155. *The Stereochemical Course of the Conversion of 2-Ureido-alcohols into Oxazolidines. Part I.*

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N-Cyano- (I) and *N*-carbamyl- (II; R = H) -(±)-ephedrine are converted quantitatively by treatment with acid into (±)-2-imino-3 : 4-dimethyl-5-phenyloxazolidine (IV) with *inversion* of configuration. *N*-Carbamyl-(±)-ψ-ephedrine on identical treatment gives (±)-3 : 4-dimethyl-5-phenyloxazolid-2-one (VII) with *retention* of configuration.

The cyclisations of the two diastereoisomers are strongly stereospecific, differing both in their end-products and in their mechanisms. This supports the concept that ephedrine and ψ-ephedrine are not only of different configuration, but that different conformations are stable in each diastereoisomer.

With cyanogen bromide each diastereoisomer cyclises with retention of configuration, giving the two imino-oxazolidines (IV) and (VIII; R = H). An explanation of this stereochemical process is given.

It is known (Fodor, *Proc. Chim. Acad. Sci. Hungar.*, 1951, in the press; cf. Fodor, Koczka, and Szekeres, *Hungarica Chim. Acta*, 1951, in the press) that *O*-benzoyl-*N*-methyl-(±)-ephedrine and cyanogen bromide give *O*-benzoyl-*N*-cyano-(±)-ephedrine (I). We now find that, whereas alkaline hydrolysis of (I) leads to ephedrine (III), hydrolysis with dilute acid gives, in high yield, 2-imino-3 : 4-dimethyl-5-phenyloxazolidine (IV), the configuration of (IV) being proved by its alkaline hydrolysis yielding exclusively ψ-ephedrine (V). This inversion of configuration can clearly occur either before or after the splitting off of the benzoyl group from the urea (II; R = Bz), presumably formed by the addition of water to (I). In order to decide between these two alternatives, *N*-carbamyl-(±)-ephedrine (II; R = H), prepared from (±)-ephedrine (III) hydrochloride, was also treated with dilute acid; (IV) was again obtained. It therefore seems reasonable to assume that inversion of configuration was induced by a nucleophilic attack by the ureido-oxygen atom, *trans* placed with respect to the hydroxyl group.

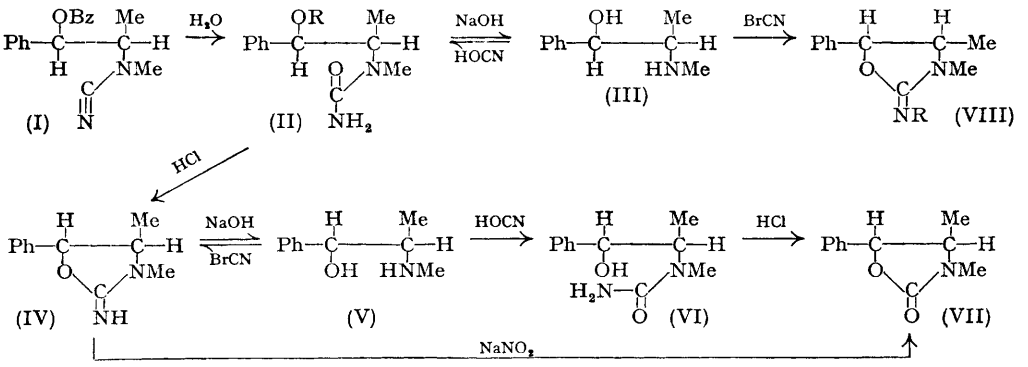
The preparation of substituted oxazoles by cyclisation of β-substituted alkyl-, *cyclo*-alkyl-, and aryl-ureas (which were sometimes too unstable for isolation) has frequently been reported (Stickings, *J.*, 1928, 3131; Pierron, *Ann. Chim.*, 1908, **15**, 191; Childs, Goldsworthy, Harding, Plant, and Weeks, *J.*, 1948, 2320; Gabriel, *Ber.*, 1917, **50**, 826; Takeda and Kuroda, *J. Pharm. Soc., Japan*, 1914, No. 449; 1921, No. 467; and Birckenbach and Linhard, *Ber.*, 1931, **64**, 1086), but apparently the stereochemical course of these cyclisation reactions has not been investigated.

As marked stereospecificity had already been noted among acylated diastereomeric 2-amino-alcohols, *e.g.* in N ⟶ O acyl migration reactions (Welsh, *J. Amer. Chem. Soc.*, 1947, **69**, 128; Fodor *et al.*, *J. Org. Chem.*, 1949, **14**, 340; *Nature*, 1949, **163**, 287; **164**, 917; 1951, **167**, 690) and in the thionyl chloride induced formation of the oxazole ring (Nagai and Kanao, *Annalen*, 1929, **470**, 157; Fodor *et al.*, *J. Org. Chem.*, 1949, **14**, 339), we have investigated the stereochemical course of the reaction of these diastereoisomeric 2-cyano-amino- and 2-ureido-alcohols with acid.

Close (*J. Org. Chem.*, 1950, **15**, 1131) has observed that fusion of (±)-ephedrine with urea furnishes a tetrahydroketoglyoxaline whereas from (+)-ψ-ephedrine an oxazolidone is obtained. This he regarded as evidence for the *cis*- and the *trans*-conformation of ψ-ephedrine and ephedrine, respectively, in agreement with our previous suggestions. It remains to be proved (Close, personal communication) whether the formation of the glyoxaline occurred with inversion or retention of configuration.

By treatment of (±)-ψ-ephedrine hydrochloride with potassium cyanate the urea (VI) was obtained. However, in conditions identical with those used for the conversion of (III) into (IV), (VI) gave (±)-3 : 4-dimethyl-5-phenyloxazolid-2-one (VII) by loss of ammonia [Close obtained the (+)-form, m. p. 50—52°, by fusion of (+)-ψ-ephedrine with urea]. The oxazolidone (VII) must have been formed directly from (VI) and not *via* (IV),

as the latter was not affected by similar treatment. The configuration of (VII) is proved by its preparation from (±)-ψ-ephedrine and carbonyl chloride and from (IV) and nitrous acid.



The stereochemical course of the preparation of oxazolidones by treatment of amino-alcohols with carbonyl chloride (Stratton and Wilson, *J.*, 1932, 1132), urea (Close, Tiffany, and Spielman, *J. Amer. Chem. Soc.*, 1949, **71**, 1265), or alkyl carbonates (*inter al.*, Homeyer, U.S.P. 2 437 388) has not been examined previously, except in Close's recent work (*J. Org. Chem.*, 1950, **15**, 1131).

Our experiments show that the diastereoisomeric ephedrines react according to different mechanisms to furnish different products. Winstein and Boschan (*J. Amer. Chem. Soc.*, 1950, **72**, 4669) believe that cyclisation associated with inversion is caused by the rearward nucleophilic attack of the *trans*-placed neighbouring groups. In carbamyl-ephedrine the hydroxyl and the ureido-group must accordingly be *trans*-placed.

This stereochemical difference between ephedrine and ψ-ephedrine is greater than could be accounted for merely in terms of *configurational* differences, free rotation being assumed for identical conformations. Therefore, these experiments support our previous conclusions of a *conformational* difference between ephedrine and ψ-ephedrine (Fodor *et al.*, *loc. cit.*; Fodor, Kiss, and Sallay, *J.*, 1951, 1858).

The experimental observation that ephedrine and ψ-ephedrine can both form diastereo-isomeric oxazolidines with aldehydes (Welsh, *J. Assoc. Agr. Chem.*, 1948, **31**, 528) with retention of configuration seems apparently at variance with our suggestions. The reaction of ψ-ephedrine with cyanogen bromide under anhydrous conditions gave (IV), already obtained from (I) and from (±)-ephedrine *via* (II; R = H). Presumably cyanogen bromide reacted first with the hydroxyl group, and the derivative was then converted into the imino-oxazolidine of *trans*-conformation in respect of the phenyl and the *C*-methyl group. Under identical conditions ephedrine (III) furnished an isomeric product; this could be ephedrine cyanate or an imino-oxazolidine of *cis*-conformation in respect of the phenyl and the *C*-methyl group (*i.e.*, of ephedrine configuration). Hydrolysis of the benzoyl derivative of the product with dilute alkali gave benzamide and (±)-ephedrine. Consequently, the compound is the diastereoisomer (VIII; R = H) of the imino-oxazolidine (IV) obtained from ψ-ephedrine. Hence, like aldehydes, cyanogen bromide effected the formation of a cyclic compound from ephedrine with change of conformation but without inversion of configuration; while the diastereoisomer is formed from ψ-ephedrine without any stereochemical change. It is noteworthy that in the ephedrine series the process occurred in neutral or alkaline solution; in our conception of the Walden inversion, the splitting off of a hydroxyl anion must be assumed in all inversion reactions (Olson, *J. Chem. Phys.*, 1933, **1**, 418; Meer and Polanyi, *Z. physikal. Chem.*, 1932, *B*, **19**, 164), and this is undoubtedly facilitated by the presence of protons, either as hydroxyl-ion acceptors or as an electrophilic reagent (Welsh, *J. Amer. Chem. Soc.*, 1949, **71**, 3500). It is, therefore, hardly conceivable that (II; R = H), assumed to be an intermediate in the urea-fusion reaction (Close, *loc. cit.*), could cyclise in the presence of an excess of urea, with *inversion* of configuration.

From these experimental results it can be concluded that inversion does not occur during the cyclisation of ψ-ephedrine derivatives, in either acid or alkaline medium. This is because the rate of interaction of the functional groups, which are spatially near to each other, is always greater than that of inversion; before an inversion reaction could be significant a shift of the alcoholic hydroxyl group to a *trans*-position relative to the amino-group would be necessary. In acylated ephedrines, however, a nucleophilic attack by the *trans*-acylamino- or -ureido-group seems very likely, and it is evident that the rate of the inversion reaction is now greater. For retention of configuration, the groups in *trans*-conformation would have first to take up the *cis*-conformation, and the condensation could occur only thereafter; from energy considerations this procedure seems unlikely, as also is the possibility of inversion in alkaline or neutral medium, for then liberated hydroxyl anions cannot be neutralised. Hence in alkaline medium the rate of the inversion process is diminished to such an extent that the otherwise slow processes associated with retention of configuration can predominate. On the basis of different postulates, and assuming a *trans*-relationship for the phenyl and the *C*-methyl group, Welsh (*loc. cit.*) and Close (*loc. cit.*) reached similar conclusions.

The results of investigations of N ⟶ O acyl migrations in diastereoisomeric 2-acylamino*cyclo*pentanols (Fodor and Kiss, *J.*, in the press) support this conclusion, as *trans*-2-acylamino*cyclo*pentanols behave as do acylated ephedrines, whereas the behaviour of the *cis*-compounds compares with that of ψ-ephedrines.

Our original concept of the difference in the conformations of ephedrine and ψ-ephedrine seems therefore to be justified. Further investigations are necessary to establish whether the stereochemical course of the reaction of the ureido-derivatives is of general value in deciding the conformation and configuration of the diastereoisomeric 2-amino-alcohols.

Experimental

The assignments *trans* and *cis* are related in the amino-alcohols to the conformation of the functional groups, and in the oxazolidines to that of the phenyl and the *C*-methyl group.

O-Benzoyl-*N*-cyano-(±)-ephedrine (I) was prepared as described by Fodor, Koczka, and Szekeres (*loc. cit.*).

(±)-*Ephedrine from* O-*Benzoyl*-N-*cyano*-(±)-*ephedrine*.—A solution of sodium hydroxide (2·7 g.) in water (40 ml.) was added to one of *O*-benzoyl-*N*-cyano-(±)-ephedrine (10 g.) in methanol (40 ml.), and the mixture heated for 6 hours on the steam-bath. The alcohol was distilled off in a vacuum, the residue was shaken with benzene (4 × 50 ml.), the combined extracts were dried (Na_2SO_4), and the solvent was evaporated. The residue (5·4 g., 93·5%) was crystallised from light petroleum (70 ml.) and gave pure (±)-ephedrine (4·0 g.), m. p. 72—75° (Found: N, 8·6. Calc. for $C_{10}H_{15}ON$: N, 8·4%).

(±)-trans-2-*Imino*-3 : 4-*dimethyl*-5-*phenyloxazolidine* (IV) *Hydrochloride*.—*O*-Benzoyl-*N*-cyano-(±)-ephedrine (10 g.) was heated under reflux with 2N-hydrochloric acid (100 ml.) for 6 hours. Addition of excess of 2N-hydrochloric acid to the ice-cooled solution caused an oil to separate; this was extracted with ether (200 ml.). The residue, after removal of the solvent, was treated with ethanolic hydrogen chloride. Evaporation of the alcohol gave the *hydrochloride* (6·8 g., 88%), m. p. 232—234°; after recrystallisation from acetone–methanol (20 ml.) by addition of ether (20 ml.) this had m. p. 235° (Found: C, 59·4; H, 7·2; N, 12·5; Cl, 15·6. $C_{18}H_{19}ON_2Cl$ requires C, 58·5; H, 6·65; N, 12·35; Cl, 15·3%).

(±)-ψ-*Ephedrine from the Hydrochloride of* (IV).—The hydrochloride (5 g.) of (IV) was heated for 4 hours on the steam-bath with an aqueous solution (100 ml.) of sodium hydroxide (1·77 g.), with shaking, and the cooled solution then extracted portionwise with benzene (50 ml.). The solvent was removed from the dried extract leaving (±)-ψ-ephedrine (3·5 g., 85%), which, after crystallisation from ether, had m. p. 117—118°, not depressed on admixture with an authentic specimen.

With larger quantities of the hydrochloride, two mols. of aqueous sodium hydroxide were added to an aqueous solution of the hydrochloride followed by as much alcohol as was needed to effect solution. The solution was refluxed for 4 hours, the alcohol distilled off, and the product isolated as before.

N-*Carbamyl*-(±)-*ephedrine* (II; R = H).—Potassium cyanate (2 g., 0·025 mole) was added to (±)-ephedrine hydrochloride (5 g., 0·025 mole) in water (25 ml.), and the solution then refluxed for 2½ hours, during which a small amount of oil separated, and cooled in ice-salt. The

dried, white plates of the *urea* (3 g., 57·7%) were crystallised from ethyl acetate and then had m. p. 126—127° (Found: C, 63·4; H, 7·7; N, 13·4. $C_{11}H_{16}O_2N_2$ requires C, 63·5; H, 7·7; N, 13·5%).

N-*Carbamyl*-(±)-*ψ*-*ephedrine* (VI).—(±)-*ψ*-Ephedrine hydrochloride (5 g., 0·025 mole) in methanol (50 ml.) was added to a solution of potassium cyanate (2 g., 0·025 mole) in methanol (150 ml.), and the mixture heated under reflux for an hour. Potassium chloride was filtered off and the filtrate evaporated to dryness. The residue was crystallised from ethyl acetate (20 ml.), giving white plates of the *urea* (2·2 g.); after repeated recrystallisation this had m. p. 140—141° (Found: C, 63·25; H, 7·8; N, 13·2%).

Action of Hydrochloric Acid on the Diastereoisomeric Carbamyl Derivatives.—(±)-trans-2-*Imino*-3 : 4-*dimethyl*-5-*phenyloxazolidine* (IV) *hydrochloride from* N-*carbamyl*-(±)-*ephedrine*. A solution of *N*-carbamyl-(±)-ephedrine (1·56 g., 0·075 mole) in water (24 ml.) and 2N-hydrochloric acid (15 ml.) was refluxed for 3 hours; when the clear solution cooled the oxazolidine (IV) hydrochloride was obtained. This was purified by conversion into the base which was extracted with benzene. The solvent was removed from this, and the residue converted into the hydrochloride (1·9 g., 84%), m. p. 225—229°, of (IV), identical with that already obtained.

(±)-trans-3 : 4-*Dimethyl*-5-*phenyloxazolid*-2-*one* (VII) *from* N-*carbamyl*-(±)-*ψ*-*ephedrine*. A solution of *N*-carbamyl-(±)-*ψ*-ephedrine (1·56 g., 0·075 mole) in water (24 ml.), to which 5·13N-hydrochloric acid had been added, was refluxed for 3 hours, by which time the oil had crystallised. The solid (0·98 g., 66%) was dried and then crystallised from ether–light petroleum (1 : 1); the *oxazolidone* (VII) formed long white needles, m. p. 59—61° (Found: C, 69·1; H, 6·7; N, 7·3. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·1; N, 7·3%). Close (*loc. cit.*) recorded m. p. 50—52° for the (+)-isomer. Ammonium chloride (0·04 g., 100%) was obtained from the mother-liquors.

(±)-trans-3 : 4-*Dimethyl*-5-*phenyloxazolid*-2-*one* (VII) *from* (±)-*ψ*-*ephedrine*. A benzene (5 ml.) solution of carbonyl chloride (0·8 g., 0·008 mole) was added to one of (±)-*ψ*-ephedrine (4 g., 0·024 mole) in benzene (50 ml.), which was then set aside for 12 hours. The precipitate (3·0 g., 64% based on ephedrine input) was shown by its m. p. to be *ψ*-ephedrine hydrochloride. The residue (1·5 g., 35% based on ephedrine input), obtained on evaporation of the filtrate, was crystallised from a mixture of ether (6 ml.) and light petroleum (6 ml.), and yielded long, white needles (1·2 g.), m. p. 57—61° not depressed on admixture of the sample with the oxazolidone (VII), obtained from *N*-carbamyl-*ψ*-ephedrine.

(±)-trans-3 : 4-*Dimethyl*-5-*phenyloxazolid*-2-*one* (VII) *from* trans-(±)-2-*imino*-3 : 4-*dimethyl*-5-*phenyloxazolidine* (IV) *hydrochloride*. Sodium nitrite (0·516 g., 0·075 mole) was added to a solution of the hydrochloride (1·69 g., 0·075 mole) of (IV) in water (9 ml.), and the solution was then boiled for ½ hour. When the solution cooled the separated yellow oil crystallised; the solid had m. p. 50—56°, mixed m. p. with authentic (VII) 57—61°. It was recrystallised from a mixture of ether (10 ml.) and light petroleum (10 ml.), and gave the oxazolidone (1·2 g., 84%), m. p. 59—61°.

(±)-*Tetrahydro*-2-*keto*-3 : 4-*dimethyl*-5-*phenylglyoxaline*.—Finely powdered *N*-carbamyl-(±)-ephedrine (3·12 g., 0·015 mole), urea (1·8 g., 0·03 mole), and ammonium chloride (0·8 g.) were heated to 170°, and the temperature kept at 170—175° for ½ hour, then raised to 200—210°, and kept at that value for a further 1 hour. The product, when cold, was washed portionwise with hydrochloric acid (5%; 60 ml.); the residue (1·8 g., 65%) had m. p. 140—145°, not depressed on admixture with Close's authentic compound obtained from (±)-ephedrine on urea fusion.

(±)-cis-2-*Imino*-3 : 4-*dimethyl*-5-*phenyloxazolidine* (VIII; R = H).—An ethereal (60 ml.) solution of cyanogen bromide (3·5 g., 0·033 mole) was added to one of (±)-ephedrine (11 g., 0·066 mole) in ether (200 ml.); ephedrine hydrobromide (8·1 g., 50% based on ephedrine input), m. p. 186—188°, was filtered off and the filtrate concentrated in a vacuum to 25 ml. Needles (1·5 g.), m. p. 71—73°, of the cis-*oxazolidine* separated and were crystallised from ether (Found: C, 68·8; H, 8·0; N, 14·2. $C_{11}H_{14}ON_2$ requires C, 69·4; H, 7·3; N, 14·7%). The filtrate was concentrated further and the residual oil treated with ethanolic hydrogen chloride. The product was crystallised from a mixture of chloroform (25 ml.), acetone (10 ml.), and ether (5 ml.), yielding the *hydrochloride* (4·2 g.), m. p. 215—217° (raised on further recrystallisation to 217°) (Found: C, 58·5; H, 6·6; N, 12·25; Cl, 15·6. $C_{11}H_{14}ON_2$,HCl requires C, 58·5; H, 6·8; N, 12·35; Cl, 15·3%).

(±)-cis-2-*Benzimido*-3 : 4-*dimethyl*-5-*phenyloxazolidine* (VIII; R = Bz).—(*a*) The crystalline base (VIII; R = H), obtained in the previous experiment from (±)-ephedrine (11 g.), was set aside at 0° with benzoyl chloride (0·89 g.) in pyridine (12 ml.) for 2 days. The mixture was then poured into water (100 ml.), the crystalline benzimido-compound (1·4 g.), m. p. 149—152°, being obtained.

(*b*) The crude base (3·6 g.) was benzoylated in pyridine (36 ml.) with benzoyl chloride (2·66 g.); the product (3·2 g.) had m. p. 148—151° and was identical with that from (*a*).

The combined products from (*a*) and (*b*) (4·6 g., 62%) were recrystallised from ethyl acetate; the *benzimido*-compound formed white plates, m. p. 151—153° (Found: C, 74·7; H, 6·8; N, 9·6. $C_{18}H_{18}O_2N_2$ requires C, 73·4; H, 6·1; N, 9·8%).

Hydrolysis of the Benzimido-oxazolidine (VIII; R = Bz).—A solution of sodium hydroxide (0·39 g., 0·01 mole) in water (20 ml.) was added to one of the benzimido-compound (1 g., 0·0033 mole) in alcohol (40 ml.). After the mixture had been refluxed for 3 hours, it was concentrated to 20 ml. and an equal volume of light petroleum added. The needles which separated were transformed during 24 hours into plates; these had m. p. 126—128°, undepressed on admixture with an authentic specimen of benzamide. The mother-liqueur gave a second crop of benzamide; the total yield was 73·2%. The most soluble product was (±)-ephedrine hydrochloride (0·15 g.), m. p. 184—186°.

trans-(±)-2-*Imino*-3 : 4-*Dimethyl*-5-*phenyloxazolidine* (IV) *Hydrochloride from* (±)-ψ-*Ephedrine*.—An ethereal solution (40 ml.) of cyanogen bromide (1·75 g., 0·0165 mole) was added to one of (±)-ψ-ephedrine (5·5 g., 0·033 mole) in ether (100 ml.) and benzene (80 ml.). In addition to ψ-ephedrine hydrochloride (3·9 g.), a hydrochloride (2·2 g.), m. p. 233°, was obtained when the oily product was treated with ethanolic hydrogen chloride. This gave no depression of melting point when mixed with an authentic specimen of (IV) hydrochloride.

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