408. *Configurational Correlation of Chloramphenicol with Nor-ψ-ephedrine.*

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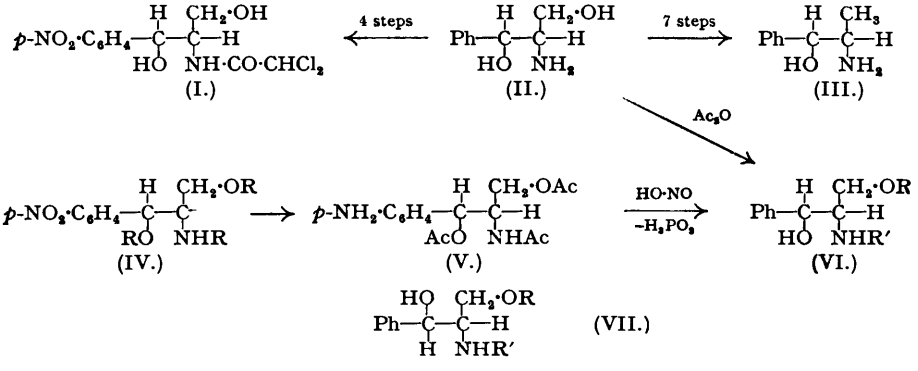
The conformation of some acylated derivatives of chloramphenicol (I) has been proved by comparative acyl migration experiments to be identical with that of nor-ψ-ephedrine (III). The configurational relation of (I) to nor-ψ-ephedrine was established by means of chemical interconversions. These investigations (cf. preliminary report, *Nature*, 1951, **167**, 690) proved the correctness of previous assumptions regarding the stereochemistry of (I), based on optical rotation data (Rebstock *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 2458), and on the behaviour of its diacyl derivatives in N ⟶ O acyl migration reactions.

EARLIER work (Fodor, Koczka, and Szekeres; Fodor, Kiss, *et al.*, *Hungarica Acta Chim.*, in the press) have related (*a*) (±)-2-amino-1-*p*-hydroxyphenylpropanol, m. p. 164°, and (±)-2-amino-1-*p*-methoxyphenylpropanol, m. p. 117—118°, to (±)-norephedrine, and (*b*) (±)-2-dimethylamino-1-phenylpropanol, m. p. 63·5°, to (±)-ephedrine. The present paper records experimental proof of the configurational relation of chloramphenicol ("Chloromycetin") (I) to nor-ψ-ephedrine.

Rebstock *et al.* (*J. Amer. Chem. Soc.*, 1949, **71**, 2458), who elucidated the chemical structure of chloramphenicol, assumed on the basis of optical rotation data that its configuration was that of (−)-nor-ψ-ephedrine. Fodor and Kiss (*Nature*, 1949, **164**, 917) have shown acyl migration from nitrogen to oxygen to be stereospecific for diastereoisomeric αβ-amino-alcohols, and we have used this reaction in our present work. We applied it, however, not to chloramphenicol itself, but to the acyl derivatives of the related diastereoisomeric 2-amino-1-phenylpropane-1 : 3-diols.

The diastereoisomer (II) of m. p. 86° leads by consecutive acetylation, nitration, and deacetylation to (±)-2-amino-1-*p*-nitrophenylpropane-1 : 3-diol (IV; R = H), whence (±)-chloramphenicol (I) is obtained by dichloroacetylation (Controulis, *J. Amer. Chem. Soc.*, 1949, **71**, 2463). However, the configurational correlation thus indicated requires proof that no inversions have intervened: the triacetyl derivative (IV; R = Ac) was hydrogenated to (V)

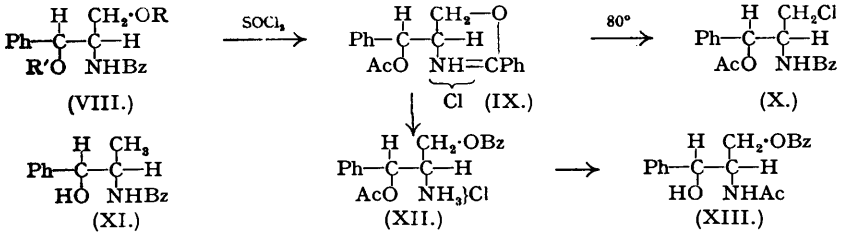


and the aromatic amino-group then eliminated reductively, but concomitant partial deacetylation led to isolation of the *ON*-diacetyl compound (VI; R = R′ = Ac); the proof of correlation of chloramphenicol with (II) and its acyl derivatives is thus complete.

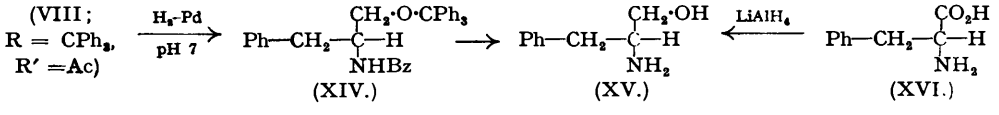
In the diastereoisomeric O^3N-diacetyl * derivatives (VI and VII; R = R′ = Ac) acyl migration from nitrogen to oxygen can occur in one direction only, namely, to O^1. When the diacetyl derivative of the amino-diol (II) of m. p. 86° was treated with alcoholic hydrogen chloride acyl migration readily occurred, whereas the *erythro*-isomer (Controulis *et al.*, *loc. cit.*) was recovered unchanged. Similar results attended experiments with the O^3-acetyl-*N*-benzoyl derivatives (VI and VII; R = Ac, R′ = Bz). Thus, for the acylated *threo*-amino-diols (VI) the hydroxyl group at $C_{(1)}$ and the acylamino-group at $C_{(2)}$ are spatially near to each other, and

* The oxygen atom attached to $C_{(1)}$ which carries the phenyl group is termed O^1, and the other O^3.

in the *erythro*-isomers (VII) are remote from one another. We thus assign the *cis*-conformation to (VI), and the *trans*-conformation to (VII) (for the conception of " conformation " see Wheland, " Advanced Organic Chemistry," 1949, p. 180), although according to Freudenberg (" Stereochemie," 1933, pp. 667, 668) such assignments could not previously be made. Chloramphenicol, being related to (VI), has the *cis*-conformation of the O^1-hydroxyl and the amino-group. However, assignment of conformation does not necessarily prove the configurations of the individual carbon atoms. The suggestion by Fodor *et al.* (*J. Org. Chem.*, 1949, **14**, 337) that in αβ-amino-alcohols the conditions necessary for restricted rotation are present is supported by calculations of the action spheres of van der Waals forces of atoms and atomic groupings in this series (Á. Kiss, unpublished); also Welsh (*J. Amer. Chem. Soc.*, 1949, **71**, 3500) concludes as a result of considerations of models, that for ephedrine and ψ-ephedrine and their derivatives the molecule is most stable if the methyl and aryl groups are *trans* to one another. Our experimental results and these theoretical considerations, taken together, show that in chloramphenicol not only has the hydroxyl and the amino-group in *cis*-conformation but also is related to ψ-ephedrine. The projection formulæ used by us (cf. Close, *J. Org. Chem.*, 1950, **15**, 1131) reflect the *cis*-conformation of ψ-ephedrine derivatives (for configuration see Freudenberg, *J. Amer. Chem. Soc.*, 1932, **54**, 234; Welsh, *loc. cit.*); we propose to denote the conformations also in the nomenclature, regarding ψ-ephedrine and its configurationally related derivatives as *cis*, and ephedrine and its configurationally related derivatives as *trans*.



Our conclusions were further confirmed by conversion of the *N*-benzoyl derivative (VIII; R = R′ = H), m. p. 165—166°, of 2-amino-1-phenylpropane-1 : 3-diol (II) into a nor-ψ-ephedrine derivative. For our purposes we desired to prepare a compound in which the 3-hydroxyl group was replaced by halogen. Reaction of (VIII; R = R′ = H) with methanesulphonyl chloride gave unexpectedly 4-methanesulphonyloxymethyl-2 : 5-diphenyloxazoline, which was of no use for configurative tests since oxazoline ring formation is usually associated with inversion (Johnson and Schubert, *ibid.*, 1950, **72**, 2187). To block the secondary hydroxyl group, the 3-triphenylmethyl ether (VIII; R = CPh_3, R′ = H) was prepared and acetylated to give (VIII; R = CPh_3, R′ = Ac) which by hydrogenolysis should afford the O^1-acetyl-O^3-hydroxy-derivative. In neutral solution, however, hydrogenolysis removed the acetyl rather



than the triphenylmethyl group : the product was shown to be (XIV) by stepwise hydrolysis of the triphenylmethoxy- and benzoyloxy-groups, leading to DL-2-amino-3-phenylpropanol (XV) which had been obtained from 3-phenyl-DL-alanine (XVI) by Karrer *et al.* (*Helv. Chim. Acta*, 1948, **31**, 1717). Hydrogenation in presence of a small amount of hydrogen chloride as proton-donor gave the desired 3-acetoxy-2-benzamido-3-phenylpropanol (VIII; R = H, R′ = Ac) together with triphenylmethane; the acetate could also be obtained by acidolysis (Reynold, *Org. Synth.*, 1942, **22**, 56). However, at pH >7 this compound underwent $O^1 \longrightarrow O^3$ acyl migration, giving 3-acetoxy-2-benzamido-1-phenylpropanol (VIII; R = Ac, R′ = H), which was also obtained by partial acetylation of the amino-diol and, in contrast to its isomer, gave no triphenylmethyl derivative. The two acetates also gave different oxazoline derivatives; that from the second monoacetate was later shown also to belong to the *cis*-series, and with an excess of acetic anhydride both monoacetates yielded the same diacetate (VIII; R = R′ = Ac), thus establishing that the acetyl migration involved no change of configuration.

Halogenation of the primary alcohol (VIII; R = H, R′ = Ac) proved difficult. Under mild conditions it afforded a methanesulphonate but if the temperature was not controlled

di-(3-acetyl-2-benzamido-3-phenylpropyl) ether was obtained. Attempts to convert the methanesulphonyloxy-group into the iodide or chloride by means of sodium iodide or lithium chloride respectively, or into the methyl group by means of lithium aluminium hydride, failed.

Phosphorus tribromide alone or in pyridine gave a mixture. Thionyl chloride alone yielded the 1 : 3-dichloride, but in ethyl acetate gave the hydrochloride of the oxazoline (IX). To decide whether oxazoline ring formation involved inversion, the salt was hydrolysed to 1-acetoxy-2-amino-3-benzoyloxy-1-phenylpropane (XII), which was also obtained by the action of hydrochloric acid on 3-acetoxy-2-benzamido-3-phenylpropanol (VIII; R = H, R′ = Ac), thus proving that ring closure occurred with retention of configuration. The action of alkali, however, on (XII) leads to 2-acetamido-3-benzoyloxy-1-phenylpropanol (XIII). The migration of the acetyl group from O^1 to N was obviously more rapid than the reverse migration of the benzoyl group from O^3. This fact also provides evidence for the proximity of hydroxyl and benzamido-groups at $C_{(1)}$ and $C_{(2)}$.

Subsequently, the conversion of the oxazoline salt (cf. IX) into the desired chloro-derivative (X) was attempted. Heating (analogous cases are recorded by Fry, *J. Org. Chem.*, 1949, **14**, 887) resulted in the covalent bonding of the chlorine ion, but a partial replacement of the acetoxy-group by chlorine occurred simultaneously. Heating in dioxan or ethyl acetate proved more successful, yielding (X) quantitatively.

Hydrogenolysis of (X) in an alcoholic barium hydroxide suspension with palladium–charcoal as catalyst, gave a crystalline chlorine-free compound, which by virtue of its analysis and mixed melting point was (±)-*N*-benzoylnor-ψ-ephedrine (XI), the 1-acetoxy-group having undergone a simultaneous Kunz hydrolysis. The conclusion is thus justifiable that 2-amino-1-phenylpropane-1 : 3-diol of m. p. 86° (and consequently chloramphenicol) and nor-ψ-ephedrine have related configurations. Thus the correctness of the configurational conclusion deduced from optical rotation data, as well as from N ⟶ O acyl migration, has been proved.

Experimental.

Acyl Migration N ⟶ O *among the Diastereomeric* O^3N-*Diacyl Derivatives of* 2-*Amino*-1-*phenylpropane*-1 : 3-*diols*.—(±)-*cis*-2-Acetamido-3-acetoxy-1-phenylpropanol, m. p. 167°, and its diastereoisomer, m. p. 110—111°, were prepared according to Controulis *et al.* (*loc. cit.*).

(±)-cis-3-*Acetoxy*-2-*benzamido*-1-*phenylpropanol* was prepared from the corresponding benzamido-diol, m. p. 165° (3·7 g.; 0·0136 mol.) by allowing it to react for 2 hours at 25° with acetic anhydride (1 c.c.; 0·0098 mol.). Evaporation and recrystallization of the residue from water (60 c.c.) afforded crystals (1·5 g.), m. p. 131—132° (Found: C, 69·0; H, 6·6; N, 4·75. $C_{18}H_{19}O_4N$ requires C, 69·1; H, 6·1; N, 4·55%).

Its diastereoisomer was prepared by hydrogenation of β-acetoxy-α-benzamidopropiophenone (Long and Troutman, *J. Amer. Chem. Soc.*, 1949, **71**, 2471) (6·2 g.; 0·02 mol.) in anhydrous ethanol (290 c.c.) over palladium–charcoal (5 g.; 14% of palladium). Recrystallization from 69% ethanol (180 c.c.) afforded crystals, m. p. 165—166° (Found: N, 4·7%). Controulis *et al.* (*loc. cit.*) recorded the same m. p for their *erythro*-isomer.

Acyl migration N ⟶ O.—(±)-cis-1 : 3-*Diacetoxy*-2-*amino*-1-*phenylpropane* (1·2 g.) was obtained on keeping a solution of the O^3 : *N*-diacetyl derivative (VI; R = R′ = Ac) (1·5 g., 0·006 mol.) in a 15·3% solution of hydrogen chloride in anhydrous methanol (18 c.c.; 0·057 mol.) overnight. Evaporation of the solvent *in vacuo*, followed by recrystallization from alcohol (18 c.c.) and ether (10 c.c.), gave the diacetate, unchanged m. p. 186° (Found: Cl^-, 12·4, 12·2. $C_{13}H_{18}O_4NCl$ requires Cl^-, 12·4%).

Basification effected the reverse (O ⟶ N) migration, furnishing the *cis*-O^3 : *N*-diacetate, m. p. 168—169°.

The *erythro*-diastereoisomer (VII; R = R′ = Ac) (1·5 g.) furnished on similar treatment only unchanged material (1·45 g.), m. p. 110—111°.

(±)-cis-3-*Acetoxy*-2-*amino*-1-*benzoyloxy*-1-*phenyl propane hydrochloride* (0·66 g.) was prepared by keeping the amide (VI; R = Ac, R′ = Bz) (1·24 g., 0·004 mol.) overnight in dioxan (10 c.c.) and 6N-hydrogen chloride in dioxan (2 c.c.; 0·012 mol.). The hydrochloride, m. p. 175—176°, could be recrystallized from alcohol, its m. p. rising thereby to 182—184° (decomp.) (Found: N, 4·3; Cl^-, 10·3. $C_{18}H_{20}O_4NCl$ requires N, 4·0; Cl^-, 10·1%).

Basification of the aqueous solution (2 c.c.) of this salt (0·3 g.) furnished, owing to O ⟶ N acyl migration, the amide (VI; R = Ac, R′ = Bz) (0·20 g.), m. p. 131°.

The diastereoisomer (VII; R = Ac, R′ = Bz) (1·243 g.) was dissolved in absolute dioxan (10 c.c.), and 6N-hydrogen chloride in dioxan added. The crystals (0·68 g.), which separated after 12 hours, were filtered off, and had m. p. 165—166°, undepressed on admixture with the starting material. Evaporation of the mother-liquor and recrystallization of the residue from 60% alcohol (18 c.c.) afforded a further crop (0·36 g.), m. p. 163—164°. Formation of a hydrochloride could not be detected.

(±)-cis 2-*Amino*-1-p-*nitrophenylpropane*-1 : 3-*diol*.—(±)-*cis*-2-Amino-1-phenylpropane-1 : 3-diol, m. p. 86°, prepared according to Fodor, Kovács, and Tóth from cinnamyl acetate (unpublished), was identical with a sample obtained according to Controulis *et al.* (*loc. cit.*). The triacetyl derivative, m. p. 79°, was converted, by the American authors' method into the nitro-triacetate, m. p. 146—147° and this, in turn,

hydrolyzed to 2-amino-1-*p*-nitrophenylpropane-1 : 3-diol, m. p. 142°. The reverse process, acetylation of the amino-nitro-diol, furnished the same triacetate, m. p. 146—147°.

(±)-cis-2-*Acetamido*-1 : 3-*diacetoxy*-1-p-*aminophenylpropane Hydrochloride*.—This *salt* (1·72 g.) was obtained as a deliquescent solid froth by hydrogenation of the nitro-triacetate (1·55 g., 0·0046 mol.) in alcohol (25 c.c.) and 6N-ethanolic hydrogen chloride (2·9 c.c., 0·0174 mol.) over palladium–charcoal (0·5 g.) (Found : Cl^-, 10·3. $C_{15}H_{21}O_5N_2Cl$ requires Cl^-, 10·3%).

The hydrochloride (1·5 g., 0·0044 mol.) in concentrated hydrochloric acid (1·5 c.c.) and water (10 c.c.) was diazotized by sodium nitrite (0·322 g., 0·0045 mol.) in water (6 c.c.) at 0°. Reduction was then carried out with hypophosphorous acid, freshly prepared from the calcium salt (4·12 g., 0·02 mol.) in water (14 c.c.) by means of concentrated sulphuric acid (1·23 c.c.). Evolution of nitrogen ceased after 12 hours. Extraction with ethyl acetate (100 c.c.), washing with sodium hydrogen carbonate solution, drying, and evaporation furnished crystals (0·62 g.). Recrystallization from ethyl acetate–light petroleum (2 : 1; 6 c.c.) afforded crystals (0·192 g.), m. p. 166—167°, undepressed by authentic (±)-*cis*-3-acetoxy-2-acetamido-1-phenylpropanol (Controulis *et al.*, *loc. cit.*) (Found : N, 5·8. Calc. for $C_{13}H_{17}O_4N$: N, 5·6%).

Conversion of (±)-cis-2-*Amino*-1-*phenylpropane*-1 : 3-*diol into* (±)-N-*Benzoylnor-ψ-ephedrine*.—(±)-*cis*-2-Acetamido-3-acetoxy-1-phenylpropane (VI; R = R′ = Ac), obtained from (±)-*cis-OON*-triacetyl-2-amino-1-*p*-nitrophenylpropane-1 : 3-diol, was also prepared from (±)-2-amino-1-phenylpropane-1 : 3-diol (II), m. p. 86°, by acetylation. (II) furnished on benzoylation (Controulis *et al.* (*loc. cit.*) the *N*-benzoyl derivative (VIII; R = R′ = H), m. p. 165—166°. Its conversion into (±)-nor-ψ-ephedrine was carried out as follows.

(±)-cis-2-*Benzamido*-1-*phenyl*-3-*triphenylmethoxypropanol*. (VIII; R = R′ = H) (70 g., 0·258 mol.) and triphenylmethyl chloride (71 g., 0·258 mol.) in anhydrous pyridine (180 c.c.) were heated for 30 minutes on the steam-bath, set aside for 12 hours at 25°, and poured into water (1 l.). The precipitated gum crystallized when stirred for several hours. The crude product (85·7 g., 65%; m. p. 176—182°), when recrystallized from alcoho l(1020 c.c.), afforded a pure *ether* (65·6 g.), m. p. 185—186° (Found : C, 81·5; H, 6·7. $C_{35}H_{31}O_3N$ requires C, 81·8; H, 6·1%).

(±)-cis-1-*Acetoxy*-2-*benzamido*-1-*phenyl*-3-*triphenylmethoxypropane*. The foregoing ether (70 g., 0·1365 mol.) and acetic anhydride (18·6 c.c.; 0·197 mol.) in pyridine (274 c.c.) were heated for 30 minutes on the steam-bath and then kept for 12 hours at 25°. Carbon disulphide (500 c.c.) was added, and the whole extracted consecutively with water (4 × 100 c.c.), N-hydrochloric acid (5 × 100 c.c.), and water (4 × 100 c.c.) until free from pyridine. The dried solution was concentrated to 225 c.c. *in vacuo*, and then light petroleum (896 c.c.) was added. On cooling, plates separated (66·6 g. 87·9%), m. p. 141—142° (Found : C, 80·3; H, 6·5; N, 2·55. $C_{37}H_{33}O_4N$ requires C, 80·0; H, 5·9; N, 2·7%).

(±)-4-*Methanesulphonyloxymethyl*-2 : 5-*diphenyloxazoline*. To a solution of diol (VIII; R = R′ = H) (2·71 g., 0·01 mol.) in pyridine (25 c.c.) methanesulphonyl chloride (4·6 c.c., 0·068 mol.) in pyridine (28 c.c.) was added dropwise at −10° with stirring. After 16 hours, ether (200 c.c.) was added, and the solution washed with water and dilute sulphuric acid, dried, and evaporated. The residual *oxazoline*, recrystallized from trichloroethylene (9 c.c.) and light petroleum (8 c.c.), had m. p. 113—114° (Found : C, 61·9; H, 5·3. $C_{17}H_{17}O_4NS$ requires C, 61·7; H, 5·1%).

(±)-cis-3-*Acetoxy*-2-*benzamido*-3-*phenylpropanol* (VIII; R = H, R′ = Ac). (*a*) Hydrogenolysis of (VIII; R = CPh_3, R′ = Ac) (11·1 g., 0·02 mol.) in anhydrous alcohol (250 c.c.) over palladium–charcoal (6 g.) in the presence of alcoholic 3N-hydrogen chloride (6·25 c.c.; 0·019 mol.) took place within 70 minutes. The filtrate was neutralized with alcoholic N-sodium hydroxide (methyl-red) with stirring, filtered, and evaporated *in vacuo* to dryness. The residual solid (11·2 g.) was extracted with light petroleum (400 c.c.) to eliminate triphenylmethane, the insoluble part was dissolved in benzene (60 c.c.), and subsequently light petroleum (75 c.c.) was added. Cooling afforded crystals (1 g.), m. p. 120—125°. Recrystallization from ethanol (30 c.c.)–light petroleum afforded a pure *acetate*, m. p. 126—127° (Found : C, 68·7; H, 6·6; N, 4·55. $C_{18}H_{19}O_4N$ requires C, 69·1; H, 6·1; N, 4·4%). A mixture with the isomeric acetate (m. p. 135°) melted at 100—115°. On repeating the experiment but neutralizing the hydrogenation mixture to phenolphthalein, the O^3-acetate derivative (VIII; R = Ac, R′ = H) was isolated, m. p. 131—132°, undepressed by a sample obtained by monoacetylation of the diol; its treatment with triphenylmethyl chloride furnished only unchanged material.

(*b*) The ether acetate (VIII; R = CPh_3, R′ = Ac) (14·02 g., 0·025 mol.) in glacial acetic acid (66 c.c.) was hydrolysed by a 7·85N-solution of hydrogen bromide in acetic acid (5·8 c.c., 0·044 mol.) at 0° (stirring) within 45 seconds. The reaction mixture was rapidly poured into ice-water (1 l.), with stirring, furnishing the crude propanol (VIII; R = H, R′ = Ac) (7·1 g.), m. p. 110—126°. Recrystallization from dioxan (28 c.c.)–light petroleum (35 c.c.) afforded crystals (4·9 g.), m. p. 126—127°, undepressed by a specimen obtained as in (*a*).

(*c*) Reconversion of (VIII; R = H, R′ = Ac) (0·313 g., 0·001 mol.) into the ether (VIII; R = CPh_3, R′ = Ac) was effected in pyridine (1 c.c.) on addition of triphenylmethyl chloride (0·28 g., 0·001 mol.) and heating of the mixture for 30 minutes on the steam-bath. Next morning carbon disulphide (50 c.c.) was added, and the whole then worked up as described above. Recrystallization furnished the pure ether, m. p. 140—142°, undepressed by an authentic sample (Found : C, 81·7; H, 6·5%).

(*d*) Acetylation of (VIII; R = H, R′ = Ac) (1·35 g., 0·0043 mol.) took place in anhydrous pyridine (5 c.c.) with acetic anhydride (2 c.c., 0·0195 mol.) on the steam-bath (90 minutes). Dilution with water (10 c.c.) then gave needles of 1 : 3-*diacetoxy*-2-*benzamido*-1-*phenylpropane* (VIII; R = R′ = Ac) (1·4 g.), m. p. 140—141°. Recrystallization from benzene (20 c.c.) afforded crystals, m. p. 143—144° (Found : C, 67·9; H, 6·4. $C_{21}H_{21}O_5N$ requires C, 67·6; H, 6·9%).

The same product was obtained on acetylating the acetate (VIII; R = Ac, R′ = H) or the benzamido-diol (VIII; R = R′ = H) (3·7 g., 0·0136 mol.) in pyridine (15 c.c.) with acetic anhydride (5 c.c., 0·05 mol.) for 2 hours at 25°.

(±)-cis-2-*Benzamido*-3-*methanesulphonyloxy*-1-*phenylpropanol* (VIII; R = Ac, R′ = $MeSO_2$). To a solution of (VIII; R = H, R′ = Ac) (4·88 g., 0·0156 mol.) in pyridine (30·5 c.c.) a solution of methanesulphonyl chloride (11·6 g., 0·102 mol.) in pyridine (46·4 c.c.) was added dropwise with shaking at −15°. The red solution was poured after 12 hours on ice (50 g.), and the precipitated *propanol* (4·95 g., 82%; m. p. 108—135°) were then recrystallized from dioxan (60 c.c.)–light petroleum (330 c.c.), forming plates (2·39 g.), m. p. 171—172° (Found: C, 58·8; H, 6·1; N, 3·7; S, 9·2. $C_{19}H_{21}O_6NS$ requires C, 58·3; H, 5·4; N, 3·6; S, 8·2%). The same reactants (0·3 g. of the acetate in 5 c.c. of pyridine with 0·5 c.c. of the chloride), if not cooled, gave *di*-(3-*acetoxy*-2-*benzamido*-3-*phenylpropyl*) *ether*, m. p. 141—143° after recrystallization from ethyl acetate (4 c.c.)–light petroleum (15 c.c.) (Found: C, 71·3; H, 6·4; N, 4·8. $C_{36}H_{35}O_7N$ requires C, 71·2; H, 6·1; N, 4·65%).

Attempts to convert (VIII; R = Ac, R′ = $Me{\cdot}SO_2$) *into the halogeno-derivative.* (a) Owen and Robins's method (*J.*, 1949, 326). The methanesulphonate with sodium iodide in acetone under various conditions gave no crystallisable product.

(b) Use of dry lithium chloride in anhydrous ethanol at 100° gave amorphous chlorine-free products.

(c) The ester (0·505 g.) in benzene (20 c.c.) with 7·1% solution of lithium aluminium hydride in dry ether (6 c.c.), when boiled for 14 hours (Strating and Backer, *Soc. Chim. Neérl.*, 1950, **69**, 4) gave an uncrystallizable gum.

Direct halogenation of the propanol (VIII; R = H, R′ = Ac). (*a*) To 3-acetoxy-2-benzamido-3-phenylpropanol (0·95 g., 0·003 mol.), phosphorus tribromide (2·3 c.c., 0·0144 mol.) was added. Next morning it was triturated with light petroleum, and the residual deliquescent powder (0·76 g.) showed m. p. 90° (decomp.). Attempts to recrystallize it failed. It contained phosphorus. Subsequent experiments with ethyl acetate, benzene, or pyridine as solvents furnished products containing ionic bromine.

(*b*) The propanol (0·11 g., 0·00035 mol.) was added to thionyl chloride (1·1 c.c., 0·0154 mol.) and heated on the steam-bath for 60 minutes. The residue was treated with ether. The resultant crystals (0·083 g.; m. p. 131—132°) proved to be of 2-*benzamido*-1 : 3-*dichloro*-1-*phenylpropane* (Found: N, 4·6; Cl, 23·3. $C_{16}H_{15}ONCl_2$ requires N, 4·6; Cl, 23·1%).

(±)-cis-4-α-*Acetoxybenzyl*-2-*phenyloxazolinium chloride* (IX). To a solution of 3-acetoxy-2-benzamido-3-phenylpropanol (1·5 g., 0·0048 mol.) in ethyl acetate (12 c.c.), thionyl chloride (1·5 c.c., 0·021 mol.) was added and the solution set aside overnight at 25°. The precipitated colourless *oxazolinium chloride* (0·88 g.) had m. p. 124—126° (Found: C, 65·9; H, 5·9; N, 4·3; Cl^-, 10·15; total Cl, 10·25. $C_{18}H_{18}O_3NCl$ requires C, 65·2; H, 5·4; N, 4·2; Cl^-, 10·6%).

The *oxazoline* base, m. p. 145—147°, was obtained on treatment of the chloride (0·1 g.) with water (1 c.c.) (Found: N, 5·2. $C_{18}H_{17}O_3N$ requires N, 5·2%). It was reconverted into the chloride (IX), m. p. 131°, by hydrogen chloride in dry ether.

1-*Acetoxy*-2-*amino*-3-*benzoyloxy*-1-*phenylpropane hydrochloride* (cf. XII). The oxazolinium chloride (IX) (0·42 g., 0·00127 mol.), dissolved in hot commercial dioxan (5 c.c.) and then cooled, underwent ring-fission to this *hydrochloride* (0·21 g.), which recrystallized from dioxan (6 c.c.) in needles, m. p. 182—183° (decomp.) (Found: C, 61·4; H, 6·2; N, 4·0; Cl^-, 10·1. $C_{18}H_{19}O_4N,HCl$ requires C, 61·8; H, 5·4; N, 4·0; Cl^-, 10·1%). The same product was obtained when a mixture of 3-acetoxy-2-benzamido-3-phenylpropanol (0·616 g.) in dry dioxan (10 c.c.) and a 6N-solution of hydrogen chloride in dioxan (2 c.c.) was kept for 12 hours at 25°. The resultant crystals (0·53 g.) did not depress the m. p. of the previous sample.

When the hydrochloride (0·5 g., 0·00142 mol.) in water (10 c.c.) was treated with concentrated sodium carbonate solution, crystals (0·28 g.), m. p. 159—160°, were obtained after being recrystallized from benzene (5 c.c.)–light petroleum (12 c.c.). Mixed with the diol (VIII; R = R′ = H) they had m. p. 140—150°, and with the monoacetate (VIII; R = H, R′ = Ac) they had m. p. 120—150°. Consequently, they are 2-*acetamido*-3-*benzoyloxy*-1-*phenylpropanol* (XIII) (Found: C, 68·8; H, 6·3; N, 4·1. $C_{18}H_{19}O_4N$ requires C, 69·1; H, 6·1; N, 4·4%).

(±)-4-*Acetoxymethyl*-2 : 5-*diphenyloxazolinium chloride*. This *salt* (0·12 g.) is obtained on treatment of the acetoxy-compound (VIII; R = Ac, R′ = H) (1·2 g.; 0·00313 mol.) with thionyl chloride (2 c.c., 0·0282 mol.) in dry benzene (70 c.c.) at room temperature for 3 hours, evaporation *in vacuo* at 40—50°, and recrystallization from ethyl acetate (8 c.c.)–light petroleum (5 c.c.). It has m. p. 186° (decomp.) (Found: C, 65·55; H, 6·1; N, 4·3. $C_{18}H_{18}O_3NCl$ requires C, 65·2; H, 5·4; N, 4·2%).

Recrystallization of a sample (0·14 g.) from wet dioxan (5 c.c.) furnished (±)-*cis*-3-acetoxy-2-amino-1-benzoyloxy-1-phenylpropane hydrochloride, which on basification affords the acetoxy-compound (VIII; R = Ac, R′ = H). As ring opening of oxazolines with water never results in a Walden inversion (Fry, *J. Org. Chem.*, 1949, **14**, 887), oxazoline formation could also occur in this case with retention of configuration. Conversely, the *trans*-O^3-acetyl-*N*-benzoyl derivative (0·59 g., 0·0016 mol.) with thionyl chloride (2 c.c.; 0·027 mol.) underwent inversion at $C_{(1)}$ and gave the same *cis*-oxazolinium salt.

(±)-cis-2-*Benzamido*-3-*chloro*-1-*phenylpropanol* (X). A solution of the oxazolinium chloride (IX) (3 g., 0·0091 mol.) in dry dioxan (20 c.c.) was refluxed for 4 minutes and then treated with warm light petroleum (150 c.c.). The precipitated *chloride* (1·8 g.) was filtered off and recrystallized from dioxan–light petroleum (1 : 10; 275 c.c.), affording colourless plates, m. p. 132° (Found: C, 65·2; H, 5·9; N, 4·3; Cl, 10·65. $C_{18}H_{18}O_3NCl$ requires C, 65·2; H, 5·4; N, 4·2; Cl, 10·65%). It did not contain ionic chlorine.

(±)-N-*Benzoylnor*-ψ-*ephedrine* [(±)-cis-2-*benzamido*-1-*phenylpropanol*) (XI)]. The chloro-derivative (X) (0·87 g., 0·0026 mol.) was hydrogenated in anhydrous ethanol (20 c.c.) containing palladium–charcoal (0·5 g.) and barium hydroxide hydrate (2 g., 0·0063 mol.) at room temperature. One mole (69 c.c.) of hydrogen was absorbed in 5 hours. The solution was neutralized with 2N-sulphuric acid, filtered from the barium sulphate, and evaporated *in vacuo*. The solid residue, recrystallized from benzene (5 c.c.)–light petroleum (8 c.c.), had m. p. 128—128·5°, undepressed by an authentic specimen

(Fodor *et al.*, *J. Org. Chem.*, 1949, **14**, 337) (Found: C, 73·1; H, 6·45. Calc. for $C_{18}H_{19}O_3N$: C, 72·7; H, 6·4%).

(±)-2-*Benzamido*-3-*phenyl*-1-*triphenylmethoxypropane*.—The ether acetate (VIII; R = CPh_3, R′ = Ac) (1·11 g., 0·002 mol.) in ethanol (30 c.c.) was hydrogenated over palladium–charcoal (0·3 g.) at 64°. One mole (45 c.c.) of hydrogen was absorbed in 50 minutes. The solution was diluted with warm water (10 c.c.), whereupon 2-*benzamido*-3-*phenyl*-1-*triphenylmethoxypropane* separated in needles (0·65 g.), m. p. 173—174° (Found: C, 83·85; H, 6·3; N, 4·3. $C_{35}H_{31}O_2N$ requires C, 84·3; H, 6·2; N, 4·3%).

(±)-2-*Benzamido*-3-*phenylpropanol*.—The foregoing ether (1·14 g.) in anhydrous alcohol (120 c.c.) containing alcoholic 3N-hydrogen chloride (0·67 c.c.) was hydrogenated over palladium–charcoal at 25°. After the uptake of 1 mole (51 c.c.) of hydrogen the solution was evaporated, the oily residue extracted with light petroleum (100 c.c.) and the insoluble part recrystallized from benzene (30 c.c.). The resultant *alcohol* (0·21 g.) had m. p. 149—150° (Found: C, 74·9; H, 6·95. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7%).

(±)-2-*Amino*-3-*phenylpropanol*.—2-Benzamido-3-phenylpropanol (0·16 g.) was refluxed with 12% hydrochloric acid (25 c.c.) for 3 hours, then filtered and evaporated. The residue was extracted with ether (100 c.c.) and the insoluble hydrochloride recrystallized from anhydrous ethanol (0·5 c.c.)–ethyl acetate (3 c.c.). Colourless needles (0·08 g.) of the *hydrochloride*, m. p. 139—141°, were obtained (Found: C, 57·5; H, 8·0; N, 7·6. $C_{19}H_{14}ONCl$ requires C, 57·6; H, 7·5; N, 7·45%). The free base, liberated by alkali and extracted with ether, had m. p. 87—88°, after recrystallization from benzene–light petroleum. Karrer (*loc. cit.*) recorded for his racemic compound m. p. 67—68°.

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