closed evacuated apparatus. The mixture was left overnight and then extracted with 3N-hydrochloric acid. The acidic extract was made alkaline with ammonia and extracted with ether (4 × 30 ml.). Evaporation of the ethereal extract and crystallisation of the residue from low-boiling light petroleum gave 3-(1′-*hydroxy*-4′ : 5′ : 5′-*trimethylpyrrolidin*-2′-*yl*)-4 : 5 : 5-*trimethyl*-Δ^1-*pyrroline* 1-*oxide* (VII) (0·27 g., 13%) as clusters of small colourless needles, m. p. 142° [Found: C, 66·1; H, 10·0; N, 11·1%; *M* (thermistor method[8]), 278. $C_{14}H_{26}O_2N_2$ requires C, 66·1; H, 10·3; N, 11·0%; *M*, 254], $\lambda_{max.}$ 236 (ε 6000) in 95% ethanol, 249 mμ (ε 11,800) in *cyclo*hexane, $\nu_{max.}$ 3240 (Nujol mull) and 3680, 3560, and 1583 cm.$^{-1}$ (in chloroform).

Spontaneous Dimerisation of 2 : 4 : 4-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide.*—A sample of the pyrroline oxide (*ca.* 25 g.) which had been stored in the refrigerator for five months deposited a mass of crystals. This was collected on sintered glass, washed with benzene–light petroleum, and recrystallised from the same solvents to give a product (0·76 g.), possibly 2-(1′-*hydroxy*-2′ : 4′ : 4′-*trimethylpyrrolidin*-2′-*ylmethyl*)-4 : 4-*dimethyl*-Δ^1-*pyrroline* 1-*oxide* (XVIII), as small colourless needles, m. p. 115° (Found: C, 66·3; H, 10·2; N, 10·8; active H, 0·52. $C_{14}H_{26}O_2N_2$ requires C, 66·1; H, 10·3; N, 11·0; active H, 0·40%], $\lambda_{max.}$ (in ethanol) 234 mμ (ε 9500), $\nu_{max.}$ 3320 and 1610 cm.$^{-1}$.

Aerial oxidation of the product (0·1 g.) in water (5 ml.) containing ammonia (1 ml.; *d* 0·880) and copper sulphate (10 mg.) gave, after extraction with methylene chloride, a dinitrone as a colourless hygroscopic gum. The *picrate* formed bright yellow prisms (from ethanol), m. p. 120° (Found: C, 50·0; H, 5·7; N, 15·7. $C_{20}H_{27}O_9N_5$ requires C, 49·9; H, 5·7; N, 14·55%). The base was regenerated from the picrate by passage of a methylene chloride solution through a short column of alumina. On evaporation the dinitrone was again obtained as a resin which could not be crystallised. The infrared spectrum showed maxima 1600 and 1591 cm.$^{-1}$.

Action of Toluene-p-*sulphonyl Chloride and Triethylamine on a Bishydroxylamine.*—1 : 1′-Dihydroxy-4 : 4 : 4′ : 5′ : 5′-pentamethyl-2 : 2′-dipyrrolidinylmethane, m. p. 156° (0·26 g.), and toluene-*p*-sulphonyl chloride (0·57 g., 3 mol.) were dissolved in dry pyridine (2·5 ml.), and the solution set aside for 30 min. Dry triethylamine (2·5 ml.) was then added, and the solution heated under reflux for a further 30 min. The solution was evaporated to dryness under reduced pressure and the residue shaken with ether and dilute ammonia. Evaporation of the ethereal solution gave a red gum, which was chromatographed in benzene–light petroleum (1 : 1) on a column of neutral alumina (25 g.). Benzene–light petroleum eluted a pale yellow gum (0·1 g.) (fraction A) and further elution with pure benzene gave a yellow gum (0·06 g.) (fraction B).

Fraction A on treatment with a slight excess of ethanolic picric acid afforded a crystalline *picrate*, which recrystallised from ethanol in lemon-yellow needles, m. p. 157° (Found: C, 52·5; H, 6·0; N, 11·7. $C_{27}H_{35}O_{10}N_5S$ requires C, 52·2; H, 5·7; N, 11·3%).

This picrate was converted into the free base by passage of its benzene solution through a short column of alumina. Evaporation of the benzene eluate and crystallisation of the residue from low-boiling light petroleum gave colourles platelets of 7 : 8 : 8 : 4′ : *4′-pentamethyl-1′-toluene-*p*-sulphonyl-2-oxa-*1*-aza*bicyclo[3 : 3 : 0]*octane-*3-spiro-*2′-pyrrolidine* (XIV), m. p. 86—87° (Found: C, 64·4; H, 8·1; N, 7·0. $C_{21}H_{32}O_3N_2S$ requires C, 64·2; H, 8·2; N, 7·1%), $\lambda_{max.}$ (in 95% ethanol) 228 mμ (ε 9900) with an inflexion at 260—265 mμ (ε 1800), $\nu_{max.}$ (mull) 1600, 1498, 1349, and 1157 cm.$^{-1}$.

Fraction B on treatment with ethanolic picric acid precipitated a very sparingly soluble *picrate*, which was recrystallised from ethanol to give yellow prisms, m. p. 232° (decomp.) (Found: C, 53·5; H, 5·5; N, 11·6. $C_{27}H_{33}O_9N_5S$ requires C, 53·7; H, 5·5; N, 11·6%).

This was also converted into the base by chromatography on alumina from benzene solution. The crude base was recrystallised from light petroleum to give large colourless prisms of 2-(4′ : *4′-dimethyl-1′-toluene-*p*-sulphonylpyrrolidin-2′-ylidenemethyl)*-4 : 5 : *5-trimethyl-*Δ^1*-pyrroline* (XVI), m. p. 142° (Found: C, 67·3; H, 7·9; N, 7·7. $C_{21}H_{30}O_2N_2S$ requires C, 67·3; H, 8·1; N, 7·5%), $\lambda_{max.}$ (in 95% ethanol) 227 (ε 12,900) and 278 mμ (ε 12,400), $\nu_{max.}$ (mull) 1637, 1600, 1580, 1495, 1343, and 1164 cm.$^{-1}$.

Action of Phosphoryl Chloride and Triethylamine on a Bishydroxylamine.—To a solution of 1 : 1′-dihydroxy-4 : 4 : 4′ : 5′ : 5′-pentamethyl-2 : 2′-dipyrrolidinylmethane, m. p. 156° (4·80 g.), in anhydrous benzene (100 ml.) a solution of phosphoryl chloride (6·0 g.) in benzene (10 ml.) was added with cooling. A solution of triethylamine (9 ml.) in benzene (10 ml.) was then added dropwise, and the mixture was left at room temperature for 4 hr. After acidification with 3N-hydrochloric acid the mixture was distilled to remove benzene, and the remaining aqueous solution was cooled and extracted with ether (2 × 25 ml.) to remove non-basic material. 10N-Hydrochloric acid (50 ml.) was added, and the solution heated under reflux for 4 hr. It was then cooled, made strongly alkaline with sodium hydroxide, and extracted with ether (4 × 40 ml.). Evaporation of the ethereal extract gave a yellow gum which, on sublimation at 100° (bath-temperature)/20 mm., yielded substantially pure 2-(4′ : *4′-dimethylpyrrolidin-2′-ylidenemethyl*)-4 : 5 : *5-trimethyl-*Δ^1*-pyrroline* (XVII) as a pale yellow crystalline mass (2·61 g., 63%). Resublimation for analysis gave colourless crystals, m. p. 42° [Found: C, 76·4; H, 11·0; N, 12·9; *M* (micro-Rast), 231. $C_{14}H_{24}N_2$ requires C, 76·3; H, 11·0; N, 12·7%; *M*, 220], $\lambda_{max.}$ (in ether) 300 mμ (ε 17,500), (in 95% ethanol) 320 mμ (ε 43,500), (in 90% ethanol, 0·5N in HCl) 320 mμ (ε 44,000), (in 85% ethanol, N/20 in KOH) 303 mμ (ε 19,200), $\nu_{max.}$ (supercooled film) 3200, 1630, and 1550 cm.$^{-1}$, pK'_a 12·1 (in water).

The *picrate* formed yellow needles (from ethanol), m. p. 189° (Found: C, 53·2; H, 6·1; N, 15·6. $C_{20}H_{27}O_7N_5$ requires C, 53·4; H, 6·1; N, 15·6%).

The base (80 mg.) in methanol (3 ml.) was added to a solution of cobalt nitrate (200 mg.) in aqueous ammonia [1 ml. (*d* 0·880) + 5 ml. of water]. The yellow precipitate formed was extracted with methylene chloride, and the methylene chloride evaporated to give a yellow solid. Purification of this by recrystallisation from ethereal solution by addition of methanol gave the *cobalt complex* as orange prisms, m. p. 137° (Found: C, 67·6; H, 9·7; N, 11·0. $C_{28}H_{46}N_4Co$ requires C, 67·6; H, 9·3; N, 11·3%), $\lambda_{max.}$ (in *cyclo*hexane) 271 (ε 10,800), 324 (ε 29,400), and 431 mμ (ε 1600). A copper complex was readily obtained in a similar manner but this, a deep blue gum, could not be obtained crystalline. Both complexes were readily soluble in low-boiling light petroleum.

The toluene-*p*-sulphonyl derivative was obtained from the base (0·5 g.) by the action of toluene-*p*-sulphonyl chloride (0·5 g.) and triethylamine (0·5 ml.) in benzene (5 ml.). It crystallised from light petroleum in large colourless prisms (0·6 g.), shown by comparison of infrared spectra and by m. p. and mixed m. p. (142°) to be identical with the toluene-*p*-sulphonyl base previously obtained directly by the action of toluene-*p*-sulphonyl chloride and triethylamine on the bishydroxylamine (see above).

*Ozonolysis of Toluene-*p*-sulphonyl Derivative* (XVI).—This compound (0·25 g.) was dissolved in a mixture of glacial acetic acid (10 ml.) and ethyl acetate (5 ml.), and a stream of 3% ozonised oxygen was passed through the solution for 20 min. at 0°. Water (15 ml.) and zinc dust (0·5 g.) were added, and the solution was shaken at room temperature for 1 hr. After filtration the filtrate was evaporated to dryness below 60°, and water (10 ml.) added. The crystalline precipitate which separated was recrystallised from methylene chloride–light petroleum to give colourless platelets of 4 : *4-dimethyl-1-toluene-*p*-sulphonylpyrrolid-2-one* (0·14 g.), m. p. 129° (Found: C, 58·2; H, 6·5; N, 5·3. $C_{13}H_{17}O_3NS$ requires C, 58·4; H, 6·4; N, 5·2%), $\nu_{max.}$ (mull) 1734, 1730, 1595, 1488, 1360, 1166, and 1160 cm.$^{-1}$.

The above pyrrolidone (0·1 g.) was heated with a solution of potassium hydroxide (0·2 g.) in 50% aqueous ethanol (3 ml.) for 30 min. Acidification and extraction with ether yielded ββ-dimethyl-γ-toluene-*p*-sulphonamidobutyric acid as needles (from ether–low-boiling light petroleum), m. p. 148°, undepressed in admixture with an authentic specimen[9] (Found: C, 54·7; H, 6·9; N, 4·9. Calc. for $C_{13}H_{19}O_4NS$: C, 54·7; H, 6·7; N, 4·9%), $\nu_{max.}$ (mull) 3270, 2700, 1600, 1498, 1310, and 1153 cm.$^{-1}$.

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[9] Brown, Clark, and Todd, preceding paper.