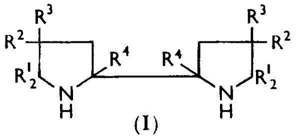
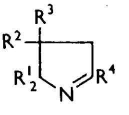
428. *Experiments towards the Synthesis of Corrins. Part VII.* The Reductive Dimerisation of a Δ^1-Pyrroline* 1-*Oxide. Oxidative Degradation of* 2 : 2′- *and* 2 : 3′-*Bipyrrolidinyl Derivatives.*

By V. M. Clark, B. Sklarz, and Sir Alexander Todd.

Sodium–potassium alloy in ethylene glycol dimethyl ether reduces 5 : 5-dimethyl-Δ^1-pyrroline 1-oxide to a 1 : 1′-dihydroxy-2 : 2′-dipyrrolidinyl. Oxidation by sodium metaperiodate readily distinguishes between the 2 : 2′- and 2 : 3′-dipyrrolidinyl series.

THE 2 : 2′-dipyrrolidinyl system (I), parent of the A–D bicyclic component of the corrins, can be formally regarded as the product of the reductive dimerisation of the Δ^1-pyrroline (II), the relationship being analogous to that of a carbonyl compound and its corresponding pinacol. The reductive dimerisation of ketones to pinacols is readily accomplished by using a variety of reagents;[1-3] moreover, electrolytic methods[4] can give high yields. The acyloin reaction[5] might be regarded as a related example. However, application of such methods to azomethines with the object of generating 1 : 2-diamines has received little attention though Anselmino[6] has recorded the reductive dimerisation of benzylideneaniline to *N* : *N*′ : 1 : 2-tetraphenylethane-1 : 2-diamine (III; R = R′ = Ph) using aluminium amalgam in moist ether, and Thies and Schoenenberger[7] have obtained the related product (III; R = Ph, R′ = Et) from benzylidene-ethylamine under the same conditions and by the action of *tert.*-butylmagnesium chloride in ether. The formation of compounds (III; R = Ph) is presumably facilitated by the stability of the intermediary benzyl-type radical-ion (IV; R = Ph), reduction of which by the addition of a further electron is slow, dimerisation supervening. Such stabilisation is absent in the aliphatic series and only one example of the reductive dimerisation of an aliphatic azomethine has been recorded, Picon[8] having obtained *NN*′-diethylbutane-2 : 3-diamine (III; R = Me, R′ = Et) from the action of sodium in liquid ammonia upon *N*-ethylidene-ethylamine. In our hands, sodium in liquid ammonia reduced benzylidene-ethylamine to *N*-ethylbenzylamine but was without action upon 2 : 4 : 4-trimethyl-Δ^1-pyrroline (II; R^1 = H, R^2 = R^3 = R^4 = Me), as was magnesium and mercuric chloride in dry benzene. Aluminium amalgam in moist ether reduced the Δ^1-pyrroline (II; R^1 = R^2 = Me, R^3 = R^4 = H) to the corresponding pyrrolidine.


(I)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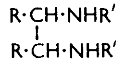
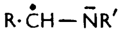

$$\begin{array}{c}\mathrm{R{\cdot}CH{\cdot}NHR'}\\ |\\ \mathrm{R{\cdot}CH{\cdot}NHR'}\end{array}$$
(III)


$$\mathrm{R{\cdot}\dot{C}H{-}\bar{N}R'}$$
(IV)

The addition of the first electron to R•CH=NR′ gives the radical-ion (IV), addition of a second electron to which is facilitated by prior protonation of the *N*-atom, thereby preventing the formation of the dianion, R•$\bar{\mathrm{C}}$H–$\bar{\mathrm{N}}$R′, and giving instead R•$\bar{\mathrm{C}}$H–NHR′. Absence of a proton source would be expected to favour the dimerisation of a radical-ion (IV) to

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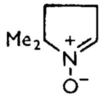
* Part VI, preceding paper.

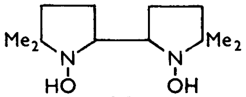
[1] Squire, *J. Amer. Chem. Soc.*, 1951, **73**, 2586.
[2] Newman, *ibid.*, 1940, **62**, 1683.
[3] Gaertner, *J. Org. Chem.*, 1950, **15**, 1006.
[4] Allen, *J. Amer. Chem. Soc.*, 1951, **73**, 3503.
[5] Prelog, *Helv. Chim. Acta*, 1947, **30**, 1741; Stoll and Hulstkamp, *ibid.*, p. 1815.
[6] Anselmino, *Ber.*, 1908, **41**, 621.
[7] Thies and Schoenenberger, *Chem. Ber.*, 1956, **89**, 1918.
[8] Picon, *Compt. rend.*, 1922, **175**, 695.

the dianion of (III) rather than its reduction to $R{\cdot}CH_2{\cdot}NHR'$. Wilkinson and his co-workers[9] have recently shown that liquid sodium–potassium alloys are soluble in ethylene glycol dimethyl ether and that such solutions convert benzyl chloride into dibenzyl and initiate polymerisation of isoprene, styrene, and acrylonitrile. When this aprotic reducing system was used the Δ^1-pyrrolines (II; $R^1 = R^2 = Me$, $R^3 = R^4 = H$; and $R^1 = H$, $R^2 = R^3 = R^4 = Me$) gave oils, and in the second case the Δ^1-pyrroline was partly recovered. However, the Δ^1-pyrroline 1-oxide (V) gave, in low yield, the bishydroxylamine (VI) identical with the product from borohydride reduction of the dimer (VII) obtained from (V) by the action of sodamide in liquid ammonia (preceding paper).

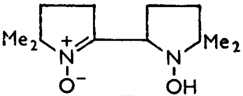
The structure of the nitrone-hydroxylamine (VII) had been previously established, but confirmation was sought in the oxidative degradation of the bishydroxyamine (VI), in particular, by the 1 : 2-glycol-splitting reagents, lead tetra-acetate and sodium metaperiodate. The cleavage of carbon–carbon bonds by both these reagents is not restricted to linked oxygenated carbon atoms, for lead tetra-acetate cleaves α-amino-alcohols[10] and α-amino-acids, and periodate[11] has been reported to oxidise ethylenediamine[12] and piperazine[13] with carbon–carbon bond-cleavage. In our hands lead tetra-acetate was found to oxidise ethylenediamine in glacial acetic acid at 60° and, though no formaldehyde was detected, *N*-formylethylenediamine was isolated. The diamine (III; R = Ph, R′ = Et) consumed two mols. of the reagent, carbon–carbon cleavage occurring with the formation of two mols. of benzaldehyde, isolated as the 2 : 4-dinitrophenylhydrazone. However, 1 : 3-diaminopropane also reacted under the same conditions and although no product was isolated it was apparent that lead tetra-acetate was not sufficiently selective as a reagent to distinguish between the 2 : 2′-bipyrrolidinyl series (VI; VII) and the isomeric 2 : 3′-bipyrrolidinyl series (VIII; IX).



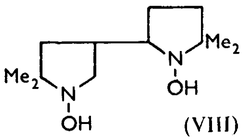
(V)



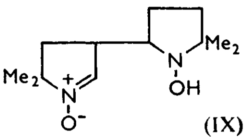
(VI)



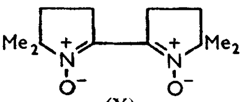
(VII)



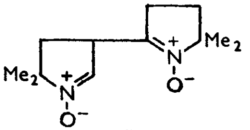
(VIII)



(IX)



(X)



(XI)

Sodium metaperiodate was found to oxidise ethylenediamine (one mole per mole) to formaldehyde (cf. ref. 12), whilst with 1 : 3-diaminopropane there was no reaction. The diamine (III; R = Ph, R′ = Et) was oxidised to a mixture of benzylidene-ethylamine and benzaldehyde, the uptake of periodate again being one mole per mole of diamine. Periodic acid itself also reacted with ethylenediamine and with the amine (III; R = Ph, R′ = Et) although only to a small extent; with 1 : 3-diaminopropane there was again no reaction. The suppression of oxidation of the 1 : 2-diamines under acidic conditions accords with

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[9] Down, Lewis, Moore, and Wilkinson, *Proc. Chem. Soc.*, 1957, 209.

[10] Criegee, *Angew. Chem.*, 1940, **53**, 321; Leonard and Rebenstorf, *J. Amer. Chem. Soc.*, 1945, **67**, 49.

[11] Cf. McCasland and Smith, *ibid.*, 1951, **73**, 5164; Nicolet and Shinn, *ibid.*, 1939, **61**, 1615; Bragg and Hough, *J.*, 1958, 4050.

[12] Fleury, Courtois, and Grandchamp, *Bull. Soc. chim. France*, 1949, 88.

[13] Wickstrøm and Valseth, *Ann. Pharm. franç.*, 1954, **12**, 777.

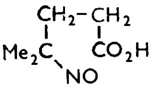
McCasland and Smith's observations [11] on the aminocyclanols where the rates of oxidation were approximately proportional to the amount of unprotonated substrate.

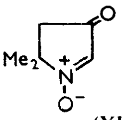
In the 2 : 2′-bipyrrolidinyl series, sodium metaperiodate oxidised the bishydroxylamine (VI) and the hydroxylamine-nitrone (VII) to the α-dinitrone (X), the consumption of periodate after 18 hr. at room temperature being 2·1 and 0·9 mole respectively. Considerably higher periodate absorption was observed in the 2 : 3′-linked series (VIII) and (IX) (see Table), oxidation beyond the β-dinitrone stage (XI) occurring, with the development of a bright blue colour: the β-dinitrone (XI) gave an immediate blue colour with periodate and during 12 hours the pH fell to 3 and a colourless crystalline product separated: analysis, spectra, and its blue melt are consistent with its being the dimer of 4-methyl-4-nitrosopentanoic acid (XII). Periodate oxidation of the bishydroxylamine (VIII) and nitrone-hydroxylamine (IX) gave the same nitroso-acid (XII) together with the keto-nitrone (XIII) isolated as its 2 : 4-dinitrophenylhydrazone, which was identical with that prepared from the parent nitrone (V) by oxidation with selenium dioxide.[14] This 2 : 4-dinitrophenylhydrazone gave a deep purple colour in alkaline solution due, presumably, to the anion (XIV). Oxidation of the hydroxamic acid, 1-hydroxy-5 : 5-dimethylpyrrolid-2-one (XV) also gave the nitroso-acid (XII) with the uptake of one mol. of periodate.

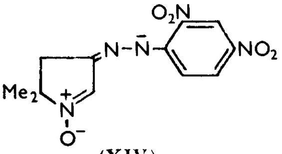
Periodate uptake (mol.) by bipyrrolidinyl derivatives.

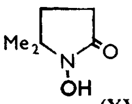
Substrate	After 18 hr.	After 42 hr.
2 : 2′-Series		
Bishydroxylamine (VI)	2·1	2·8
Nitrone-hydroxylamine (VII)	0·9	0·98
α-Dinitrone (X)	0	0
2 : 3′-Series		
Bishydroxylamine (VIII) [a]	4·3	4·8 [b]
Nitrone-hydroxylamine (IX)	4·0	4·6
β-Dinitrone (XI)	2·3 [c]	2·8 [c]

[a] In aqueous dioxan. [b] Unchanged after 96 hr. [c] Based on dihydrate.

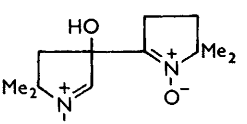

(XII)


(XIII)


(XIV)


(XV)

From the periodate consumption in the 2 : 2′-series and the isolation of the α-dinitrone (X) from both the bishydroxylamine (VI) and nitrone-hydroxylamine (VII) the first stage of oxidation is conversion of the secondary hydroxyamino-groups into nitrones;[15] in the 2 : 3′-series the initial reactions are similar. However, the 3′-carbon atom of the β-dinitrone (XI) is adjacent to two nitrone groups and periodate has been shown to oxidise activated methylene groups,[16] hydrogen being replaced by hydroxyl, the normal cleavage reaction then ensuing. The course of oxidation of the 2 : 3′-compound (XI) is consistent with oxidation to the 3′-hydroxy-derivative (XVI), cleavage of which gives the keto-nitrone (XIII) and the hydroxamic acid (XV), the latter being further oxidised to the nitroso-acid (XII).


(XVI)

EXPERIMENTAL

1 : 1′-*Dihydroxy*-5 : 5 : 5′ : 5′-*tetramethyl*-2 : 2′-*bipyrrolidinyl* (VI).—Freshly distilled 5 : 5-dimethyl-Δ^1-pyrroline 1-oxide (V) (5 g.) was added to a stirred suspension of sodium–potassium

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[14] Cf. Brown, Clark, and Todd, *J.*, 1959, 2105.

[15] Cf. Utzinger and Regenass, *Helv. Chim. Acta*, 1954, **37**, 1892; Thesing and Mayer, *Annalen*, 1957, **609**, 46.

[16] Huebner, Ames, and Bubl, *J. Amer. Chem. Soc.*, 1946, **68**, 1621; Wolfrom and Bobbitt, *ibid.*, 1956, **78**, 2489.

alloy (25% Na; 1·5 g.) in anhydrous ethylene glycol dimethyl ether (150 ml.) which was cooled in an acetone–solid carbon dioxide bath and kept under oxygen-free nitrogen. The blue colour of the suspension was slowly discharged and excessive cooling of the alloy was avoided by removing the cooling-bath at intervals. After 4 hr., only a trace of alloy remained suspended in the yellowish-green solution and it was destroyed by cautiously adding ethanol (10 ml.). The solution was then evaporated under reduced pressure to a thick paste, and water (20 ml.) was added. Extraction with ether gave a sticky solid which was stirred with light petroleum, and the crystalline product (0·5 g.) collected and recrystallised from ethanol. The bishydroxyamine formed colourless needles, m. p. 163° (Found: C, 63·2; H, 10·9; N, 12·4. Calc. for $C_{12}H_{24}O_2N_2$: C, 63·1; H, 10·6; N, 12·3%). It showed no depression in m. p. when mixed with a specimen (m. p. 163°) prepared from the corresponding nitrone-hydroxylamine (VII) by reduction with borohydride.

Periodate Oxidation of Bipyrrolidinyl Derivatives (*cf. Table*).—(a) *Estimations.* In the case of the 2 : 2′-bipyrrolidinyl derivatives (VI, VII, X), a weighed amount (*ca.* 20 mg.) of the substance was added to sodium metaperiodate solution (0·09 g. in 10 ml.), and the mixture diluted to 100 ml. with water, giving a clear solution [it was necessary to use 20 ml. of dioxan to bring (VI) into solution]. Controls were also made up with and without dioxan and aliquot parts of the solutions were titrated after 18 and 42 hr. with 0·0109N-sodium arsenite.

The 2 : 3′-bipyrrolidinyl compounds (VIII, IX, XI) were similarly treated but 20 ml. of reagent solution were used in each case.

(b) *Preparative experiments*: (1) Oxidation of (VI) and (VII). The 2 : 2′-bishydroxylamine (VI) (0·1 g.) was dissolved in methanol (6 ml.), and sodium metaperiodate (200 mg. in 2 ml.). added. More water (6 ml.) was added to re-dissolve a slight precipitate, and the solution was set aside overnight. Methanol was then removed under reduced pressure, the aqueous solution extracted with chloroform (6 × 10 ml.), and the extract dried ($MgSO_4$) and evaporated; recrystallisation of the residue from chloroform–light petroleum gave the dioxide (X), identified by direct comparison with an authentic specimen (m. p., mixed m. p. and infrared spectrum). The same 2 : 2′-dinitrone was obtained by a similar oxidation of the nitrone-hydroxylamine (VII).

(2) Oxidation of 1-hydroxy-5 : 5-dimethylpyrrolid-2-one. When aqueous sodium metaperiodate (0·47 g. in 5 ml.) was added to 1-hydroxy-5 : 5-dimethylpyrrolid-2-one (0·25 g.) the solution at once became blue and a white precipitate formed. After 18 hr. the precipitate was collected and recrystallised first from water and then from chloroform. The colourless crystalline product, believed to be the dimeric form of *4-methyl-4-nitrosopentanoic acid* (XII), melted at 109—110° to a blue liquid (Found: C, 49·6; H, 7·6; N, 9·5. $C_6H_{11}O_3N$ requires C, 49·6; H, 7·6; N, 9·7%); its infrared spectrum showed a band at 1720 cm.$^{-1}$.

(3) Oxidation of the 2 : 3′-dinitrone (XI). On addition of aqueous sodium metaperiodate (0·57 g. in 4 ml.) to a solution of the dinitrone (0·135 g.) in water (1 ml.) the mixture at once became blue and after 2 hr. colourless crystals began to separate. After 18 hr. these were collected; they melted at 106—107°, giving a blue liquid. The recrystallised product was identical with that obtained as in (2) above (mixed m. p., infrared).

(4) Oxidation of (VIII) and (IX). The bishydroxylamine (VIII) (0·45 g.) in dioxan (5 ml.) was added to aqueous sodium metaperiodate (2 g. in 10 ml.). The solution became first blue, then green, and after 18 hr. it was concentrated to 2 ml. and extracted with chloroform. Evaporation of the dried extract gave an oil containing colourless crystals. A small amount of chloroform was added and the crystalline material collected. It had m. p. 107—110° to a blue liquid and the m. p. was undepressed in admixture with the nitroso-compound prepared as in (2) above.

The filtrate from the nitroso-compound was evaporated, and the dark oil dissolved in a little methanol and treated with 2 : 4-dinitrophenylhydrazine in methanolic sulphuric acid in the usual way. The crude 2 : 4-dinitrophenylhydrazone had m. p. 248°. The same two products were obtained by similar treatment of the nitrone-hydroxylamine (IX).

The above hydrazone, recrystallised first from chloroform–light petroleum, then from chloroform alone, formed orange needles, m. p. 256°, $\nu_{max.}$ 1538 cm.$^{-1}$, $\lambda_{max.}$ (in 95% ethanol) 385 (ε 32,500), 266 (ε 13,800) and 219 mμ (ε 13,300), $\lambda_{min.}$ 312 (ε 4930) and 250 mμ (ε 12,000). With aqueous sodium hydroxide the substance gave a purple colour. It was identified by direct comparison (m. p., mixed m. p., and infrared spectrum) as the 2 : 4-dinitrophenylhydrazone of 5 : 5-dimethyl-Δ^1-pyrrolin-3-one 1-oxide (XIII) (see below).

Oxidation of 5 : 5-*Dimethyl*-Δ^1-*pyrroline* 1-*Oxide with Selenium Dioxide.*—The nitrone (V) (1 g.) in methanol (10 ml.) containing selenium dioxide (1 g.) was heated under reflux for 1½ hr. The suspension was cooled, filtered (Hyflo), and evaporated, and the residue taken up in water (15 ml.) and continuously extracted with ether for 24 hr. The dried (Na_2SO_4) extract was passed through a column of magnesium carbonate, then evaporated to a yellow oil which was treated in methanol (10 ml.) with 2 : 4-dinitrophenylhydrazine (1 g.) in 1 : 3 v/v aqueous methanol (20 ml.) containing concentrated sulphuric acid (2 ml.). 5 : 5-*Dimethyl*-Δ^1-*pyrrolin*-3-*one* 1-*oxide* 2 : 4-*dinitrophenylhydrazone* (XIII) separated; it had m. p. 255° after recrystallisation from ethyl acetate (Found: C, 46·7; H, 4·3; N, 22·3. $C_{12}H_{13}O_5N_5$ requires C, 46·9; H, 4·3; N, 22·8%).

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