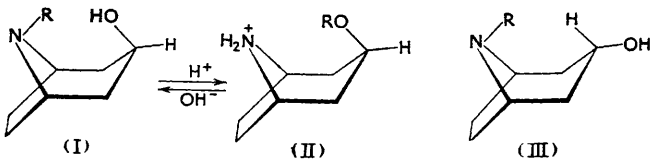
150. *The Stereochemistry of the Tropane Alkaloids. Part I. The Configuration of Tropine and ψ-Tropine.*

By GÁBOR FODOR and KÁROLY NÁDOR.

Comparison of the rates of N→O acyl migrations has shown that the relative positions of the nitrogen bridge and the $C_{(3)}$-hydroxyl group in nortropine and in nor-ψ-tropine are *trans* and *cis* respectively. Consequently, all natural alkaloids yielding on hydrolysis (nor)tropine have the *trans*-configuration, and, those affording ψ-tropine *cis*-configuration (cf. *Nature*, 1952, **169**, 462).

THE stereospecificity of N→O acyl migrations (Fodor and Kiss, *Nature*, 1949, **163**, 287) has been used to determine the conformation and the configuration of several 2-amino-alcohols, *e.g.*, the epimeric ephedrines, chloramphenicols (Fodor, Kiss, and Sallay, *J.*, 1951, 1858), 2-amino*cyclo*hexanols (Fodor and Kiss, *Nature*, 1949, **164**, 917), and the inosamines (McCasland, *J. Amer. Chem. Soc.*, 1951, **73**, 2295). Investigation of acyl migration in the epimeric 2-acylamino*cyclo*pentanols (Fodor and Kiss, *Research*, 1951, **4**, 339; *J.*, 1952, 1589; cf. van Tamelen, *J. Amer Chem. Soc.*, 1951, **73**, 5773) indicated the intramolecular mechanism of this reaction. It has already been established (Fodor and Kiss, *J. Amer. Chem. Soc.*, 1950, **72**, 3495) that the O→N acyl shift proceeds through an *ortho*-acidic intermediate.

We have now extended our studies to the heterocyclic 3-amino-alcohols, tropine and ψ-tropine, which are known to be $C_{(3)}$-epimers (Willstätter and Bode, *Ber.*, 1900, **33**, 416; Willstätter and Bommer, *Annalen*, 1921, **422**, 18; Barrowcliff and Tutin, *J.*, 1909, **95**, 1967), in which the relative configurations (*cis* or *trans*) of the ring nitrogen and the $C_{(3)}$-hydroxyl group have not been established.



(I) (II) (III)

(*a*) R = Ac; (*b*) R = Bz.

Inspection of models reveals that in one of the epimers the nitrogen atom and the oxygen atom of the $C_{(3)}$-hydroxyl group can be joined through one additional atom if the piperidine ring has the boat form; this is impossible in the other epimer. That " bridge " can, of course, be transitory, such as occurs during N→O acyl migration.

To check the correctness of this deduction, *N*-benzoylnor-ψ-tropine and its epimer have been treated with excess of hydrogen chloride in dioxan solution, under identical conditions. The former rearranged into *O*-benzoylnor-ψ-tropine (II*b*) hydrochloride, while the epimer (III) remained unchanged. The amino-ester hydrochloride structure of (II*b*) is supported by (i) its identity with a sample obtained by *O*-benzoylation of nor-ψ-tropine hydrochloride, (ii) electrometric titration with N/10-sodium hydroxide which gives a curve (curve 5) typical of ammonium salts, differing sharply from those of *N*-acylamine salts, and (iii) the instantaneous rearrangement into the *N*-benzoyl derivative in the presence of alkali.

O-Benzoylnortropine hydrochloride does not rearrange with alkali; the base forms a picrate, while *N*-benzoylnortropine does not. This agrees with the known stability of the naturally occurring nortropine ester bases, *e.g.*, poroidine (Barger, Martin, and Mitchell, *J.*, 1938, 1685; 1940, 1155), and also with the fact that nor-ψ-tropine bases have hitherto not been detected in Nature.

The epimeric *N*-acetyl derivatives also behave differently in respect of acyl migration. Hydrogen chloride in dioxan converts both epimers into the corresponding *N*-acetylnortropine hydrochlorides. These are directly titratable potentiometrically with sodium hydroxide (see curves 1 and 2). Welsh (*J. Amer. Chem. Soc.*, 1947, **69**, 128) observed the same phenomenon with *N*-acetylephedrine hydrochloride. The *N*-acetylnortropine hydro-

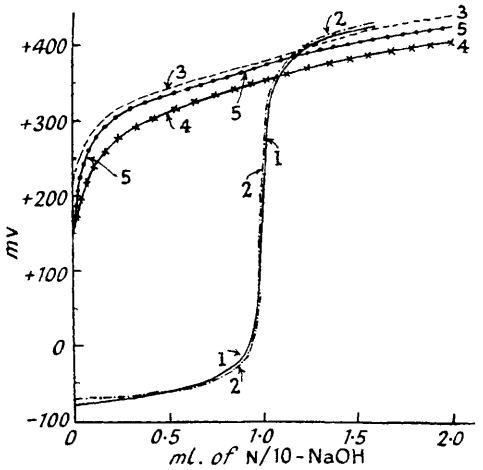
chloride has been described by Polonovski (*Bull. Soc. chim.*, 1926, **39**, 1147), while the hydrochloride of (I*b*) was unknown.

Above its melting point the ψ-hydrochloride isomerises to the *O*-acetyl hydrochloride. This is a characteristic amino-ester salt (curve 3) and is also obtained by *O*-acylation of nor-ψ-tropine hydrochloride. Alkali reconverts it into the *N*-acetyl compounds (I*a*). In contrast *N*-acetylnortropine hydrochloride does not resolidify after being melted; the melt affords traces of the *O*-acetyl hydrochloride (curve 4) together with unchanged *N*-acetyl hydrochloride. The unimolecular formation of the amino-ester salt by thermal rearrangement is, however, rather doubtful.

From these results we conclude that in nor-ψ-tropine and its derivatives the ring-nitrogen and the $C_{(3)}$-hydroxyl are *cis*-placed, while the corresponding derivatives of nortropine are in the *trans*-configuration.

The configuration of such tropane alkaloids (*e.g.*, cocaine, scopolamine) as cannot be correlated directly to the tropan-3-ols will be dealt with in forthcoming communications.

Nomenclature.—We have already proposed the replacement of the terms tropine and ψ-tropine by *anti*tropine or *anti*tropan-3-ol and *syn*tropine or *syn*tropan-3-ol, respectively.



1. N-*Acetylnortropan-3β-ol hydrochloride.*
2. N-*Acetylnortropan-3α-ol hydrochloride.*
3. O-*Acetylnortropan-3β-ol hydrochloride.*
4. O-*Acetylnortropan-3α-ol hydrochloride.*
5. O-*Benzoylnortropan-3β-ol hydrochloride.*

On the advice of the Referees and the Editors we now propose a general stereochemical notation for the tropane alkaloids, based on that now standard in the steroid and triterpenoid fields. The reference group is the >NR bridge, and substituents will be denoted by β or α according to whether they are on the same side or the opposite side, respectively, of the general plane of the ring as the reference group. Nortropine and nor-ψ-tropine are therefore nortropan-3α-ol and -3β-ol, respectively.

Experimental

N-*Acetylnortropan*-3β-*ol.*—This was obtained from the carbamate [m. p. 138—140° (decomp.); Willstätter, *Ber.*, 1896, **29**, 1637, 2231] and acetic anhydride. The m. p. (128°) agrees with that recorded by Polonovski (*Bull. Soc. chim.*, 1928, **43**, 364). The *hydrochloride* was obtained by the action of 5·15N-hydrogen chloride in dry dioxan; it formed very hygroscopic crystals, m. p. 155° (after sintering at 150°), from ethanol–ether (Found : N, 6·7; Cl^-, 17·1. $C_9H_{15}O_2N$,HCl requires N, 6·8; Cl^-, 17·1%). Potentiometric titration with 0·1N-sodium hydroxide showed it to be an acylamine salt.

N-*Benzoylnortropan*-3β-*ol.*—This was obtained by Schotten–Baumann benzoylation of the carbamate (Willstätter, *loc. cit.*); it had m. p. 166°.

O-*Benzoylnortropan*-3β-*ol Hydrochloride.*—Nortropan-3β-ol carbamate (2·98 g.) in N-hydrochloric acid was evaporated in a vacuum to dryness, benzoyl chloride (2·82 g.) was added, and the mixture was heated on the steam-bath for 5 hours. The last trace of acid chloride was removed with dry ether, and the residue crystallised from ethanol–ether. The O-*benzoyl hydrochloride* (4·2 g.) had m. p. 212° (Found : N, 5·15; Cl^-, 13·0. $C_{14}H_{17}O_2N$,HCl requires N, 15·25; Cl^-, 13·25%).

O-Acetylnortropan-3β-ol Hydrochloride.—Nortropan-3β-ol hydrochloride (0·6 g.) was refluxed with acetyl chloride (1·5 ml.) for 1 hour. The product (0·45 g.; m. p. 207°) gave the *O-acetyl* derivative as hygroscopic needles, m. p. 213—214°, from alcohol–ether (Found: C, 51·7; H, 8·0; N, 6·8; Cl^-, 16·7. $C_9H_{15}O_2N$,HCl requires C, 52·5; H, 7·8; N, 6·8; Cl^-, 17·1%). The curve obtained on electrometric titration with 0·1N-sodium hydroxide was different from that of the *N*-acetyl derivative and resembled that of ammonium salts.

N-Benzoylnortropan-3α-ol.—Prepared as described by Willstätter (*Ber.*, 1896, **29**, 1575), this had m. p. 125°.

O-Benzoylnortropan-3α-ol Hydrochloride.—Nortropan-3α-ol hydrochloride was refluxed with excess of benzoyl chloride for 5 hours, the mixture filtered, and the *salt* washed with dry ether (Found: N, 5·45. $C_{14}H_{17}O_2N$,HCl requires N, 5·25%). It had m. p. 214—216°.

N-Acetylnortropan-3α-ol Hydrochloride.—Prepared from *N*-acetylnortropan-3α-ol (0·75 g.), dioxan (2 ml.), and 5N-hydrogen chloride in dioxan (2 ml.), the hydrochloride (0·75 g.) formed needles (from ethanol–ether), m. p. 160—163° [Found: C, 51·9; H, 8·0; N, 6·7; Cl^- (determined potentiometrically), 16·4. Calc. for $C_9H_5O_2N$,HCl: C, 52·5; H, 7·8; N, 6·8; Cl^-, 17·3%]. Polonovski (*Bull. Soc. chim.*, 1927, **41**, 1190) gave m. p. 162° and analytical data for chlorine content only. Potentiometric titration with 0·1N-sodium hydroxide gave a typical acylamine curve.

O-Acetylnortropan-3α-ol Hydrochloride.—Tropan-3α-yl carbamate (0·6 g.) was converted by treatment with 5N-hydrogen chloride in dioxan (0·5 ml.) into the hydrochloride (0·614 g.), which was acetylated with excess of boiling acetyl chloride. The *O-acetyl hydrochloride* formed colourless needles (0·6 g.), m. p. 192—194° (Found: C, 52·6; H, 7·9; N, 6·7; Cl^-, 17·1%). Potentiometric titration gave a curve typical of ammonium salts.

N→O and O→N acyl-migration experiments.

Benzoyl Derivatives of Nortropan-3β-ol.—*N→O migration.* 5N-Hydrogen chloride (0·4 ml.) was added to *N*-benzoylnortropan-3β-ol (0·230 g.) in hot anhydrous dioxan (5 ml.), and the solution set aside at 25° for 24 hours. Removal of the solvent under reduced pressure and crystallisation (ethanol–ether) gave crystals (0·150 g.), m. p. 214° alone or mixed with *O*-benzoylnortropan-3β-ol hydrochloride (Found: C, 62·35; H, 6·9; N, 15·4; Cl^-, 13·0%). Potentiometric titration gave a typical ammonium salt curve.

O→N migration. 2N-Sodium hydroxide (2 ml.) was added to the *O*-benzoyl derivative (0·267 g.) in water (5 ml.). Crystallisation from ethyl acetate–light petroleum of the solid (0·230 g.), obtained when the gummy product was set aside, gave the *N*-benzoyl derivative, m. p. and mixed m. p. 166°.

Benzoyl Derivatives of Nortropan-3α-ol.—*Attempted N→O migration.* *N*-Benzoylnortropan-3α-ol was recovered unchanged after treatment by the method which converted *N*-benzoylnortropan-3β-ol into the corresponding *O*-benzoyl compound.

Attempted O→N migration. The *O*-benzoyl hydrochloride was treated with N-sodium hydroxide. Crystalline material could not be obtained from the product, which was therefore converted into the *picrate*. This formed golden-yellow needles, m. p. 232° (Found: C, 52·4, 51·9; H, 4·3, 4·4; N, 12·4. $C_{12}H_{17}O_2N,C_6H_3O_7N_3$ requires C, 52·2; H, 4·3; N, 12·25%). No picrate could be obtained, under identical conditions, from *N*-benzoylnortropan-3α-ol; the picrate must therefore be that of the *O*-benzoyl compound.

Acetyl Derivatives of Nortropan-3β-ol.—*N→O migration.* When *N*-acetylnortropan-3β-ol hydrochloride (0·350 g.) was heated at 160° for 10 minutes, it melted and then solidified. The residue, on crystallisation from alcohol–ether, gave the *O*-acetyl isomer (0·220 g.), m. p. 213°, identified by mixed m. p. and potentiometric titration with a sample prepared by *O*-acetylation of nortropan-3β-ol hydrochloride.

O→N migration. The *O*-acetyl hydrochloride was neutralised with 0·1N-sodium hydroxide, and the solution extracted with ethyl acetate. The *N*-acetyl compound obtained had m. p. and mixed m. p. 125—126°.

Acetyl Derivatives of Nortropan-3α-ol.—*Attempted N→O migration.* *N*-Acetylnortropan-3α-ol hydrochloride (192 mg.) was heated at 160° for 10 minutes. Repeated recrystallisation of the product gave crystals (*ca.* 0·5 mg.), m. p. 192—194° not depressed on admixture with the *O-acetyl* compound, prepared by *O*-acetylation of nortropan-3α-ol hydrochloride (Found: C, 52·6; H, 7·9; Cl^-, 17·1. $C_9H_{15}O_2N$,HCl requires C, 52·5; H, 7·8; Cl^-, 17·3%).

INSTITUTE OF ORGANIC CHEMISTRY,
THE UNIVERSITY, SZEGED, HUNGARY.

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