329. *The β-Phenylserine Series. Part IV.**

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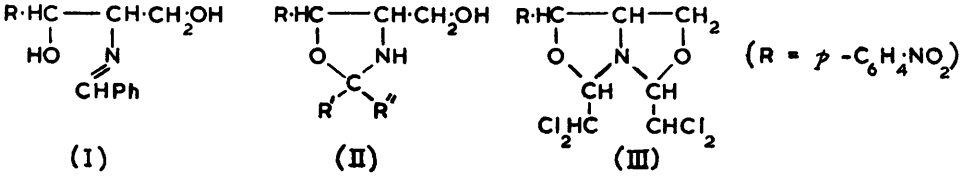
Condensation of the diastereoisomeric 2-amino-1-*p*-nitrophenylpropane-1 : 3-diols, of *threo*- and *erythro*-phenylserine ethyl ester, and of (±)-ephedrine with aldehydes and ketones has been studied. The structures of the products (oxazolidines or Schiff's bases) have been determined with the aid of the infrared spectra. No difference has been observed in the behaviour of the diastereoisomerides; the reactions are not accompanied by change in configuration.

From the two 2-amino-1-*p*-nitrophenylpropane-1 : 3-diols and an excess of dichloroacetaldehyde, diastereoisomeric 3 : 7-dioxa-1-aza-*bicyclo*[3 : 3 : 0]-octane derivatives (III) were formed by double condensation.

The α-amino-alcohol grouping in β-phenylserine, in chloramphenicol, and in related compounds appeared likely to condense with carbonyl compounds. As α-amino-alcohols with aldehydes and ketones give either oxazolidines of Schiff's bases, depending on the structure of the reactants,[1] it appeared of interest to study whether the configuration or conformation of the above-named substances influences the course of the reaction or its rate. According to Fodor and his co-workers,[2] the 1-hydroxy- and the 2-amino-group in *threo*-chloramphenicol are near to each other, in the *erythro*-isomer in a *trans*-like position. Thus, ephedrine and *ψ*-ephedrine react differently with urea[4] and their *N*-carbamoyl derivatives cyclise differently; and the *N*-thiobenzoyl derivatives of *threo*-amino-alcohols cyclise to Δ^2-thiazolines, whilst in the *erythro*-series Δ^2-oxazolines are formed.[5] However, the expectation has not been fulfilled.

2-Amino-1-*p*-nitrophenylpropane-1 : 3-diol was condensed with dichloroacetaldehyde, diethyl ketone, *cyclo*hexanone, and benzaldehyde by azeotropic distillation. With benzaldehyde, only the *threo*-, but not the *erythro*-derivative, gave a crystalline product. As in other similar cases,[1] the *threo*-product proved to be the Schiff's base (I) (infrared band

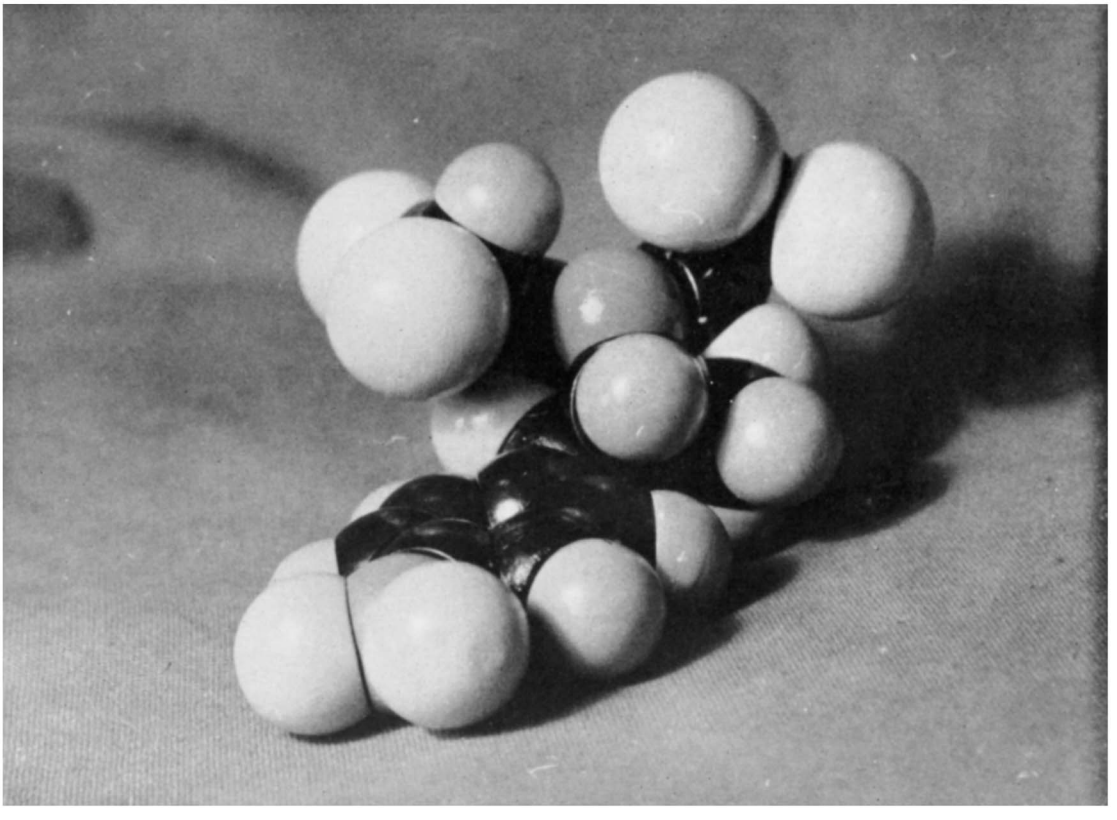


at 1670 cm.$^{-1}$ due to the azomethine system). In the other cases studied, the products had a cyclic structure (II) showing in the 1080—1200 cm.$^{-1}$ region bands characteristic of the oxazolidine ring.[6] The ultraviolet spectra of the compounds of both series show two bands (2320—2345 Å; 2700—2750 Å) which correspond to those of nitrobenzene.[7] The assumption that the secondary, and not the primary, hydroxy-group participates in the formation, is based on the strong infrared band in the region characteristic of a primary hydroxyl group (1030—1060 cm.$^{-1}$). It appears that the phenyl group activates the neighbouring hydroxyl group as in benzyl alcohol.

The products of the *threo*- and the *erythro*-series were different and homogeneous. In their formation, a small but significant difference in rate was observed. For complete

* Part III, *J.*, 1954, 1064.

[1] Bergmann, *Chem. Rev.*, 1953, **53**, 309.
[2] Fodor *et al.*, (*a*) *J.*, 1951, 1858; (*b*) *J.*, 1952, 850; (*c*) *J. Org. Chem.*, 1949, **14**, 337.
[3] Cf. Kanzawa, *Pharm. Bull.* (*Japan*), 1955, **3**, 71.
[4] Close, *J. Org. Chem.*, 1950, **15**, 1131.
[5] Sicher, 14th Internat. Congr. Pure Appl. Chem., Zürich, 1955.
[6] Bergmann, Zimkin, and Pinchas, *Rec. Trav. chim.*, 1952, **71**, 168.
[7] Wolf and Herold, *Z. phys. Chem.*, 1931, **13**, *B*, 201.



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reaction (which was measured by the quantity of water liberated azeotropically) the following times (in minutes) were required :

	$CHCl_2$·CHO	$COEt_2$	*cyclo*Hexanone
threo	120	110	175
erythro	180	170	190

Whilst diethyl ketone and *cyclo*hexanone gave the oxazolidines (II) even when employed in excess, an excess of dichloroacetaldehyde led to the formation of a *threo*- and an *erythro*-3 : 7-dioxa-1-aza*bicyclo*[3 : 3 : 0]octane derivative (III). The infrared spectrum proves the absence of the C=N system and the presence of oxazolidine rings. A model shows (Plate) that for steric reasons only aldehydes will be able to give a system such as (III); even two methylene or methyl groups in the immediate vicinity of the carbonyl group would cause too great a deformation of the molecular structure. After this paper had been completed, Pedvazzoli [8] reported similar observations.

threo- and *erythro*-Phenylserine ethyl ester were condensed with benzaldehyde, *p*-nitrobenzaldehyde, *p*-anisaldehyde, 2 : 4-dichlorobenzaldehyde, butyraldehyde, *cyclo*pentanone, *cyclo*hexanone, and *cyclo*heptanone. The reactions went easily to completion, but mostly gave resins; only from *cyclo*hexanone were two crystalline derivatives obtained; benzaldehyde gave a well-defined compound with the *threo*-ester. These three products were Schiff's bases, showing the C=N frequency at 1678, 1670, 1665 cm.$^{-1}$, respectively, and the hydroxyl frequency at 3380, 3310, and 3450 cm.$^{-1}$. The location of the hydroxyl bands makes it probable that the products contain hydrogen bonds involving the ester carbonyl group.

For comparison, the behaviour of (±)-ephedrine (*erythro*) towards aldehydes and ketones was studied: in this case, condensation is bound to lead to oxazolidines. Davies,[9] Schmidt,[10] and Welsh [11] have already shown that both ephedrine and ψ-ephedrine give oxazolidines on reaction with benzaldehyde. Whilst di-*n*-butyl ketone, di*iso*butyl ketone, diethyl ketone, acetophenone, 4-methylacetophenone, and *p*-dimethylamino- and *p*-benzyloxy-benzaldehyde failed to react, condensation products were obtained with *cyclo*pentanone, *cyclo*hexanone, *m*-nitrobenzaldehyde, and dichloroacetaldehyde. Freudenberg and Geiger [12] recently described the condensation of acetone with (−)-ephedrine. Whilst for the condensation with the aldehydes azeotropic distillation with benzene was sufficient, the two ketones mentioned reacted only in boiling xylene and in presence of catalytic quantities of iodine.[6] As expected, the products showed the typical oxazolidine infrared spectrum; in some cases, four, not three, bands were observed in the expected region. For the *cyclo*pentanone derivative, the molecular refraction was determined; it showed the depression characteristic for five-membered rings of this type.[1]

Several of the oxazolidines derived from *threo*-2-amino-1-*p*-nitrophenylpropane-1 : 3-diol have been tested for bacteriostatic or bactericidal activity against a strain of *E. coli*, which was inhibited to 50% by 2·5 μg. and completely by 5·0 μg. of chloroamphenicol per ml. None of the products, not even the dichloromethyl compound which resembles the natural antibiotic, showed any activity in doses of 2·5—50 μg./ml. This tends to show that for the action of the antibiotic an open structure of the side chain is essential.

Experimental

The condensations were carried out by azeotropic distillation of the components with benzene, unless indicated otherwise; in order to avoid autoxidation, an atmosphere of nitrogen was employed. Light petroleum had b. p. 60—80°, and ligroin, b. p. 90—120°. Most of the infrared spectra were determined in suspensions of the compounds in paraffin oil, by use of a Perkin-Elmer single beam instrument and a sodium chloride prism. The ultraviolet spectra were measured with a Beckman Quartz Spectrophotometer, with alcohol as solvent (figures in parentheses being log ε).

[8] Pedvazzoli, 14th Internat. Congr. Pure Appl. Chem., Zürich, 1955.
[9] Davies, *J.*, 1932, 1580.
[10] Schmidt, *Arch. Pharm.*, 1914, **252**, 89.
[11] Welsh, *J. Assoc. Offic. Agric. Chemists*, 1948, **31**, 528.
[12] Freudenberg and Geiger, *Annalen*, 1952, **575**, 145.

threo-2-*Dichloromethyl*-4-*hydroxymethyl*-5-p-*nitrophenyloxazolidine*.—A solution of *threo*-2-amino-1-*p*-nitrophenylpropane-1 : 3-diol (6·4 g., 0·03 mole) and dichloroacetaldehyde (3·4 g., 0·03 mole) in benzene (80 ml.) was refluxed azeotropically until the theoretical quantity of water had been collected. The solution was evaporated and the solid residue crystallised from methanol–ether, giving the *oxazolidine* as needles, m. p. 175—176° (Found : C, 42·8; H, 4·0; N, 9·0; Cl, 22·7. $C_{11}H_{12}O_4N_2Cl_2$ requires C, 43·0; H, 3·9; N, 9·1; Cl, 23·1%). Infrared bands at 3230 (primary OH), 1106, 1127, 1147 (oxazolidine), 1064 cm.$^{-1}$ (primary OH). Ultraviolet bands at 2320 (3·50), 2730 Å (4·22). Analogously, the following substances were prepared :

erythro-2-*Dichloromethyl*-4-*hydroxymethyl*-5-p-*nitrophenyloxazolidine* (from methanol), needles, m. p. 203—204° (Found : C, 42·8; H, 3·6; N, 8·8; Cl, 23·0. $C_{11}H_{12}O_4N_2Cl_2$ requires C, 43·0; H, 3·9; N 9·1; Cl, 23·1%). Infrared bands at 3210, 1110, 1134, 1168, 1945 cm.$^{-1}$. Ultraviolet bands at 2325 (3·51), 2740 Å (4·23).

threo-2 : 2-*Diethyl*-4-*hydroxymethyl*-5-p-*nitrophenyloxazolidine* (from methyl*cyclo*hexane), prisms, m. p. 124—125° (Found : C, 59·9; H, 6·8; N, 9·9. $C_{14}H_{20}O_4N_2$ requires C, 60·0; H, 7·1; N, 10·0%). Infrared bands at 3248, 1091, 1107, 1152, 1043 cm.$^{-1}$. Ultraviolet bands at 2345 (3·40), 2700 Å (4·00).

erythro-2 : 2-*Diethyl*-4-*hydroxymethyl*-5-p-*nitrophenyloxazolidine*. The viscous product crystallised when triturated at 0° with acetone–ligroin. Recrystallisation from the same mixture gave prismatic needles, m. p. 131—132° (Found : C, 59·8; H, 7·1; N, 10·1%). Infrared bands at 3255, in the oxazolidine region without fine structure, and at 1054 cm.$^{-1}$. Ultraviolet bands at 2325 (3·41), 2750 Å (4·10).

threo-4-*Hydroxymethyl*-5-p-*nitrophenyloxazolidine*-2-spirocyclo*hexane* (from acetone–ligroin), m. p. 107—108° (Found : C, 61·2; H, 6·6; N, 9·5. $C_{15}H_{20}O_4N_2$ requires C, 61·6; H, 6·8; N, 9·6%). Infrared bands at 3355, broad max. at 1127, and at 1027 cm.$^{-1}$. Ultraviolet bands at 2340 (3·50), 2750 Å (4·15).

erythro-4-*Hydroxymethyl*-5-p-*nitrophenyloxazolidine*-2-spirocyclo*hexane*. The product, triturated with alcohol and recrystallised from acetone–ligroin, had m. p. 125—126° (Found : C, 61·4; H, 6·8; N, 9·3%). Infrared spectrum as for the *threo*-isomer, but max. at 1056 instead of 1027 cm.$^{-1}$. Ultraviolet bands at 2325 (3·50) and 2730 Å (4·10).

threo-2-*Benzylideneamino*-1-p-*nitrophenylpropane*-1 : 3-*diol* (from methanol), m. p. 152—153° (Found : C, 64·0; H, 5·2; N, 9·0. $C_{16}H_{16}O_4N_2$ requires C, 64·0; H, 5·3; N, 9·3%). Strong infrared band at 1670 cm.$^{-1}$ (C=N).

threo-2 : 8-*Bisdichloromethyl*-4-p-*nitrophenyl*-3 : 7-*dioxa*-1-*aza*bicyclo[3 : 3 : 0]*octane* (III). Azeotropic distillation of a solution of *threo*-2-amino-1-*p*-nitrophenylpropane-1 : 3-diol (6·4 g.) and dichloroacetaldehyde (6·9 g.) for 4 hr. gave 2 mols. of water. The solid residue from the benzene solution was recrystallised from methanol–ether; this derivative melted at 193—198° (Found : C, 39·2; H, 3·3; N, 7·4; Cl, 34·9. $C_{13}H_{12}O_4N_2Cl_4$ requires C, 38·8; H, 3·0; N, 7·0; Cl, 35·3%). The erythro-*isomer* (from methanol) formed needles, m. p. 178—182° (Found : C, 39·3; H, 3·1; N, 7·2; Cl, 34·8%).

threo-N-cyclo*Hexylidenephenylserine ethyl ester*. *threo*-Phenylserine ethyl ester (m. p. 84—85°, from light petroleum) (3·1 g.) and *cyclo*hexanone (1·5 g.) were dissolved in toluene (70 ml.) and subjected to azeotropic distillation. Within 2 hr. the reaction was complete. From ether, containing a little methanol, crystals, m. p. 61—62°, of the cyclo*hexylidene derivative* (Found : C, 70·6; H, 7·8; N, 4·5. $C_{17}H_{23}O_3N$ requires C, 70·6; H, 7·9; N, 4·8%) separated. Infrared bands at 1678 (C=N), 1720, 3180, 3380 cm.$^{-1}$ (hydroxyl).

Condensation of the *erythro*-ester was carried out in benzene and required 3 hr. The erythro-*product*, crystallised from ether containing a little methanol, had m. p. 64—65° and gave a large depression on admixture with its isomer (Found : C, 70·8; H, 7·6; N, 4·7%). Infrared bands at 1670, 1700, 3310 cm.$^{-1}$.

threo-N-*Benzylidenephenylserine ethyl ester* (obtained in benzene; 4 hr.) formed leaflets, m. p. 98—99°, from acetone–ligroin (Found : C, 72·3; H, 6·0; N, 4·6. $C_{18}H_{19}O_3N$ requires C, 72·7; H, 6·4; N, 4·7%). Infrared bands at 1665, 3450 cm.$^{-1}$.

erythro-3 : 4-*Dimethyl*-5-*phenyloxazolidine*-2-spirocyclo*hexane*. The reaction between (±)-ephedrine (4·95 g.) and *cyclo*hexanone (5·94 g.) in boiling xylene (90 ml.), carried out in the presence of a small quantity of iodine, required 4 hr. for completion. The product solidified and crystallised from propan-2-ol in needles, m. p. 78—79° (55%) (Found : C, 78·1; H, 9·2; N, 5·7. $C_{16}H_{23}ON$ requires C, 78·4; H, 9·4; N, 5·7%). Infrared bands at 1067, 1087, 1125, 1149 cm.$^{-1}$. Ultraviolet bands at 2480 (3·41), 2590 Å (2·60).

erythro-3 : 4-*Dimethyl*-5-*phenyloxazolidine*-2-spirocyclo*pentane*. The reaction carried out as above, but without addition of iodine, required 7 hr. The *product* was an oil, b. p. 178—180°/

23 mm., 140—141°/3 mm, n_D^{25} 1·5240, d_4^{25} 1·0270, $[M]_D$, 68·70 (calc. 68·05) (yield, 22%) (Found : C, 77·5; H, 9·0; N, 5·8. $C_{15}H_{21}ON$ requires C, 77·9; H, 9·1; N, 6·0%). Infrared bands at 1070, 1128, 1142, 1174 cm.$^{-1}$. Ultraviolet bands at 2440 (2·25), 2650 Å (2·39).

erythro-3 : 4-*Dimethyl*-2-m-*nitrophenyl*-5-*phenyloxazolidine*. The reaction required 3 hr. in boiling benzene. The *product* formed needles, m. p. 75·5—76·5°, from light petroleum (Found : C, 68·2; H, 5·9; N, 9·2. $C_{17}H_{18}O_3N_2$ requires C, 68·4; H, 6·0; N, 9·4%). Infrared bands at 1061, 1092, 1137, 1192 cm.$^{-1}$. Ultraviolet bands at 2310 (3·56), 2600 Å (3·90).

erythro-2-*Dichloromethyl*-3 : 4-*dimethyl*-5-*phenyloxazolidine*. Reaction in benzene required 4 hr., giving the *product* (from benzene–light petroleum), m. p. 207—208° (Found : C, 55·2; H, 5·4; N, 5·4; Cl, 27·0. $C_{12}H_{15}ONCl_2$ requires C, 55·4; H, 5·7; N, 5·4; Cl, 27·3%). Infrared bands at 1091, 1133, 1158 cm.$^{-1}$. Ultraviolet bands at 2325 (1·82), 2575 Å (1·40). For comparison, the spectrum of (±)-ephedrine was determined in EtOH, *viz.*, 2400 (1·78), 2590 Å (2·26).

The infrared spectra were measured by Dr. S. Pinchas, Weizmann Institute of Science, Rehovoth, the ultraviolet spectra by Mr. Ch. Eger of this Department.

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