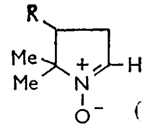
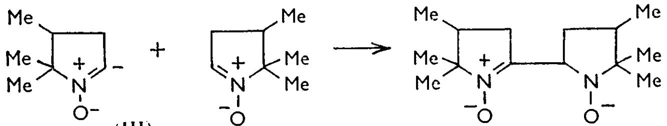
429. *Experiments towards the Synthesis of Corrins. Part IX.*[1] *The Nature of the Sodamide-catalysed Dimerisation of 1-Pyrroline 1-Oxides*

By R. F. C. BROWN, V. M. CLARK, and LORD TODD

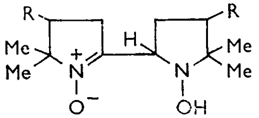
The formation of the 2,2′-bipyrrolidinyl derivative (II; R = Me) by the action of sodamide in liquid ammonia on 2-deutero-4,5,5-trimethyl-1-pyrroline 1-oxide is accompanied by exchange of hydrogen for deuterium in the monomer. The anion (III) is a probable intermediate in the dimerisation reaction.

WHEREAS in the presence of ethereal triphenylmethylsodium, dimerisation of 4,5,5-trimethyl-1-pyrroline 1-oxide (I; R = Me)[2] and 5,5-dimethyl-1-pyrroline 1-oxide (I; R = H)[3] affords 2,3′-dimers of the aldol type, sodamide-catalysed dimerisation in liquid ammonia gives[3] 2,2′-dimers (II; R = Me or H) in a reaction formally analogous to that involved in the formation of benzoin. Although it is still uncertain why these two base-solvent pairs produce different dimers, further evidence concerning the 2,2′-dimerisation has been obtained using the 4,5,5-trimethyl compound (I; R = Me)[3] as substrate. A plausible mechanism requires proton abstraction (by the amide ion) from one molecule of the pyrroline 1-oxide to produce the anion (III); addition of this to a second molecule of compound (I) would give the anion (IV) of the final dimeric product. The experiments described below were designed to detect the formation of the anion (III) by showing that exchange of hydrogen with the solvent and dimerisation are concurrent. Evidence for this


(I)


(III)

(IV)


(II)

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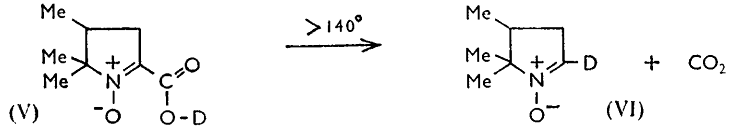
[1] Part VIII, W. D. S. Bowering, V. M. Clark, R. S. Thakur, and Lord Todd, *Annalen*, 1963, **669**, 106.

[2] R. F. C. Brown, V. M. Clark, I. O. Sutherland, and Sir A. Todd, *J.*, 1959, 2109.

[3] R. F. C. Brown, V. M. Clark, M. Lamchen, and Sir A. Todd, *J.*, 1959, 2116.

exchange was sought by analysis of the monomer recovered from the reaction of the deutero-compound, an isotopic test analogous to that used by Skell and Hauser [4] in their study of the mechanism of β-elimination from β-phenylethyl bromide.

The readily available 2-carboxy-4,5,5-trimethyl-1-pyrroline 1-oxide [5] was converted into the deutero-acid by evaporation with deuterium oxide. Decarboxylation of this acid (V) occurred smoothly above 140° [5] giving the 2-deutero-compound (VI); the properties of the pyrroline oxide so obtained (sample *A*) were in agreement with this formulation. The 2-proto-compound (I; R = Me) exhibited infrared absorptions at 3060 (nitrone C–H stretching) and at 1000 cm.$^{-1}$ (nitrone C–H deformation), whereas the spectrum of the deuterated sample *A* showed a band at 2290 cm.$^{-1}$ (C–D stretching) and only very weak absorption at 1000 cm.$^{-1}$. In the region 1320—1600 cm.$^{-1}$ these spectra were indistinguishable. Moreover, in sample *A*, the nitrone C–H peak (at $\tau = 3{\cdot}40$ in the nuclear magnetic resonance spectrum of the 2-proto-compound) was very weak. Mass spectrometric analysis of sample *A*, kindly undertaken by Dr. R. I. Reed, University of Glasgow, showed that it contained 90% of the deutero-compound (VI).



(V) (VI)

The deuterated pyrroline oxide, sample *A*, in dilute solution (~0·05M) in liquid ammonia was treated with 1·1 equiv. of sodamide and after 20 min. the reaction was quenched by the addition of ammonium chloride. The dimer (II; R = Me) was obtained in some 10% yield, and crude monomer (57%) was recovered by distillation. The deuterium content of the dimer was not investigated since it can easily undergo exchange at C-2′ irrespective of any exchange in the monomer. Its infrared spectrum (Nujol mull) was indistinguishable from that of the normal dimer (II; R = Me) bearing hydrogen at C-2′. The recovered pyrroline oxide, sample *B*, was shown by mass spectrometry to contain 39% of deutero-compound. Extension of the reaction time to 40 min. gave a higher yield (23%) of dimer, and the recovered monomer (sample *C*, 51%) contained 18% of deutero-compound as estimated by examination of the C–H deformation band at 1000 cm.$^{-1}$. When 2·2 equiv. of sodamide per mol. of pyrroline oxide were used, with a reaction time of 60 min., no crystalline dimer could be obtained from the non-volatile fraction; presumably this contained a nitrone-pyrroline of the type previously reported,[3] whilst the recovered monomer (sample *D*, 46%) contained approximately 13% of deutero-compound.

The substantial exchange of deuterium in these experiments provides strong evidence not only for the stability of the anion (III) but also for the role it plays in the dimerisation reaction, provided that the latter is essentially irreversible. Were the reaction easily reversible, then the monomer might lose deuterium through the operation of the following equilibria, regardless of the mechanism of dimerisation.

$$\begin{tikzcd}
\text{2-deutero-monomer} \arrow[r, shift left] & \text{deutero-dimer} \arrow[l, shift left] \arrow[d, shift left, "\text{NH}_2^-,\ \text{NH}_3"] \\
\text{2-proto-monomer} \arrow[r, shift left] & \text{proto-dimer} \arrow[l, shift left] \arrow[u, shift left]
\end{tikzcd}$$

Treatment of the dimer (II; R = Me) in liquid ammonia for 35 min. with sodamide (1·3 equiv.: a slight excess) led to a recovery of 89% of starting material; the mother-liquors from purification contained insufficient 4,5,5-trimethyl-1-pyrroline 1-oxide to be detected by paper chromatography. We conclude that deuterium exchange occurs by the direct attack of the amide ion on the 1-pyrroline 1-oxide with formation of the anion (III).

[4] P. S. Skell and C. R. Hauser, *J. Amer. Chem. Soc.*, 1945, **67**, 1661.
[5] R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and Sir A. Todd, *J.*, 1959, **2094**.

Such anions of 2-pyrroline 1-oxides may be included in the interesting and highly reactive group of heterocyclic anions derived from thiazolium salts and related systems.[6]

EXPERIMENTAL

Liquid ammonia was dried by distillation from sodamide before use.

2-*Deutero-4,5,5-trimethyl-1-pyrroline* 1-*Oxide*.—2-Carboxy-4,5,5-trimethyl-1-pyrroline 1-oxide [5] (2·0 g.) was dried by azeotropic evaporation with benzene (20 ml.). Deuterium oxide (5·0 g., 99·8%) in anhydrous tetrahydrofuran (15 ml.) was added in five portions to the residual acid; after each addition the solution was slowly evaporated at 20 mm. by gentle warming with an infrared lamp. Finally the residual deutero-acid was heated for 10 min. at 150—160° to effect decarboxylation. Distillation of the crude product at 0·5 mm. gave a yellow oil which on redistillation afforded the 2-deutero-compound (1·08 g.) as a colourless oil, b. p. 78—80°/0·8 mm., $\nu_{max.}$ 2290 and 1567 cm.$^{-1}$ (liquid film). Mass spectrometric analysis showed that this sample *A* contained 90% of deutero-compound.

The *picrate* formed lemon-yellow prisms, m. p. 115°, from ethanol (Found: C, 43·5; H, 4·6; N, 15·3. $C_{13}H_{15}DN_4O_8$ requires C, 43·7; H + D, 4·8; N, 15·7%).

Deuterium-exchange Reactions.—(*a*) The 2-deutero-pyrroline 1-oxide, sample *A* (300 mg.) was dissolved in benzene (15 ml.) and dried by distillation (of 5 ml. of benzene). The remaining solution was added to one of sodamide (from 60 mg., 1·1 atom, of sodium) in liquid ammonia (50 ml.). After 20 min. the sodamide was decomposed by addition of ammonium chloride (300 mg.) followed by water (10 ml.). After evaporation of the ammonia the benzene layer was separated, and the aqueous layer extracted with chloroform (6 × 5 ml.). Evaporation of the combined benzene and chloroform extracts gave a yellow oil which deposited crystals when stirred with light petroleum (b. p. 40—60°) followed by 12 hr. in the refrigerator. The solid was recrystallised twice from methylene chloride–light petroleum to give the 2,2′-dimer (II; R = Me) (31 mg., 10%), identified by its m. p. and mixed m. p. with an authentic sample, 176—177°. The infrared spectrum of this product in Nujol mull was indistinguishable from that of the dimer of normal hydrogen isotopic composition.

The combined mother-liquors were evaporated to give an oil which was distilled from a small Hickman still at 100° (bath)/1 mm. to give a colourless distillate (172 mg., 57%). This was redistilled slowly at 80° (bath)/1 mm. to give recovered 1-pyrroline 1-oxide, sample *B*, which was shown by mass spectrometric analysis to contain 39% of deutero-compound.

(*b*) The pyrroline oxide, sample *A* (300 mg.), on treatment as in (*a*) with sodamide (1·1 equiv.) for 40 min. afforded the 2,2′-dimer (68 mg., 23%), m. p. 176—177°, and recovered pyrroline oxide, sample *C* (152 mg., 51%). The latter was estimated to contain 18% of deutero-compound by the infrared spectral method described below.

(*c*) The pyrroline oxide, sample *A* (200 mg.), was treated as in (*a*) with sodamide (2·2 equiv.) for 60 min. No crystalline dimer was obtained from this reaction, but the products were separated by vacuum distillation into a semi-solid pot-residue (79 mg.) and recovered pyrroline oxide, sample *D* (92 mg., 46%). The latter was estimated by the infrared spectral method to contain 13% of deutero-compound.

Estimation of Percentage Deutero-compound by Infrared Spectrophotometry.—The infrared spectrum of 4,5,5-trimethyl-1-pyrroline 1-oxide in liquid film contains a sharp band of medium intensity at 1000 cm.$^{-1}$; in the spectrum of the 2-deuterated substance (sample *A*) this band is very weak, and it may therefore be assigned to the nitrone C–H deformation mode. Thus, the intensity of this band in a partially 2-deuterated sample may, in principle, be used to determine its isotopic composition. However, the pyrroline oxides are intensely hygroscopic liquids which, when manipulated on a small scale, contain varying small amounts of water (weak infrared absorption at 3410 and *ca.* 1660 cm.$^{-1}$). For this reason the spectra of thin liquid films of the pyrroline oxide samples were recorded with a Perkin-Elmer Infracord 137 spectrophotometer, and values of log I_0/I at 1000 cm.$^{-1}$ were compared with those of the sharp methyl deformation band at 1369 cm.$^{-1}$. The use of the latter band as an internal standard avoided the necessity of knowing the concentration or exact film thickness of the pyrroline oxide. A plot of the ratio $O.D._{1000}/O.D._{1369}$ against percentage deutero-compound (determined mass spectrometrically) for samples *A* and *B* and the pure 2-hydrogen compound (*E*) gave

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[6] R. Breslow, *J. Amer. Chem. Soc.*, 1958, **80**, 3719; R. B. Woodward, R. A. Olofson, and H. Mayer, *ibid.*, 1961, **83**, 1010.

a straight line from which the compositions of samples *C* and *D* could be read. The method involves several assumptions, *e.g.*, of the constancy of ε at 1369 cm.$^{-1}$ regardless of deuterium substitution at C-2 or the presence of small amounts of water. The values of $\text{O.D.}_{1000}/\text{O.D.}_{1369}$ were reproducible to ± 2—3% using different film thicknesses, and the final errors may be greater, but approximate compositions can easily be determined by this method. Results are tabulated below.

	% 2-H Compound		
Sample	Known	Found	$\text{O.D.}_{1000}/\text{O.D.}_{1369}$
A	10		0·070
B	61		0·326
C		82	0·417
D		87	0·440
E	100		0·502

Action of Sodamide in Liquid Ammonia on a 2,2′-Dimer.—The dimer (II; R = Me) (462 mg., 1 mol.) was added in one portion to liquid ammonia (75 ml.) containing sodamide (from sodium, 54 mg., 1·3 atom) and the solution was left for 35 min. with occasional swirling. Ammonium chloride (200 mg.) and water (50 ml.) were added. The ammonia was allowed to evaporate, and the aqueous solution was extracted with chloroform (6 × 10 ml.). Evaporation of the chloroform extract and crystallisation of the residue from light petroleum gave the 2,2′-dimer (409 mg., 89% recovery), identified by the m. p. and mixed m. p., 177°, and by a comparison of infrared spectra.

Evaporation of the mother-liquors gave a solid residue (38 mg.) which was examined by paper chromatography in the system di-isopropyl ether–s-butanol–water–citric acid (20 : 10 : 20 : 1). On development with iodine vapour it showed a strong spot on the solvent front, but no spot corresponding to the monomer, 4,5,5-trimethyl-1-pyrroline 1-oxide, R_F 0·63.

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