213. *The Acetylation of* d-ψ-*Ephedrine and* l-*Ephedrine.*

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Acetyl-*d*-ψ-ephedrine and *acetyl*-l-*ephedrine* have been prepared. Since these readily yielded *nitroso*-derivatives, they are shown to be *O*-acetyl compounds; acetyl-*d*-ψ-ephedrine had previously been regarded as the *N*-acetyl derivative (Schmidt, *Arch. Pharm.*, 1914, **252**, 111). The equilibrium between *l*-ephedrine and *d*-ψ-ephedrine on heating with hydrochloric acid is discussed with particular reference to the hydrolysis of the acetylephedrines.

ACETYL-*d*-ψ-EPHEDRINE was prepared by Schmidt and Calliess (*Arch. Pharm.*, 1912, **250**, 154) by the vigorous acetylation of the hydrochloride of either *l*-ephedrine or *d*-ψ-ephedrine; it was then assumed to be the *N*-acetyl derivative. Further work by Schmidt (*ibid.*, 1914, **252**, 111) claimed to confirm this structure. By *gentle* acetylation of the corresponding bases it has now been found possible to prepare both acetyl-*d*-ψ-ephedrine and *acetyl*-l-*ephedrine*. On treatment with nitrous acid these readily yield the corresponding *nitroso-acetylephedrines* (I), so the acetylephedrines must now be regarded as *O*-acetyl compounds (II). Nitrosoacetyl-*d*-ψ-ephedrine yielded nitroso-*d*-ψ-ephedrine on gentle hydrolysis; the latter was also prepared directly from the alkaloid, as was *nitroso*-l-*ephedrine*. The two nitroso-compounds readily gave the corresponding alkaloids on hydrolysis, though Schmidt and Calliess (*loc. cit.*) stated that both alkaloids gave the same nitroso-derivative, which yielded *d*-ψ-ephedrine on hydrolysis. The compound described by Schmidt (*loc. cit.*) as " phenylmethylacetylaminobromopropane," and which played an essential part in his argument for the *N*-acetyl structure, has been shown to be O-*acetyl*-d-ψ-*ephedrine hydrobromide*.

l-Ephedrine and *d*-ψ-ephedrine are known to be mutually interconvertible on heating with hydrochloric acid (Schmidt, *ibid.*, 1908, **246**, 210, etc.; Späth and Göhring, *Monatsh.*, 1920, **41**, 319). In view of the commercial importance of the conversion of *d*-ψ-ephedrine into its more useful isomer (which can readily be effected by at least one unpublished and several patented methods of quite different nature) it seems unfortunate that the hydrochloric acid method should appear so frequently in the literature without its being made sufficiently clear that it is much more easy so to convert *l*-ephedrine into *d*-ψ-ephedrine than to effect the more important reverse reaction. The hydrolysis of the acetylephedrines illustrates this. Acetyl-*d*-ψ-ephedrine readily yields *d*-ψ-ephedrine on either acid or alkaline

hydrolysis, but acetyl-*l*-ephedrine gives *l*-ephedrine only on hydrolysis with alkali; even with quite dilute (4%) hydrochloric acid the product consists of a mixture of *l*-ephedrine and *d*-ψ-ephedrine.

(I.) CHPh(OAc)·CHMe·NMe·NO CHPh(OAc)·CHMe·NHMe (II.)

Experimental.

Acetylation of the Ephedrines.—The base (20 g.) in acetic anhydride (18 ml.) was maintained at 70° for 10 minutes. The acetylated product was extracted by chloroform after dilution with water and basification with sodium hydroxide. Acetyl-*d*-ψ-ephedrine formed colourless prisms from 45% aqueous alcohol, m. p. 103—104° (corr.) (Schmidt and Calliess gave m. p. 101°), $[\alpha]_D^{20°}$ + 110·0° (*c*, 5·0 in absolute alcohol) (Found: C, 69·6; H, 7·9; N, 7·0. Calc. for $C_{12}H_{17}O_2N$: C, 69·6; H, 8·2; N, 6·8%); yield, 86%. Salts were made by direct neutralisation, etc. The hydrochloride formed colourless, tabular prisms from alcohol–ether, m. p. 187° (corr.), $[\alpha]_D^{20°}$ + 99·5° (*c*, 5·0 in water) (Schmidt and Calliess gave m. p. 176°, $[\alpha]_D^{20°}$ + 96·8°) (Found: C, 59·5; H, 7·5; N, 5·9; Cl, 14·0. Calc. for $C_{12}H_{17}O_2N$,HCl: C, 59·1; H, 7·4; N, 5·8; Cl, 14·6%). The *hydrobromide* formed colourless, tabular prisms from alcohol–ether, m. p. 181—182° (corr.), $[\alpha]_D^{20°}$ + 82·0° (*c*, 5·0 in water) (Found: C, 50·2; H, 6·6; N, 5·2; Br, 28·1. $C_{12}H_{17}O_2N$,HBr requires C, 50·0; H, 6·3; N, 4·9; Br, 27·8%).

Acetyl-l-ephedrine formed large, colourless, tabular crystals from 45% aqueous alcohol, m. p. 52° (corr.), $[\alpha]_D^{20°}$ + 5·0° (*c*, 5·0 in absolute alcohol). This material lost 15·4% of its weight on drying at 100°, and appeared to be the dihydrate. It effloresced on exposure to a warm, dry atmosphere; the resultant white powder was anhydrous, m. p. 87° (corr.), $[\alpha]_D^{20°}$ + 7·0° (*c*, 5·0 in absolute alcohol) (Found: C, 70·0; H, 8·1; N, 6·8. $C_{12}H_{17}O_2N$ requires C, 69·6; H, 8·2; N, 6·8%); yield, 80%. Numerous attempts to prepare the hydrochloride and hydrobromide gave ill-defined products contaminated with acetyl-*d*-ψ-ephedrine simultaneously formed by the action of the acids.

Nitrosoacetylephedrines.—The acetylephedrine base (5 g.) in 10% hydrochloric acid (20 ml.) was treated at room temperature with sodium nitrite (3·5 g.) in water (20 ml.). An almost colourless oil rapidly separated; after 12 hours it was extracted with ether and dried over sodium sulphate, and the solvent removed. The syrupy residue rapidly crystallised.

Nitrosoacetyl-d-ψ-*ephedrine* formed colourless, felted needles from 45% aqueous alcohol, m. p. 51—52° (corr.), $[\alpha]_D^{20°}$ + 148·0° (*c*, 5·0 in absolute alcohol) (Found: C, 61·2; H, 6·8; N, 12·2. $C_{12}H_{16}O_3N_2$ requires C, 61·0; H, 6·8; N, 11·9%); yield, 63%. This product (3 g.) was refluxed for ½ hour with 5% aqueous sodium hydroxide (20 ml.). After the liquid had been almost neutralised with hydrochloric acid, the product was extracted with ether and dried over sodium sulphate, and the solvent removed. The syrupy residue (2·4 g.) rapidly crystallised on cooling; yield, 99%. It formed yellow prisms from warm ether, m. p. 86° (corr.), not depressed by authentic nitroso-*d*-ψ-ephedrine.

The crude nitrosoacetyl-*l*-ephedrine (2·1 g.) crystallised on standing, m. p. 85° (rather indefinite). Recrystallisation was unsatisfactory; the material was probably contaminated with nitrosoacetyl-*d*-ψ-ephedrine simultaneously formed. Hydrolysis gave a product which separated from warm ether in colourless prisms, m. p. 88—90° (corr.), depressed by either nitroso-*l*-ephedrine (93°) or nitroso-*d*-ψ-ephedrine (86°); it was probably a mixture of the two.

Nitrosoephedrines.—The alkaloid (5 g.) in 10% hydrochloric acid (10 ml.) was treated at room temperature with sodium nitrite (3 g.) in water (5 ml.). In each case, the yellow oil which rapidly separated was extracted with ether after 12 hours and dried over sodium sulphate, the solvent removed, and the residual yellow syrup, which rapidly solidified on cooling, crystallised from warm ether. Nitroso-*d*-ψ-ephedrine formed bold, yellow prisms, m. p. 86° (corr.), $[\alpha]_D^{20°}$ + 124·5° (*c*, 5·0 in absolute alcohol) (Found: C, 62·0; H, 7·1; N, 14·3. Calc. for $C_{10}H_{14}O_2N_2$: C, 61·9; H, 7·2; N, 14·4%); yield, 70%. *Nitroso-l-ephedrine* formed large, yellow, hexagonal tablets, m. p. 93° (corr.), $[\alpha]_D^{20°}$ + 80·5° (*c*, 5·0 in absolute alcohol) (Found: C, 62·0; H, 7·2; N, 14·5%); yield, 63%. Hydrolysis was effected by refluxing the nitroso-compound (2 g.) in alcohol (20 ml.) with concentrated hydrochloric acid (4 ml.) for 1 hour. After neutralisation with sodium hydroxide, the alcohol was removed, and the mixture basified with ammonia and extracted with ether. The residual base was converted into hydrochloride, and this salt recrystallised from alcohol–ether, etc. Nitroso-*d*-ψ-ephedrine thus yielded 82·5% of colourless needles, $[\alpha]_D^{20°}$ + 61·0° (*c*, 5·0 in water), m. p. 183—184° (corr.), not depressed by authentic *d*-ψ-ephedrine hydrochloride, and nitroso-*l*-ephedrine gave 70·5% of colourless

needles, $[\alpha]_D^{20°}$ — 35° (*c*, 5·0 in water), m. p. 218° (corr.), not depressed by authentic *l*-ephedrine hydrochloride.

"*Phenylmethylacetylaminobromopropane.*"—α-Bromo-β-methylamino-α-phenylpropane hydrobromide (5 g.) was made by Schmidt's method, 5 g. of *d*-ψ-ephedrine hydrochloride being used. Recrystallised from alcohol–ether, it formed colourless prisms, m. p. 182° (corr.), $[\alpha]_D^{20°}$ — 91·0° (*c*, 5·0 in water) (Schmidt gave — 92·7°); the substance was slightly acid to litmus. It (3 g.) was acetylated, as described by Schmidt, and the product crystallised from alcohol–ether, 1·8 g. of colourless, tabular prisms being obtained, $[\alpha]_D^{20°}$ + 81·0° (*c*, 5·0 in water), m. p. 182° (corr.), not depressed by authentic acetyl-*d*-ψ-ephedrine hydrobromide, but heavily depressed by the original bromomethylaminophenylpropane hydrobromide (182°) from which it was prepared.

Hydrolysis of Acetylephedrines.—(A) *Acetyl*-d-ψ-*ephedrine.* (i) *Alkali.* The base (2 g.) in alcohol (10 ml.) was refluxed for 2 hours with 10% aqueous sodium hydroxide (20 ml.). The resultant alkaloidal base was isolated as hydrochloride in the usual manner; yield, 65%. (ii) *Acid.* The base (2 g.) was refluxed for 2 hours with 4% hydrochloric acid, and the resultant alkaloidal hydrochloride isolated; yield, 97·4%. In each case the product separated from alcohol–ether in colourless needles, $[\alpha]_D^{20°}$ + 61·0° (*c*, 5·0 in water), m. p. 183—184° (corr.), not depressed by authentic *d*-ψ-ephedrine hydrochloride.

(B) *Acetyl*-l-*ephedrine.* (i) *Alkali.* The hydrolysis was effected as in the above case; yield, 75·5%. The alkaloidal hydrochloride formed colourless needles from alcohol–ether, $[\alpha]_D^{20°}$ — 35° (*c*, 5·0 in water), m. p. 218·5° (corr.), not depressed by authentic *l*-ephedrine hydrochloride. (ii) *Acid.* Hydrolysis as in the above case gave a yield of 88%. The alkaloidal hydrochloride separated from alcohol–ether in rather indeterminate, colourless needles, m. p. 165—167° (corr.), $[\alpha]_D^{20°}$ + 9·0° (*c*, 5·0 in water); this was a mixture which yielded by the ordinary methods approximately 2 parts of *l*-ephedrine and 1 part of *d*-ψ-ephedrine hydrochlorides.

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