425. *Experiments towards the Synthesis of Corrins. Part IV.* The Oxidation and Ring Expansion of 2 : 4 : 4-Trimethyl-Δ¹-pyrroline 1-Oxide.*

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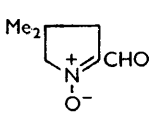
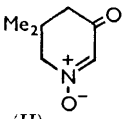
2 : 4 : 4-Trimethyl-Δ¹-pyrroline 1-oxide, on oxidation with selenium dioxide and treatment of the product with acid, undergoes ring expansion to 1 : 2 : 3 : 4-tetrahydro-3 : 3-dimethyl-5-oxopyridine 1-oxide (II); the latter, on Clemmensen reduction, gives 2 : 4 : 4-trimethyl-Δ¹-pyrroline by ring contraction.

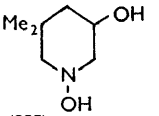
The nitrone group bears a marked resemblance to the carbonyl group both with respect to nucleophilic attack and in facilitating the removal of a proton under basic conditions from an α-carbon atom. Another well-recognised aspect of carbonyl chemistry is the oxidation of an adjacent methylene group to a carbonyl group by means of selenium dioxide;[1] with this reagent, too, the behaviour of Δ¹-pyrroline 1-oxides is clearly analogous. Thus, oxidation of 2 : 4 : 4-trimethyl-Δ¹-pyrroline 1-oxide[2] with selenium dioxide in methanol gave a dark oil whose reactions with carbonyl reagents were in accord with formula (I). However, when heated with N-hydrochloric acid, the dark oil was converted into a crystalline isomer which also gave derivatives with carbonyl reagents and to which we now assign structure (II).



(I)



(II)



(III)

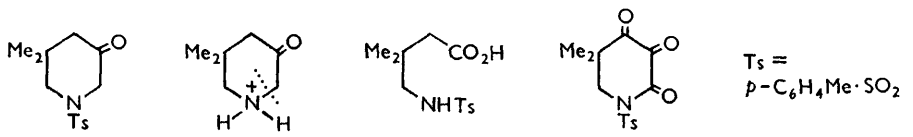
The infrared spectrum of compound (II) showed strong bands at 1653 and 1546 cm.$^{-1}$ which could be attributed to a carbonyl and a nitrone group in conjugation, and a further strong band at 3030 cm.$^{-1}$ associated with the C–H stretching mode at unsaturated carbon. In the case of aldehydes this band is generally observed[3] at 2900—2700 cm.$^{-1}$, whereas Δ¹-pyrroline 1-oxides with a hydrogen atom at position 2 show the corresponding band near 3050 cm.$^{-1}$.[2] This spectral evidence suggested that, on treatment with acid, the aldehyde (I) had undergone ring opening with re-closure to form the ketone (II). The nuclear magnetic resonance spectrum, measured at 40 Mc./sec. for a carbon tetrachloride solution, supported this interpretation for, whereas the aldehydic hydrogen in a number of aldehydes examined in this laboratory has exhibited a chemical shift, σ, of $-4{\cdot}8 \pm 0{\cdot}7$ (in parts per million relative to water), the compound (II) gave a peak at σ −1·6; reference to 3 : 3 : 5 : 5-tetramethyl-Δ¹-pyrroline 1-oxide[2] disclosed a similar peak at σ −1·05 due undoubtedly to the CH of the nitrone grouping.

Whilst both the infrared and the nuclear magnetic resonance spectra supported structure (II), Clemmensen reduction of the compound gave 2 : 4 : 4-trimethyl-Δ¹-pyrroline, the product expected of (I). Reduction of compound (II) by aqueous potassium borohydride gave the crystalline β-hydroxy-hydroxylamine (III), but attempts to reduce this further to 3 : 3-dimethylpiperidine were unsuccessful. With phosphorus and hydriodic acid at 160°, the product (III) gave 5-hydroxy-3 : 3-dimethylpiperidine, and at 210° the product was an unidentified aliphatic amine, $C_7H_{17}N$. 5-Hydroxy-3 : 3-dimethylpiperidine with toluene-*p*-sulphonyl chloride and aqueous sodium hydrogen carbonate gave an oil

* Part III, preceding paper.

[1] Rabjohn in "Organic Reactions," ed. Adams, Wiley, New York, 1949, Vol. V, p. 331.
[2] Bonnett, Brown, Clark, Sutherland, and Todd, *J.*, 1959, 2094.
[3] Bellamy, "The Infra-Red Spectra of Complex Molecules," Methuen, London, 2nd edn., 1958, p. 156.

which contained a substantial amount of the *N*-toluene-*p*-sulphonyl derivative, for on oxidation with chromic acid in acetone [4] it afforded the crystalline ketone (IV). Clemmensen reduction of this ketone removed the toluene-*p*-sulphonyl group but the product was again 2 : 4 : 4-trimethyl-Δ^1-pyrroline. The formation of this base from both ketones (II) and (IV) provides another example of the ring contraction of homocyclic α-amino-ketones on Clemmensen reduction which has been investigated in detail by Leonard and his co-workers.[5] The common intermediate, the protonated ketopiperidine (V), would be expected to undergo reductive fission as indicated, to give the amino-ketone corresponding to 2 : 4 : 4-trimethyl-Δ^1-pyrroline. The latter is reduced to the pyrrolidine particularly slowly by metal–acid combinations [6] so that the intermediate (and the mechanism [7]) are the more easily discernible. In the case of ketone (II), though not of (IV), an alternative interpretation based on the more rapid reduction of the aldehyde (I), presumed to be in



(IV) (V) (VI) (VII)

equilibrium with ketone (II) in the strongly acidic medium, is possible but less likely. Treatment of the ketone (IV) with *p*-nitrosodimethylaniline in alkaline solution, followed by acid hydrolysis, gave a mixture. The acidic fraction yielded ββ-dimethyl-γ-toluene-*p*-sulphonamidobutyric acid (VI) whose formation is consonant with the structure allotted to the ketone (IV) and, hence, with that of the original ketone (II).

Catalytic hydrogenation of the ketone (II) in ethanol over platinum gave 5-hydroxy-3 : 3-dimethylpiperidine, three mols. of hydrogen being absorbed. This ready hydrogenolysis of the N–O bond is unusual amongst cyclic nitrones; dimeric 1 : 2 : 3 : 4-tetrahydropyridine 1-oxide on hydrogenation over platinum in acidic ethanol gives only 1-hydroxypiperidine [8] and previously we have obtained only 1-hydroxypyrrolidines from hydrogenation of Δ^1-pyrroline 1-oxides. The hydrogenation was also unusual in that the solution developed a deep red colour which was discharged abruptly after two mols. of hydrogen had been absorbed: the rate of absorption of the third mol. was much slower.

Experimental

1 : 2 : 3 : 4-*Tetrahydro*-3 : 3-*dimethyl*-5-*oxopyridine* 1-*Oxide*.—2 : 4 : 4-Trimethyl-Δ^1-pyrroline 1-oxide [2] (4·5 g.) and selenium dioxide (3·93 g.) in methanol (30 ml.) were heated under reflux for 2 hr. Deposited selenium was filtered off, and the solution evaporated to leave a dark syrup. N-Hydrochloric acid (30 ml.) was added, the solution heated on the steam-bath for 30 min., and the newly precipitated selenium again removed. The new filtrate was continuously extracted with ether for 10 hr., and the extract dried (Na_2SO_4) and, after passage through a short column of alumina, evaporated to 15 ml.; addition of light petroleum (b. p. 40—60°) then induced crystallisation. Recrystallisation from ether–light petroleum gave 1 : 2 : 3 : 4-*tetrahydro*-3 : 3-*dimethyl*-5-*oxopyridine* 1-*oxide* (1·4 g., 28%) as pale yellow plates, m. p. 75° (Found: C, 59·6; H, 7·8; N, 9·9. $C_7H_{11}O_2N$ requires C, 59·6; H, 7·9; N, 9·9%), $\lambda_{max.}$ (in ethanol) 280 mμ (ε 17,500), $\nu_{max.}$ (mull) 3030, 1653, and 1546 cm.$^{-1}$. The 2 : 4-*dinitrophenylhydrazone* formed orange-red leaflets (from ethyl acetate–ethanol), m. p. 248° (decomp.) (Found: C, 48·5; H, 4·5; N, 21·8. $C_{13}H_{15}O_5N_5$ requires C, 48·6; H, 4·7; N, 21·8%), $\lambda_{max.}$ (in ethanol) 385 mμ (ε 33,400).

Clemmensen Reduction of 1 : 2 : 3 : 4-*Tetrahydro*-3 : 3-*dimethyl*-5-*oxopyridine* 1-*Oxide*.—The

[4] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2548.
[5] Leonard and Wildman, *J. Amer. Chem. Soc.*, 1949, **71**, 3089, and succeeding papers.
[6] Bonnett, Clark, Giddey, and Todd, *J.*, 1959, 2087.
[7] Leonard and Sentz, *J. Amer. Chem. Soc.*, 1952, **74**, 1704.
[8] Thesing and Mayer, *Chem. Ber.*, 1956, **89**, 2159.

oxo-compound (200 mg.) and amalgamated zinc wool (4 g.) in 10N-hydrochloric acid (5 ml.) were heated together for 8 hr., further addition of hydrochloric acid (1 ml.) being made at hourly intervals. Subsequently the mixture was made alkaline and steam-distilled. Neutralisation of the first 40 ml. of distillate with ethanolic picric acid was accompanied by precipitation of a salt which, on recrystallisation from ethanol, afforded 2 : 4 : 4-trimethyl-Δ^1-pyrroline picrate (195 mg., 40%) as yellow needles, m. p. 193°, undepressed on admixture with an authentic sample.[6]

Reduction of 1 : 2 : 3 : 4-*Tetrahydro*-3 : 3-*dimethyl*-5-*oxopyridine* 1-*Oxide with Potassium Borohydride.*—The oxo-compound (0·50 g.) and potassium borohydride (0·50 g.) were dissolved in water (10 ml.) and kept at room temperature for 48 hr. Extraction with ether followed by evaporation of the solvent gave a colourless gum which crystallised from ether–light petroleum (b. p. 40—60°) to give 1 : 5-*dihydroxy*-3 : 3-*dimethylpiperidine* (0·47 g.) as prisms, m. p. 80° (Found: C, 58·2; H, 10·6; N, 9·7. $C_7H_{15}O_2N$ requires C, 57·9; H, 10·4; N, 9·7%). It readily reduced aqueous alkaline triphenyltetrazolium chloride.[9]

Reduction of 1 : 5-*Dihydroxy*-3 : 3-*dimethylpiperidine with Phosphorus and Hydriodic Acid.*—(*a*) The 1-hydroxypiperidine (250 mg.), red phosphorus (80 mg.), and 56% hydriodic acid (3 ml.) were heated in a sealed tube at 160° for 6 hr. The mixture was made alkaline and steam-distilled, and the distillate neutralised with hydrochloric acid. Evaporation yielded a crystalline residue which, on recrystallisation from ethanol–ether, gave 5-*hydroxy*-3 : 3-*dimethylpiperidine hydrochloride* as prisms, m. p. 200° (Found: C, 50·8; H, 9·9; N, 8·6. $C_7H_{16}ONCl$ requires C, 51·0; H, 9·7; N, 8·5%). The product did not reduce aqueous alkaline triphenyltetrazolium chloride. (*b*) The 1-hydroxypiperidine (150 mg.), red phosphorus (200 mg.), and 56% hydriodic acid (3 ml.) were heated at 210° for 14 hr. The product was isolated as the *picrate* which crystallised from methylene chloride–ether as pale yellow needles, m. p. 124° (Found: C, 45·5; H, 5·7; N, 16·2. $C_7H_{17}N,C_6H_3O_7N_3$ requires C, 45·3; H, 5·9; N, 16·3%).

Catalytic Hydrogenation of 1 : 2 : 3 : 4-*Tetrahydro*-3 : 3-*dimethyl*-5-*oxopyridine* 1-*Oxide.*—The oxo-compound (72 mg.) was hydrogenated over pre-reduced platinum oxide (10 mg.) in ethanol (10 ml.) at 25°, uptake of hydrogen (37 ml., 3 mol.) being complete in 20 min. Neutralisation of the filtered solution with hydrochloric acid, followed by evaporation and crystallisation of the residue from ethanol–ether, gave 5-hydroxy-3 : 3-dimethylpiperidine hydrochloride (73 mg.) as prisms, m. p. 200° undepressed on admixture with the product from the phosphorus–hydriodic acid reduction.

3 : 3-*Dimethyl*-5-*oxo*-1-*toluene*-p-*sulphonylpiperidine.*—1 : 2 : 3 : 4-Tetrahydro-3 : 3-dimethyl-5-oxopyridine 1-oxide (1 g.) in ethanol (30 ml.) was hydrogenated over platinum oxide (50 mg.), absorption being complete after 6 hr. The β-hydroxy-piperidine was isolated as the hydrochloride which, without purification, was shaken with saturated aqueous sodium hydrogen carbonate (20 ml.) and a solution of toluene-*p*-sulphonyl chloride (1·5 g.) in acetone (20 ml.). After 1 hr., 3N-sodium hydroxide (40 ml.) was added and the mixture warmed on the steam-bath to complete the hydrolysis of unchanged toluene-*p*-sulphonyl chloride. Extraction with ether followed by evaporation yielded a viscous yellow oil (1·9 g.) whose infrared spectrum showed it to be the required 5-hydroxy-1-toluene-*p*-sulphonyl compound. The crude oil was dissolved in acetone (30 ml.), and a solution (1·5 ml.; 8N with respect to oxygen [4]) of chromic acid in aqueous sulphuric acid added.

After 10 min., a few drops of propan-2-ol were introduced, the acetone evaporated, water added, and the product extracted with ether. The ethereal extract was filtered through a short column of alumina and concentrated (to 10 ml.). Addition of light petroleum (b. p. 40—60°) and recrystallisation of the precipitated product from ether–light petroleum gave 3 : 3-*dimethyl*-5-*oxo*-1-*toluene*-p-*sulphonylpiperidine* (0·7 g., 35%) as needles, m. p. 110° (Found: C, 59·7; H, 6·9; N, 5·2. $C_{14}H_{19}O_3NS$ requires C, 59·8; H, 6·8; N, 5·0%), $\nu_{max.}$ (mull) 1726 cm.$^{-1}$. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol as yellow needles, m. p. 190° (Found: C, 52·0; H, 4·8; N, 15·2. $C_{20}H_{23}O_6N_5S$ requires C, 52·1; H, 5·0; N, 15·2%).

Clemmensen Reduction of 3 : 3-*Dimethyl*-5-*oxo*-1-*toluene*-p-*sulphonylpiperidine.*—The ketone (200 mg.), acetic acid (1 ml.), 10N-hydrochloric acid (4 ml.), toluene (2 ml.), and amalgamated zinc wool (3 g.) were heated together under reflux for 5 hr. The solution was decanted from zinc amalgam and diluted to 25 ml. with water, and the non-basic material (which had a strong smell of thio-*p*-cresol) removed by extraction with ether. The aqueous solution was then made

[9] Snow, *J.*, 1954, 2588.

alkaline and steam-distilled. Neutralisation of the distillate with picric acid, evaporation to dryness, and recrystallisation of the residue from ethanol gave 2 : 4 : 4-trimethyl-Δ^1-pyrroline picrate as yellow needles (99 mg., 41%), m. p. and mixed m. p. 193°.

Synthesis of ββ-*Dimethyl*-γ-*toluene*-p-*sulphonamidobutyric Acid.*—ββ-Dimethylglutaric anhydride was converted by ammonolysis followed by Hofmann degradation in methanol into the crude urethane, ββ-dimethyl-γ-(methoxycarbonylamino)butyric acid, as described by Brown and van Gulick.[10]

The urethane (1·30 g.) was heated under reflux for 4 hr. with 5N-hydrochloric acid (4 ml.). Neutral material was then removed from the cooled solution by extraction with ether, and the aqueous solution evaporated to dryness. The crystalline residue was recrystallised from ethanol and ether to give *γ-amino-ββ-dimethylbutyric acid hydrochloride* (0·72 g.) as needles, m. p. 140° (Found: C, 43·2; H, 8·4; N, 8·5. $C_6H_{14}O_2NCl$ requires C, 43·0; H, 8·4; N, 8·4%).

To this hydrochloride (0·3 g.) and sodium hydrogen carbonate (0·5 g.) in water (20 ml.), toluene-*p*-sulphonyl chloride (0·8 g.) in acetone (20 ml.) was added. The mixture was shaken at room temperature for 3 hr., after which the acetone was evaporated, excess of toluene-*p*-sulphonyl chloride removed by extraction with ether, and the aqueous solution acidified to give the *toluene*-p-*sulphonamido-acid* (0·16 g.), which formed needles, m. p. 148° (Found: C, 54·5; H, 6·6; N, 5·0. $C_{13}H_{19}O_4NS$ requires C, 54·7; H, 6·7; N, 4·9%).

Reaction of 3 : 3-*Dimethyl*-5-*oxo*-1-*toluene*-p-*sulphonylpiperidine* ***with*** p-*Nitrosodimethylaniline.*—The ketone (220 mg.) and *p*-nitrosodimethylaniline (120 mg., 1 mol.) in ethanol (5 ml.) containing aqueous 3N-sodium hydroxide (2 drops) were left at room temperature for 15 hr., after which the ethanol was evaporated and 10N-hydrochloric acid (3 ml.) added. The acidic solution was heated on the steam-bath for 15 min., diluted to 20 ml. with water, and extracted with ether; the extract was separated into an acidic and a neutral fraction by extraction with aqueous sodium hydrogen carbonate. The acidic fraction was crystalline and after several recrystallisations from ether–light petroleum (b. p. 40—60°) gave ββ-dimethyl-γ-toluene-*p*-sulphonamidobutyric acid (23 mg.) as needles, m. p. and mixed m. p. 148° (Found: C, 55·0; H, 6·6. Calc. for $C_{13}H_{19}O_4NS$: C, 54·7; H, 6·7%). The infrared spectra of this and the previous specimen were identical.

The neutral fraction, a small quantity of yellow oil, failed to crystallise. On treatment with 2 : 4-dinitrophenylhydrazine in ethanolic sulphuric acid it gave a bright red precipitate which was recrystallised by adding ether to its solution in dimethylformamide containing a little acetic acid. This afforded small red prisms of a *bis*-2 : 4-*dinitrophenylhydrazone*, m. p. 256° (decomp.) (Found: C, 46·9; H, 4·2; N, 19·2. $C_{26}H_{23}O_{11}N_9S$ requires C, 46·6; H, 3·5; N, 18·8%). Its infrared spectrum showed a carbonyl band at 1665 cm.$^{-1}$ in addition to bands at 1610 and 1587 cm.$^{-1}$ (Nujol mull). In the visible and ultraviolet region, maxima occurred at 397 mμ (ε 37,900) and 439 mμ (ε 36,300) (in chloroform solution containing 5% of neutral dimethylformamide). As the bis-2 : 4-dinitrophenylhydrazone of 3 : 3-dimethyl*cyclo*hexane-1 : 2-dione [11] has $\lambda_{max.}$ 351 (ε 32,600) and 388 mμ (ε 25,700) it is probable that our product is a derivative of 3 : 3-dimethyl-4 : 5 : 6-trioxo-1-toluene-*p*-sulphonylpiperidine (VII). In aqueous-ethanolic sodium hydroxide it gave a deep blue solution.

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[10] Brown and van Gulick, *J. Amer. Chem. Soc.*, 1955, **77**, 1083.
[11] Ramirez and Bellet, *J. Amer. Chem. Soc.*, 1954, **76**, 491.