446. *Photochemical Transformations. Part XVIII.* Some Experiments Related to the Synthesis of Conessine*

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Attempts to repeat earlier work on the photolytic cyclisation of azides to furnish pyrrolidines have not so far succeeded. An alternative partial synthesis of conessine has, therefore, been devised, based upon the photolysis of 3β-acetoxypregn-5-en-20β-ol nitrite to give the isomeric 18-hydroxyimino-derivative. The construction of the pyrrolidine ring from δ-hydroxy-oximes has been achieved, and the method applied to the 18-hydroxyimino-compound mentioned above.

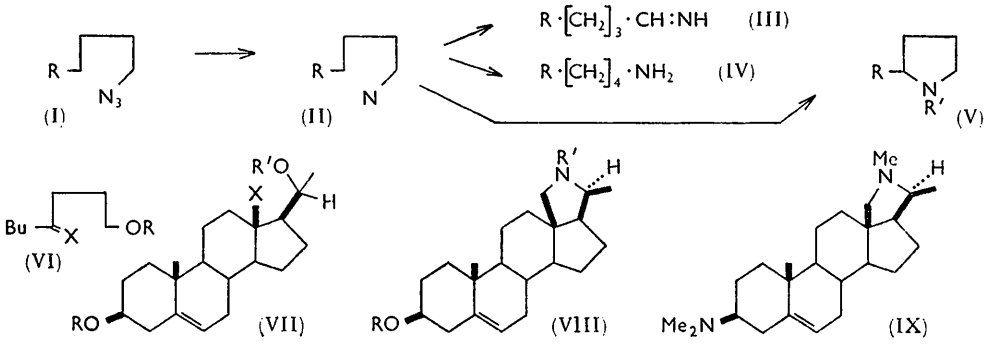
In an earlier Part of this Series we described a partial synthesis of the steroidal alkaloid conessine (IX), based upon the photolytic cyclisation of alkyl azides to pyrrolidines.[1] We represented this cyclisation by the hypothesis that alkyl azide (I) gave nitrene (II) which afforded imine (III), amine (IV), and pyrrolidine (V; R′ = H) as stable molecular products. Dr. G. Smolinsky (Bell Telephone Laboratories), who has done important work on the photolytic and pyrolytic properties of azides,[2] has informed us that he could not repeat our work on the cyclisation of aliphatic azides to pyrrolidines. We have carried out experiments on the photolysis of n-butyl and n-octyl azides under the conditions used by Professor L. R. Morgan, jun., when he worked at Imperial College, but even with a variety of lamps, we could not duplicate the earlier work (for examples, see Experimental section). The main photolytic product in our hands (A. N. S.) has always been the imine (III), in agreement with the work of Saunders and Caress.[3] However, Professor R. M. Moriarty (Catholic University of America, Washington) informs us that he has been able to repeat the photolytic cyclisation of n-octyl azide to 2-butylpyrrolidine. It is clear that the conditions for effecting this closure are still not adequately defined, and the results in the earlier Paper[1] must be regarded with reserve. Each experiment requires repetition by others before it can be finally accepted. We are, therefore, not certain as to the status of the conessine synthesis carried out by Professor Morgan. We thought it desirable to complete another partial synthesis of the alkaloid, even though three elegant total syntheses[4-6] have been reported in the meantime.

The first requirement for a partial synthesis of conessine is, as we discussed earlier,[1] a procedure for the construction of a pyrrolidine ring starting with a hydroxyl group. The photolysis of nitrites[7] provides a convenient approach. Photolysis of n-octyl nitrite gave

* Part XVII, *J.*, preceding Paper.

[1] D. H. R. Barton and L. R. Morgan, jun., *Proc. Chem. Soc.*, 1961, 206; *J.*, 1962, 622.
[2] See R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, 1964, **64**, 149.
[3] W. H. Saunders and E. A. Caress, *J. Amer. Chem. Soc.*, 1964, **86**, 861.
[4] G. Stork, S. D. Darling, I. T. Harrison, and P. S. Wharton, *J. Amer. Chem. Soc.*, 1962, **84**, 2018.
[5] J. A. Marshall and W. S. Johnson, *J. Amer. Chem. Soc.*, 1962, **84**, 1485.
[6] W. Nagata, T. Terasawa, and T. Aoki, *Tetrahedron Letters*, 1963, 865, 869.
[7] D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Amer. Chem. Soc.*, 1960, **82**, 2640.

dimeric 4-nitroso-octan-1-ol, readily converted[8] into 4-hydroxyimino-octan-1-ol (VI; X = N·OH, R = H). Reduction of this oxime with lithium aluminium hydride gave 4-amino-octan-1-ol (VI; X = H,NH_2, R = H) which was treated with excess of toluene-*p*-sulphonyl chloride to afford the bis-derivative (VI; X = H,NH·SO_2·C_7H_7, R = SO_2·C_7H_7).



This cyclised readily when treated with potassium t-butoxide, or simply warmed with pyridine, to give the toluene-*p*-sulphonamide (V; R = C_4H_9, R′ = SO_2·C_7H_7) of 2-butylpyrrolidine.

3β-Acetoxypregn-5-en-20β-ol (VII; R = Ac, R′ = H, X = Me) [9,10] was converted into its nitrite by the action of nitrosyl chloride in pyridine. Photolysis of the nitrite gave, in about 25% yield, 18-hydroxyiminopregn-5-ene-3β,20β-diol 3-acetate (VII; R = Ac, R′ = H, X = CH:N·OH). The nuclear magnetic resonance (n.m.r.) spectrum showed a quaternary (C-19) methyl group at 9·03τ (singlet) and a secondary (C-21) methyl group at 8·85τ (doublet). In addition, the aldoxime hydrogen could be seen as a singlet (one H of C*H*:N·OH) at 2·58τ. There was no signal corresponding to the C-18 methyl group.[11] Attempted reduction of the oxime with lithium aluminium hydride in ether gave 18-hydroxyiminopregn-5-ene-3β,20β-diol (VII; R = R′ = H, X = CH:N·OH). When treated with methanesulphonyl chloride in pyridine this afforded the nitrile (VII; R = R′ = $MeSO_2$, X = CN), whose n.m.r. spectrum had signals at 6·91 (3H) and at 7·00 (3H)τ corresponding to two methanesulphonate groupings. The aldoxime hydrogen, previously seen at 2·58τ (see above), had disappeared.

In contrast, reduction of the oxime with lithium aluminium hydride in dioxan under reflux gave 18-aminopregn-5-ene-3β,20β-diol (VII; R = R′ = H, X = CH_2·NH_2). When warmed in acetone this amine readily afforded the isopropylidene derivative (VII; R = R′ = H, X = CH_2·N:CMe_2). The imine formulation was confirmed by an infrared band at 1668 $cm.^{-1}$ and by two new peaks (3H each) in the n.m.r. spectrum at 7·96 and 8·13τ, indicative of olefinic-type methyl groups.

With acetic anhydride–pyridine under reflux, 18-aminopregn-5-ene-3β,20β-diol gave the triacetyl derivative (VII; R = R′ = Ac, X = CH_2·NHAc). Mild alkaline hydrolysis of the triacetate furnished the monoacetyl derivative (VII; R = R′ = H, X = CH_2·NHAc); which was also conveniently prepared by treatment of the 18-amino-diol (VII; R = R′ = H, X = CH_2·NH_2) with acetic anhydride–acetic acid at room temperature. Partial acetylation of either the 18-amino-diol or its *N*-acetyl derivative at room temperature with pyridine–acetic anhydride gave mixtures from which the diacetyl derivative (VII; R = Ac, R′ = H, X = CH_2·NHAc) could be isolated by chromatography. Treatment of the diacetyl derivative with methanesulphonyl chloride in pyridine at room temperature gave the methanesulphonate (VII; R = Ac, R′ = $MeSO_2$, X = CH_2·NHAc) which cyclised

[8] P. Kabasakalian and E. R. Townley, *J. Amer. Chem. Soc.*, 1962, **84**, 2711.
[9] P. Wieland and K. Miescher, *Helv. Chim. Acta*, 1949, **32**, 1922.
[10] H. Hirschmann, M. A. Daus, and F. B. Hirschmann, *J. Biol. Chem.*, 1951, **192**, 115.
[11] Cf. W. R. Benn, *J. Org. Chem.*, 1963, **28**, 3557.

spontaneously to the tertiary amide (VIII; R = R′ = Ac). The course of the cyclisation could be followed by the disappearance of the amide-II band at 1535 cm.$^{-1}$ and of the NH band at 3420, both bands being characteristic of the intermediary secondary amide. Mild alkaline hydrolysis of the cyclisation product gave *N*-acetylnorlatifoline [12] (VIII; R = H, R′ = Ac). Removal of the acetyl group with calcium in liquid ammonia [4] afforded norlatifoline (VIII; R = R′ = H) identical with an authentic specimen.[12]

A shorter route to norlatifoline was devised as follows. The amino-diol (VII; R = R′ = H, X = $CH_2 \cdot NH_2$), treated with methanesulphonyl chloride in pyridine, gave the dimethanesulphonyl derivative (VIII; R = R′ = $MeSO_2$). Now, the reductive removal of toluene-*p*-sulphonyl residues by use of sodium in liquid ammonia has been demonstrated.[13] The method should be useful for toluene-*p*-sulphonates or methanesulphonates which are sensitive to hydrolysis, for example, derivatives of homoallylic systems. In agreement, we have shown that reduction of cholesterol toluene-*p*-sulphonate with calcium in liquid ammonia re-forms cholesterol in good yield (80%). Reduction of the dimethanesulphonate (VIII; R = R′ = $MeSO_2$) with calcium in liquid ammonia gave norlatifoline (VIII; R = R′ = H) as the basic product.

The conversion of norlatifoline into latifoline and thence into conessine (IX) has been reported.[5,6,14] The partial synthesis of norlatifoline that we have completed amounts, therefore, to the desired partial synthesis of conessine (IX).

Experimental

Melting points were taken on a Kofler hot-stage apparatus. Unless otherwise specified, optical rotations and infrared spectra refer to chloroform solutions. Light petroleum had b. p. 60—80°. The course of reactions and of column chromatography was followed by thin-layer chromatography (t.l.c.). N.m.r. spectra were determined in deuterochloroform on a Varian Associates A-60 Spectrometer on permanent loan from the Wellcome Trust, with tetramethylsilane as internal standard.

Photolysis of Azides.—Irradiations were carried out under oxygen-free nitrogen in a quartz flask with infrared control (disappearance of azide band at 2130 cm.$^{-1}$).

Irradiation of n-octyl azide. (*a*) The azide (3·3 ml.) in dry cyclohexane (400 ml.) was irradiated for 3 hr. with a 500 w high-pressure mercury lamp 6—10 cm. from the flask. The solvent was removed *in vacuo*, and the residue in pyridine (10 ml.) treated with toluene-*p*-sulphonyl chloride (recrystallised; 5 g.) for 5 days at room temperature. The product was carefully chromatographed over alumina (Grade V; 130 g.). Thin-layer chromatography of each of the chromatogram fractions gave no indication of 2-butylpyrrolidine toluene-*p*-sulphonamide.

(*b*) n-Octyl azide (1·79 g.) in anhydrous ether (180 ml.) was irradiated with a 125 w high-pressure mercury lamp for 3 hr. A portion (40 ml.) was treated with 2,4-dinitrophenylhydrazine reagent. Filtration through alumina (40 g.; Grade I) in benzene gave octanal 2,4-dinitrophenylhydrazone [15] (560 mg., 70%), m. p. 106—107° (from ethanol) (Found: C, 54·7; H, 6·35. Calc. for $C_{14}H_{20}N_4O_2$: C, 54·55; H, 6·55%).

(*c*) n-Octyl azide (1·05 g.) in anhydrous ether (150 ml.) was irradiated for 1 hr. with a Hanau immersion lamp with high-pressure burner Q81 placed in a quartz sleeve surrounded by the azide solution. Dry hydrogen chloride was passed through the solution until saturated. Addition of water, separation of the basic fraction, treatment with toluene-*p*-sulphonyl chloride in pyridine as in the above example, and thin-layer chromatography showed, at best, only trace amounts of 2-butylpyrrolidine toluene-*p*-sulphonamide.

(*d*) n-Octyl azide (1·58 g.) in dry ether (250 ml.) was irradiated for 20 hr. with a low-pressure mercury lamp. One third of the solution gave octanal 2,4-dinitrophenylhydrazone (62%). Isolation of the basic material from the remainder ($\frac{2}{3}$) and treatment in pyridine with toluene-*p*-sulphonyl chloride as above gave, on thin-layer chromatography, only traces of material running at the same position as 2-butylpyrrolidine toluene-*p*-sulphonamide.

[12] Q. Khuong-Huu, J. Yassi, and R. Goutarel, *Bull. Soc. chim. France*, 1963, 2486.
[13] D. B. Denney and B. Goldstein, *J. Org. Chem.*, 1956, **21**, 479.
[14] W. S. Johnson, V. J. Bauer, and R. W. Franck, *Tetrahedron Letters*, 1961, 72.
[15] C. F. H. Allen, *J. Amer. Chem. Soc.*, 1930, **52**, 2955.

Irradiation of n-butyl azide. (*a*) n-Butyl azide (1·72 g.) in anhydrous ether (170 ml.) was irradiated with a 125 w high-pressure mercury lamp for 4·5 hr. A portion (40 ml.) gave n-butyraldehyde 2,4-dinitrophenylhydrazone (64%).

(*b*) n-Butyl azide (3·44 g.) in anhydrous ether (350 ml.) was irradiated as above for 5·5 hr. Part (50 ml.) gave n-butyraldehyde 2,4-dinitrophenylhydrazone (75%). A further part (50 ml.) was treated with dry hydrogen chloride, to give ammonium chloride (422 mg.). The basic fractions from further parts (50 ml.) were separately treated with benzyl chloride in pyridine and with picric acid in ethanol. No evidence for any significant quantity of pyrrolidine could be obtained.

2-Butylpyrrolidine and its Derivatives.—4-Hydroxyimino-octan-1-ol [8] (1·8 g.) in anhydrous ether (40 ml.) was heated under reflux with lithium aluminium hydride (620 mg.) for 6·5 hr. The crude product, in pyridine (10 ml.), was treated with toluene-*p*-sulphonyl chloride (4·8 g.) at room temperature for 37 hr. Chromatography of the product on alumina (Grade V) gave, on elution with light petroleum–benzene (1 : 1), an oil which did not crystallise. This was taken up in dry t-butyl alcohol (10 ml.) containing potassium t-butoxide, and heated under reflux for 1 hr. Chromatography on alumina (Grade V) gave, on elution with light petroleum and crystallisation from the same solvent, *2-butylpyrrolidine toluene-p-sulphonamide* (420 mg.), m. p. 57—58° (from ethanol) (Found: C, 63·9; H, 8·35. $C_{15}H_{23}NO_2S$ requires C, 64·0; H, 8·2%. Cyclisation of the crude toluene-*p*-sulphonyl derivative by heating under reflux in pyridine for 2 hr. gave essentially the same yield of 2-butylpyrrolidine toluene-*p*-sulphonamide. The n.m.r. spectrum showed peaks at: τ 7·58 (3H, aromatic methyl), 2·22, 2·36, 2·65, and 2·79 (4H, aromatic protons), 6·2—7·0 (3H, protons α to nitrogen), >7 (13H, aliphatic-type protons), in agreement with the assigned structure.

18-Hydroxyiminopregn-5-ene-3β,20β-diol.—3β-Acetoxypregn-5-en-20β-ol [9,10] (45 mg.), in dry pyridine (5 ml.), was treated at −20° for 15 min. with nitrosyl chloride gas. Thin-layer chromatography of the product showed a quantitative transformation into nitrite. Recrystallisation from ethanol gave *3β-acetoxypregn-5-en-20β-ol nitrite* as plates, m. p. 150—152°, $[\alpha]_D$ −81° (*c* 0·90) (Found: C, 71·1; H, 9·05. $C_{23}H_{35}NO_4$ requires C, 70·9; H, 9·05%).

This nitrite (3·9 g.), in dry benzene (270 ml.), was photolysed [7] in aliquots (45 ml.) under nitrogen until the nitrite had been decomposed (control by thin-layer chromatography). The solvent was removed *in vacuo* and the residue chromatographed on alumina (Grade III; 180 g.). Elution with benzene–ether (9 : 1) gave pregnenolone acetate (446 mg.). Elution with benzene–ether (3 : 1) afforded 3β-acetoxypregn-5-en-20β-ol (964 mg.). Elution with ether and with ether–methanol (19 : 1) gave *18-hydroxyiminopregn-5-ene-3β,20β-diol 3-acetate*, double m. p. 160—162° and then 178—179° (909 mg.) (from ethanol) $[\alpha]_D$ −16° (*c* 1·00) (Found: C, 71·05; H, 9·0. $C_{23}H_{35}NO_4$ requires C, 70·9; H, 9·05%).

When this oxime (197 mg.), in anhydrous ether (20 ml.) containing excess of lithium aluminium hydride, was heated under reflux for 5 hr. and the product (178 mg.) crystallised from ethanol, it afforded *18-hydroxyoximinopregn-5-ene-3β,20β-diol*, m. p. 224—226°, $[\alpha]_D$ −30° (*c* 0·4 in MeOH) (Found: C, 72·8; H, 9·7. $C_{21}H_{33}NO_3$ requires C, 72·6; H, 9·55%).

18-Cyanopregn-5-ene-3β,20β-diol Dimethanesulphonate.—18-Hydroxyiminopregn-5-ene-3β,20β-diol (79 mg.), in dry pyridine (5 ml.), was treated at room temperature for 2 hr. with an excess of methanesulphonyl chloride. Crystallisation of the product from chloroform–ethanol gave *18-cyanopregn-5-ene-3β,20β-diol dimethanesulphonate* (55 mg.), m. p. 159—160°, $[\alpha]_D$ −43° (*c* 0·70) (Found: C, 57·35; H, 7·2. $C_{23}H_{35}NO_6S_2$ requires C, 56·9; H, 7·25%).

18-Aminopregn-5-ene-3β,20β-diol and Derivatives.—18-Hydroxyiminopregn-5-ene-3β,20β-diol 3-acetate (320 mg.), in dry dioxan (25 ml.) containing lithium aluminium hydride (240 mg.), was heated under reflux for 2·5 hr., to give *18-aminopregn-5-ene-3β,20β-diol*, m. p. 246—248° (from methanol), $[\alpha]_D$ −62° (*c* 0·55 in methanol) (Found: C, 76·0; H, 10·7. $C_{21}H_{35}NO_2$ requires C, 75·65; H, 10·6%). On dissolution in acetone and heating under reflux for a few minutes, this compound afforded the *isopropylidene derivative* (VII; R = R′ = H, X = $CH_2{\cdot}N{:}CMe_2$), plates, m. p. 247—249° (from acetone), $[\alpha]_D$ −23° (*c* 1·23), $\nu_{max.}$ 1668 cm.$^{-1}$ (Found: C, 77·25; H, 10·2. $C_{24}H_{39}NO_2$ requires C, 77·15; H, 10·5%).

18-Aminopregn-5-ene-3β,20β-diol (170 mg.), in pyridine (2 ml.) and acetic anhydride (1 ml.), was heated under reflux for 30 min. The product, in benzene, was filtered through alumina (Grade III) and crystallised from ether–light petroleum, to give the *triacetate* (VII; R = R′ = Ac, X = $CH_2{\cdot}NHAc$) as needles, m. p. 109—111°, $[\alpha]_D$ +18° (*c* 0·92) (Found: C, 70·25; H, 8·8. $C_{27}H_{41}NO_5$ requires C, 70·55; H, 9·0%).

This triacetate (176 mg.), in methanolic potassium hydroxide (5%; 5 ml.), heated under reflux for 25 min. under nitrogen, gave the *mono*-N-*acetyl derivative* (VII; R = R′ = H, X = CH_2·NHAc), m. p. 299—301° (from ethanol), $[\alpha]_D$ +13° (*c* 0·60 in methanol) (Found: C, 73·7; H, 9·45. $C_{23}H_{37}NO_3$ requires C, 73·55; H, 9·95%). This compound was also obtained, in essentially quantitative yield, when 18-aminopregn-5-ene-3β,20β-diol (20 mg.), in glacial acetic acid (1·5 ml.) and acetic anhydride (1·5 ml.), was kept at room temperature for 1 hr.

This mono-N-acetyl compound (67 mg.), in pyridine (2·5 ml.) and acetic anhydride (0·5 ml.), was kept at room temperature for 1·7 hr. Thin-layer chromatography showed the presence of mono-, di-, and tri-acetyl derivatives. Trituration with benzene gave back some mono-*N*-acetyl derivative. Chromatography of the residue on alumina (Grade V; 4·5 g.) afforded, on elution with benzene, the triacetyl derivative. Further elution with benzene–ether (4 : 1) gave the 3β,N-*diacetyl derivative* (VII; R = Ac, R′ = H, X = CH_2·NHAc) (32 mg.), which (from aqueous ethanol) softened at 128—134°, solidified, and then melted at 194—197° $[\alpha]_D$ −10° (*c* 0·88) (Found: C, 71·7; H, 9·25. $C_{25}H_{39}NO_4$ requires C, 71·9; H, 9·4%).

Synthesis of Norlatifoline (VIII; R = R′ = H).—The diacetyl derivative (VII; R = Ac, R′ = H, X = CH_2·NHAc) (31 mg.), in dry pyridine (1 ml.), was treated for 2 hr. at room temperature with excess (10 mol.) of methanesulphonyl chloride. The oily product, in benzene, was filtered through alumina (Grade V) and shown to be homogeneous (thin-layer chromatography). It was hydrolysed by heating under reflux with methanolic potassium hydroxide (5%; 5 ml.) for 10 min. under nitrogen. Chromatography of the product on alumina (4 g.; Grade III), elution with benzene–ethyl acetate (1 : 1), and crystallisation from ethyl acetate–hexane gave *N*-acetylnorlatifoline (4·5 mg.), m. p. 177—181°, $[\alpha]_D$ +13° (Found: C, 77·2; H, 10·05. $C_{23}H_{35}NO_2$ requires C, 77·25; H, 9·85%). This compound (25 mg.) in dioxan (1 ml.) was added with stirring to calcium (150 mg.) in liquid ammonia (70 ml.).[4] After 30 min., the excess of calcium was destroyed with ammonium chloride (excess). Separation into neutral and basic (19 mg.) fractions gave norlatifoline, m. p. 187—191° (from acetone), $[\alpha]_D$ −29° (*c* 0·45), identical with an authentic specimen provided by Dr. R. Goutarel.[12]

In an alternative synthesis, 18-aminopregn-5-ene-3β,20β-diol (119 mg.), in dry pyridine (10 ml.), was treated with methanesulphonyl chloride (2 ml.) for 2·5 hr. at room temperature. The product (67 mg.), in dry toluene (50 ml.), was added with stirring to calcium (150 mg.) in liquid ammonia (100 ml.). After 1 hr. the product was separated into neutral and basic (24 mg.) fractions. Crystallisation of the latter from acetone afforded norlatifoline (11·7 mg.) (m. p., mixed m. p., and thin-layer chromatography).

Reductive Cleavage of Cholesterol Toluene-p-*sulphonate*.—Cholesterol toluene-*p*-sulphonate (44 mg.), in dry ether (50 ml.), was added with stirring to calcium (300 mg.) in liquid ammonia (60 ml.). After 2 hr. the excess of calcium was destroyed with ammonium chloride (excess). Chromatography of the product on alumina (Grade V), and elution with light petroleum–benzene (3 : 1), gave cholesterol (25 mg.) (m. p. and mixed m. p.). Similar reduction of cholesterol methanesulphonate [16] also gave cholesterol (40%).

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[16] B. Helferich and E. Günther, *Ber.*, 1939, **72**, 338.