522. *The β-Phenylserine Series. Part II.**

By Ernst D. Bergmann, H. Bendas, and Ch. Resnick.

The extent to which the synthesis of substituted phenylserine alkyl esters from glycine alkyl esters and aromatic aldehydes is applicable has been studied. Azeotropic condensation of the two reactants leads to the *erythro*-configuration, but use of an excess of the glycine ester gives the *threo*-compounds which correspond configurationally to chloramphenicol. 1-Carbethoxymethylpyridinium bromide forms, analogously, aldol condensation products (I) with aromatic aldehydes.

The two *N*-(*p*-nitrobenzylidene)-*p*-nitrophenylserine esters give, upon acetylation, the two ethyl 3-acetyl-2 : 5-di-*p*-nitrophenyloxazolidine-4-carboxylates (II).

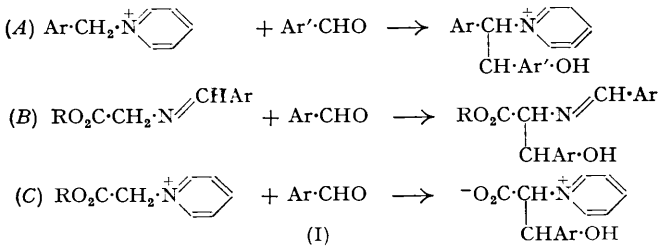
The ethyl esters of *O*-benzylserine and sarcosine condense with *p*-nitrobenzaldehyde under the influence of sunlight, to give ethyl α-amino-α-benzyloxymethyl-β-hydroxy-β-*p*-nitrophenylpropionate (IV) and ethyl 3-methyl-2 : 5-di-*p*-nitrophenyloxazolidine-4-carboxylate (VII), respectively.

The infra-red spectra of a number of the new compounds have been measured.

In Part I of this series * (cf. E. Bergmann, Bendas, and Genas, *Compt. rend.*, 1950, **231**, 361) the observation was recorded that certain aromatic aldehydes condense with glycine alkyl esters in alcohol with unexpected ease, to give Schiff bases derived from β-phenylserine, *viz.*, Ar·CH(OH)·CH(CO_2R)·N:CHAr. The condensation product, m. p. 148°, of glycine ethyl ester with *p*-nitrobenzaldehyde appears to have been obtained by Gerngross and Zuehlke (*Ber.*, 1924, **57**, 1482), who however interpreted its structure incorrectly (see Holland and Nayler, *Chem. and Ind.*, 1952, 518). Hydrolysis of this Schiff base with hydrochloric acid gives the hydrochloride of *p*-nitrophenylserine ethyl ester, NO_2·C_6H_4·CH(OH)·CH(NH_2)·CO_2Et, m. p. 188° (decomp.).

Glycine benzyl ester reacts like the aliphatic esters of glycine.

It has been assumed that the first step of the synthesis is the formation of the Schiff base, Ar·CH:N·CH_2·CO_2R, and the second the aldolisation reaction. Indeed, the reaction of *p*-nitrobenzaldehyde with glycine ethyl ester in ether can be interrupted at the stage of the Schiff base (*N*-*p*-nitrobenzylideneglycine ethyl ester), m. p. 86—87°, as already pointed out by Holland and Nayler (*loc. cit.*). This product has been obtained before by Dalgliesh (*J.*, 1949, 90) and by Billet and Marnay (*Compt. rend.*, 1951, **233**, 961), but has been erroneously assumed to be an isomer of *N*-(*p*-nitrobenzylidene)-*p*-nitrophenylserine ethyl ester, m. p. 148°.



The somewhat surprising aldolisation reaction (*B*) is analogous to the condensation (*A*) of 1-benzylpyridinium (and 1-allylpyridinium) salts with aromatic aldehydes, the methylene group, in both cases, being activated by the adjacent C:N double bond (Kroehnke and Vogt, *Ber.*, 1952, **85**, 368, and previous papers). Also the regularities governing the reactivity of the aromatic aldehydes are roughly the same in both cases : chlorine atoms and nitro-groups (the latter also in *m*-position to the aldehyde group) increase, and methoxyl and amino-groups decrease, the activity of the aldehyde group. The analogy is still more evident if one compares reaction (*B*) with that (*C*) of 1-carbethoxymethylpyridinium

* Part I, *J.*, 1951, 2673.

bromide. The latter compound condenses easily with *p*-nitro-, *p*-chloro-, and *o*-chlorobenzaldehyde in presence of one mol. of alkali. The analogous 1-*N'*-phenylcarbamylmethylpyridinium bromide responds in the same manner to *m*-nitrobenzaldehyde (Kroehnke and Vogt, *loc. cit.*). Also hydantoins and quinaldine are capable of giving aldol-type condensation products with "reactive" aromatic aldehydes (Phillips and Murphy, *J. Org. Chem.*, 1951, **16**, 954; Bahner and Pace, *J. Amer. Chem. Soc.*, 1952, **74**, 3932).

To the list of aldehydes which condense with glycine alkyl esters in the manner indicated (see Part I), there have been added 4-methyl-3-nitrobenzaldehyde and 5-nitrofurfuraldehyde. From the former, 4-methyl-3-nitrophenylserine methyl ester hydrochloride, and from the latter β-(5-nitro-2-furyl)serine ethyl ester hydrochloride and *N*-(5-nitro-2-furfurylidene)-β-(5-nitro-2-furyl)serine ethyl ester have been prepared (β-2-furylserine ethyl ester has been synthetised by Hayes and Gever, *J. Org. Chem.*, 1951, **16**, 269).

It had been tentatively assumed by Bergmann, Bendas, and Taub (*loc. cit.*) that the *p*-nitrophenylserine ethyl ester formed had the same configuration (*threo*) as Erlenmeyer's phenylserine, obtained from benzaldehyde and glycine in presence of concentrated aqueous alkali (see Part I, *loc. cit.*; Vogler, *Helv. Chim. Acta*, 1950, **33**, 2111; Billet, *Compt. rend.*, 1950, **230**, 1074; Alberti, Asero, Camerino, Sannicolo, and Vercellone, *Chim. e Ind.*, 1949, **31**, 357), and chloramphenicol. This assumption had been based on the observation that the lithium aluminium hydride reduction product of the ester showed some chloramphenicol activity. Close investigation has shown, however, that, mainly owing to an unexpected configurational instability of the *p*-nitrophenylserine system, the situation is much more complex. It can be summarised as follows :

(*a*) Whilst nitration of *threo*-β-phenylserine has so far given only ill-defined preparations of *threo*-*p*-nitrophenylserine (Billet, *Compt. rend.*, 1950, **230**, 1358; Woolley, *J. Biol. Chem.*, 1950, **185**, 293; Molho and Molho-Lacroix, *Compt. rend.*, 1951, **233**, 1067), *N*-dichloroacetylation, subsequent *O*-acetylation, and nitration of *threo*-phenylserine ethyl ester gives an *O*-acetyl-*N*-dichloroacetyl-*p*-nitrophenylserine ethyl ester (m. p. 127—128°), which undoubtedly has also the *threo*-configuration (Moersch, Rebstock, Moore, and Hylander, *J. Amer. Chem. Soc.*, 1952, **74**, 565). Equally, it has been shown by Feitelson, Gunner, Moualim, Petrow, Stephenson, and Underhill (*J. Pharm. Pharmacol.*, 1951, **3**, 149) and Kopp, Larramona, and Webuart (*Compt. rend.*, 1951, **233**, 527) that nitration of *threo-ON*-diacetylphenylserine ethyl ester leads to a *p*-nitro-ester of m. p. 120°. Alberti, Camerino, and Vercellone (*Experientia*, 1952, **8**, 261) moreover have obtained, by direct nitration of *threo*-phenylserine ethyl ester, *threo*-*p*-nitrophenylserine ethyl ester of m. p. 115·5—116° [hydrochloride, m. p. 153—155° (dec.)] (Holland and Jenkins, *Chem. and Ind.*, 1951, 1092). The following Table shows that the product obtained by direct condensation of *p*-nitrobenzaldehyde and glycine ethyl ester is different from *threo*-*p*-nitrophenylserine ethyl ester and must, therefore, be the *erythro*-compound. It may be assumed that all condensation products of glycine alkyl esters and aromatic aldehydes formed under the same conditions have the *erythro*-configuration.

(*b*) When *p*-nitrobenzaldehyde and glycine ethyl ester react in ethanolic or methanolic solution, the main crystalline product is the *erythro-N*-(*p*-nitrobenzylidene)-*p*-nitrophenylserine ethyl ester or *erythro*-*p*-nitrophenylserine ethyl ester hydrochloride, according to the method of working up. At the same time, small quantities of the *threo*-derivatives are formed; this is why in our first experiments the reduction of the crude—obviously sterically impure—ester with lithium aluminium hydride gave a product exhibiting chloramphenicol activity. That (*threo*)-*p*-nitrophenylserine can, indeed, be thus reduced to chloramphenicol has been proved by Huebner and Scholz (*J. Amer. Chem. Soc.*, 1951, **73**, 2089) and by Elphimoff-Felkin, Felkin, and Welvart (*Compt. rend.*, 1952, **234**, 1789; see Elphimoff-Felkin, Tchoubar, and Welvart, *Bull. Soc. chim.*, 1952, **19**, 252).

(*c*) The condensation of aromatic aldehydes and glycine alkyl esters can also be carried out by azeotropic condensation in presence of boiling benzene. Treatment of the crude products with hydrochloric acid gives the ester hydrochlorides of substituted β-phenylserines. In the cases studied (*p*- and *m*-nitro-, 2 : 6-dichloro-, and 4-methyl-3-nitrobenzaldehyde, and 5-nitrofurfuraldehyde), the products have been shown to possess the

erythro-configuration. In the azeotropic reaction between glycine methyl ester and *p*-chlorobenzaldehyde, the product appears to be *N* : α-di-*p*-chlorobenzylideneglycine methyl ester (see Experimental section).

M. p.s of threo- *and* erythro-p-*nitrophenylserine derivatives.*

	threo-Series	*erythro*-Series
p-Nitrophenylserine	188° [d]; 180—181° [e]	187—188° [e]
N-Acetyl-*p*-nitrophenylserine	191—192° [e]	170° [e]
p-Nitrophenylserine Et ester	115·5—116 [a, b]; 132 [l, m]; 147 [n]; 129—130°; 133—134 [p]	100—103 [b]; 112—113 [c, k]; 115—116 [l, m, n]; 114—115° [e]
p-Nitrophenylserine Et ester hydrochloride	153—155 (dec.) [b]; 157—159 (dec.) [e]	189 (dec.) [k]; 182—184 [b]; 176—179 (dec.) [e]
N-Dichloroacetyl-*p*-nitrophenylserine Et ester	145 [a, d]; 177—178; 181—183 [c, f]	131—132 [b, d]
ON-Diacetyl-*p*-nitrophenylserine Et ester	122—124 [c]; 120 [d]	138—139·5 [b, d, k]
O-Acetyl-*N*-dichloroacetyl-*p*-nitrophenylserine Et ester	127—128 [d, f, g, l]	86—87·5 [b, d]
N-(*p*-Nitrobenzylidene)-*p*-nitrophenylserine Et ester	121—121·5 [o, i]; 120 [d]	146—147 [e]; 148 [k]
N-Acetyl-*p*-nitrophenylserine Et ester	182—184 [e]	148—149 [e]

[a] Feitelson *et al., loc. cit.*; [b] Alberti, Camerino, and Vercellone, *loc. cit.*; [c] Alberti *et al., loc. cit.*; [d] Present authors; [e] Carrara *et al., Gazzetta*, 1950, **80**, 709; [f] We could not confirm this high m. p.; [g] Huebner and Scholz (*J. Amer. Chem. Soc.*, 1951, **73**, 2089) describe a hemihydrate of this compound of m. p. 108—109°. [k] E. Bergmann, Bendas, and Taub, *loc. cit.*; [i] Holland and Nayler, *loc. cit*; [k] Kopp *et al., loc. cit.*; [l] Moersch *et al., loc. cit.*; [m] Carrara, Pace, and Cristiani, *J. Amer. Chem. Soc.*, 1952, **54**, 4949; [n] Elphimoff-Felkin, Felkin, and Welvart, *Compt. rend.*, 1952, **235**, 1510; [o] Holland, Jenkins, and Nayler, *J.*, 1953, 273; [p] Elphimoff-Felkin, Felkin, and Welvart, *Compt. rend.*, 1952, **234**, 1627.

(*d*) The Schiff base, initially formed from glycine ethyl ester and *p*-nitrobenzaldehyde (see above), when kept in presence of alcohol, is gradually transformed into *erythro-N*-(*p*-nitrobenzylidene)-*p*-nitrophenylserine ethyl ester :

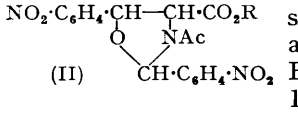
$$2NO_2\cdot C_6H_4\cdot CH{:}N\cdot CH_2\cdot CO_2Et \xrightarrow{H_2O} \underset{\textit{erythro}}{NO_2\cdot C_6H_4\cdot CH{:}N\cdot \underset{CH(OH)\cdot C_6H_4\cdot NO_2}{\underset{|}{CH}}\cdot CO_2Et} + NH_2\cdot CH_2\cdot CO_2Et$$

Conversely, the interaction of the latter product with an excess of glycine ethyl ester leads to *threo-p*-nitrophenylserine ethyl ester :

$$\underset{\textit{erythro}}{NO_2\cdot C_6H_4\cdot CH{:}N\cdot \underset{CH(OH)\cdot C_6H_4\cdot NO_2}{\underset{|}{CH}}\cdot CO_2Et} + NH_2\cdot CH_2\cdot CO_2Et \longrightarrow NO_2\cdot C_6H_4\cdot CH{:}N\cdot CH_2\cdot CO_2Et + \underset{\textit{threo}}{NO_2\cdot C_6H_4\cdot CH(OH)\cdot CH(NH_2)\cdot CO_2Et}$$

Accordingly, condensation of *p*-nitrobenzaldehyde with an excess of glycine ethyl ester without solvent leads directly to the crystalline *threo-p*-nitrophenylserine ethyl ester (Elphimoff-Felkin, Felkin, and Welvart, *Compt. rend.*, 1952, **234**, 1627; cf. *ibid.*, p. 1564).

(*e*) The *threo*- and the *erythro*-form of *N*-(*p*-nitrobenzylidene)-*p*-nitrophenylserine ethyl ester, upon acetylation, give different acetyl derivatives. Their structure is that of *N*-acetyl derivatives of the corresponding oxazolidines (ethyl 3-acetyl-2 : 5-di-*p*-nitrophenyloxazolidine-4-carboxylate) (II). Both show in the infra-red spectrum a band (1660 cm.$^{-1}$) characteristic of a disubstituted amide (see Richards and Thompson, *J.*, 1947, 1248; E. Bergmann, Zimkin, and Pinchas, *Rec. Trav. chim.*, 1952, **71**, 188) (regarding this rearrangement, see E. Bergmann, Gil-Av, and Pinchas, *J. Amer. Chem. Soc.*, 1953, **75**, 358). Also the ultra-violet spectra of the two acetyl derivatives show only a maximum at 2655 Å (log ε : *threo*, 4·35; *erythro*, 4·32) and a minimum at 2375 Å (log ε : *threo*, 3·83; *erythro*, 3·80); the corresponding Schiff bases absorb at 2700 (*threo*; log ε 4·39) and 2710 Å (*erythro*; log ε 4·42) (minima : *threo*, 2280 Å, log ε 3·91; *erythro*, 2330 Å, log ε 3·87) respectively, owing to the more extended conjugated system. Analogously, 2-hydroxy-*N*-*p*-nitrobenzylidene-ethylamine absorbs at 2750 Å, and 2 : 4 : 5 : 5-tetramethyl-2-*m*-nitrophenyloxazolidine at 2650 Å (E. Bergmann, Hirshberg, Pinchas, and Zimkin, *Rec. Trav. chim.*, 1952, **71**, 192).

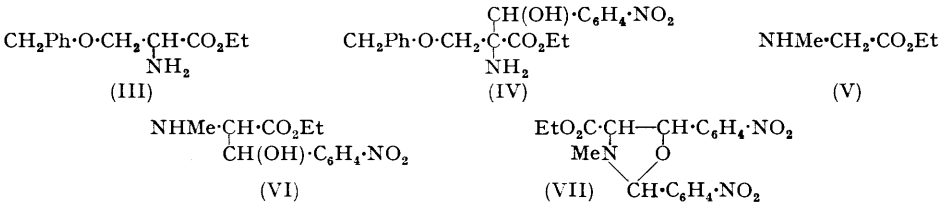


(II)

McCasland and Horswill (*J. Amer. Chem. Soc.*, 1951, **73**, 3923) have reported a number of cases in which Schiff bases derived from β-hydroxy-amines are converted into the *N*-acyl derivatives of the isomeric oxazolidines, and similar observations have been made in the thiazolidine and the tetrahydroglyoxaline series. Apart from the present case, however, diastereomeric pairs of oxazolidines are known only in the *N*-acylbenzylidene derivatives of the two 2-amino*cyclo*hexanols (McCasland and Horswill, *loc. cit.*) and in the benzylidene derivatives of ephedrine and *ψ*-ephedrine (Schmidt, *Arch. Pharm.*, 1914, **252**, 89; Davies, *J.*, 1932, 1580). In the thiazolidine series, an analogous pair has been prepared from thio-DL-threonine and thio-DL-*allo*threonine, with ethyl benzylpenaldate (Clarke, Johnson, and Sir R. Robinson, "The Chemistry of Penicillin," Oxford Univ. Press, 1949, pp. 498, 525, 642).

(*f*) The Schiff *threo*-base used in these experiments has been prepared from the *threo*-ester by azeotropic condensation in boiling benzene (see Holland and Nayler, *loc. cit.*); like the *erythro*-isomer, it is a well-crystallised, stable compound; its infra-red spectrum proves the Schiff base structure (C:N and OH absorption).

Photochemical Condensations.—The activity of the methylene group in α-amino-esters can be enhanced by irradiation to the point where the presence of the azomethine bond becomes superfluous for the aldol-condensation with aromatic aldehydes. *O*-Benzylserine ethyl ester (III) and *p*-nitrobenzaldehyde thus gave ethyl α-amino-α-benzyloxymethyl-β-hydroxy-β-*p*-nitrophenylpropionate (IV), the structure of which follows from



the presence of a free amino-group (van Slyke) and the infra-red absorption spectrum [absence of an azomethine system; presence of a hydroxyl group, hydrogen-bonded to the nitrogen atom (3275 cm.$^{-1}$; cf. E. Bergmann, Zimkin, and Pinchas, *J. Amer. Chem. Soc.*, 1953, **75**, 68)]. It may well be that the relative inactivity of the amino-group in (III), shown in the inability to condense with the aromatic aldehyde, is due to its hydrogen bonding with the ether-oxygen atom.

An analogous photochemical reaction appears to take place—at least primarily—if sarcosine ethyl ester (V) and *p*-nitrobenzaldehyde in methanol are exposed to sunlight. However, instead of the expected product (VI) a compound was obtained which was built up from one mol. of (V) and two of *p*-nitrobenzaldehyde. On the basis of the analytical data and the infra-red spectrum, formula (VII) of an ethyl 3-methyl-2 : 5-di-*p*-nitrophenyloxazolidine-4-carboxylate is assumed. It is derived from (VI) by a reaction normal for secondary β-hydroxy-amines (see E. Bergmann, Zimkin, and Pinchas, *Rec. Trav. chim.*, 1952, **71**, 229, 237).

When the mixtures of the esters of phenylalanine, glutamic, or aspartic acid with *p*-nitrobenzaldehyde were exposed to sunlight, no condensation reaction took place (cf. E. Bergmann and Bendas, *Bull. Israeli Res. Council*, 1952, **2**, 198). *NN*-Dimethylglycine ethyl ester gave a positive response; however, the reaction was accompanied by elimination of a methyl group, and the product proved identical with that formed from sarcosine ethyl ester.

Infra-red Spectra.—For a number of the substances involved in this investigation, the infra-red spectra were studied. It was hoped that the diastereomeric pairs would show differences, as it seemed possible that the strength of the hydrogen bonds which exist in these β-hydroxy-amine systems (see E. Bergmann, Zimkin, and Pinchas, *loc. cit.*) depends on the configuration. This, however, was not the case; the spectra of *threo*- and *erythro*-*p*-nitrophenylserine ethyl esters are practically identical. Also the spectra of the hydrochlorides of the two esters which were studied in form of a mull in paraffin oil, are fairly

similar although there exist certain differences. The two diastereomeric *ON*-diacetyl derivatives give identical spectra from 3400 to 1000 cm.$^{-1}$, except that the band at 1610 cm.$^{-1}$ was stronger for the *erythro*-compound; beyond 1000 cm.$^{-1}$, the *threo*-compound shows bands at 965, 920, 855, and 840 cm.$^{-1}$, whilst the *erythro*-isomer absorbs at 950, 935, 915, 900, and 855 cm.$^{-1}$.

Experimental

1-*Carbethoxymethylpyridinium Bromide*.—A mixture of pyridine (40 g.) and ethyl bromoacetate (84 g.) was stirred at 0° and subsequently at 50°, and the cake formed recrystallised from a mixture of ethyl methyl ketone and *iso*propyl alcohol. The salt (53 g., 43%) is slightly hygroscopic.

1-(1-*Carboxy*-2-p-*chlorophenyl*-2-*hydroxyethyl*)*pyridinium Betaine*.—When a solution of sodium hydroxide (0·4 g.) in methanol was added to a mixture of the foregoing salt (2·5 g.) and *p*-chlorobenzaldehyde (1·4 g.), an exothermic reaction took place. At 0°, the *product* crystallised; it was washed with ice-cold water and recrystallised from 90% methanol as prismatic needles, m. p. 146—147° (decomp.) (Found: C, 60·5; H, 4·4; N, 4·9; Cl, 12·7. $C_{14}H_{12}O_3NCl$ requires C, 60·6; H, 4·3; N, 5·1; Cl, 12·8%).

Similarly, *o*-chlorobenzaldehyde gave, after recrystallisation from methanol, the o-*chloro*-isomer as octahedra, m. p. 161° (decomp.) (Found: C, 60·7; H, 4·5; N, 4·8; Cl, 12·5. $C_{14}H_{12}O_3NCl$ requires C, 60·6; H, 4·3; N, 5·1; Cl, 12·8%). A small quantity of material did not dissolve in methanol; by recrystallisation from glacial acetic acid, it was obtained as prisms, m. p. 152° (decomp.). The analysis pointed to the structure 1-(1-*carboxy*-2-o-*chlorophenyl*-2-*hydroxyethyl*)*pyridinium acetate* (Found: C, 56·9; H, 5·0; N, 5·0; Cl, 10·7. $C_{16}H_{16}O_5NCl$ requires C, 57·0; H, 4·7; N, 4·7; Cl, 10·4%).

1-(*Carboxy*-2-*hydroxy*-2-p-*nitrophenylethyl*)*pyridinium Betaine*.—Condensation as above, with 1·5 g. of *p*-nitrobenzaldehyde, gave the *betaine*, prisms, m. p. 159° (decomp.) (from methanol) (Found: C, 58·4; H, 4·3; N, 10·0. $C_{14}H_{12}O_5N_2$ requires C, 58·3; H, 4·2; N, 9·7%). A small amount of material, which was insoluble in methanol, crystallised from acetic acid in platelets, m. p. 161° (decomp.). Analyses pointed to a *product* $C_{17}H_{18}O_8N_2$ (Found: C, 53·9; H, 4·6; N, 7·8. $C_{17}H_{18}O_8N_2$ requires C, 54·0; H, 4·8; N, 7·4%).

N-(5-*Nitro*-2-*furfurylidene*)-erythro(?)-β-(5-*nitro*-2-*furyl*)*serine Ethyl Ester and* erythro(?)-β-(5-*Nitro*-2-*furyl*)*serine Ethyl Ester Hydrochloride*.—5-Nitrofurfuraldehyde was prepared by nitration of furfuraldehyde diacetate and subsequent hydrolysis (Gilman and Wright, *J. Amer. Chem. Soc.*, 1930, **52**, 2550, 4165). To a solution of the aldehyde (2·82 g.) in dry ether (20 c.c.), freshly distilled glycine ethyl ester (0·90 g.) was added. [The excess of the aldehyde (25%) is necessary, as otherwise the solution darkens.] After 12 hr., crystals of the *Schiff base* (0·30 g.) had separated. Washed with ether and recrystallised from propyl alcohol or benzene, they had m. p. 136° (Found: C, 46·0; H, 3·7; N, 11·5; OC_2H_5, 12·5; active H, 0·29. $C_{14}H_{13}O_9N_3$ requires C, 45·8; H, 3·5; N, 11·4; OC_2H_5, 12·3; 1 H, 0·27%).

When alcoholic hydrochloric acid was added to the mother-liquor, a brown oil separated which was washed with ether and triturated with chloroform, whereupon it solidified (yield, 1·1 g.). Recrystallised from chloroform or *iso*propyl alcohol, the ester *hydrochloride* had m. p. 156° (Found: C, 38·3; H, 4·3; N, 10·0; OEt, 15·9; active H, 0·8. $C_9H_{13}O_6N_2Cl$ requires C, 38·6; H, 4·6; N, 10·0; OEt, 16·1; 2 H, 0·8%).

The same products were obtained when the condensation was carried out in ethyl alcohol at room temperature (24 hr.).

erythro(?)-4-*Methyl*-3-*nitrophenylserine Methyl Ester Hydrochloride*.—A solution of 4-methyl-3-nitrobenzaldehyde (6·3 g.) and glycine methyl ester (1·8 g.) in methanol (20 c.c.) was kept at room temperature for 24 hr.; then methanolic hydrogen chloride (15 c.c., containing 1·5 g. of HCl) and an excess of ether were added. The semi-solid bottom layer was triturated with *iso*propyl alcohol (yield, 0·5 g.) and recrystallised from the same solvent. The ester *hydrochloride* formed leaflets, m. p. 181° (decomp.) (Found: C, 45·0; H, 5·0; N, 9·3; Cl, 12·0. $C_{11}H_{15}O_5N_2Cl$ requires C, 45·5; H, 5·2; N, 9·6; Cl, 12·1%).

4-Methyl-3-nitrobenzaldehyde (Hanzlik and Bianchi, *Ber.*, 1899, **32**, 1288; Gattermann, *Annalen*, 1906, **347**, 347), purified by distillation *in vacuo*, had b. p. 162°/25 mm. [from 12 g. of *p*-tolualdehyde, 12·5 g. (76%) were obtained].

erythro(?)-m-*Nitrophenylserine Ethyl Ester Hydrochloride*.*—This had been obtained by Bergmann *et al.* (*loc. cit.*) by condensation of *m*-nitrobenzaldehyde and glycine ethyl ester in

* The m. p. of *m*-nitrophenylserine ethyl ester hydrochloride is 191° (decomp.), not 131° (decomp.), as erroneously reported by Bergmann *et al.* (*loc. cit.*).

ethanol; no analyses had been given. The *salt* formed leaflets, m. p. 184° (decomp.), from amyl alcohol (Found: C, 45·7; H, 5·3; N, 9·4; Cl, 12·1. $C_{11}H_{15}O_5N_2Cl$ requires C, 45·5; H, 5·2; N, 9·6; Cl, 12·1%).

erythro-N-(p-*Nitrobenzylidene*)-p-*nitrophenylserine Methyl Ester*.—When *p*-nitrobenzaldehyde (7·5 g.) and glycine methyl ester (2·3 g.) were kept in a little methanol at room temperature for 24 hr., the condensation *product* (9·0 g.) separated. After recrystallisation from *iso*propyl alcohol, it had m. p. 160° (Found: C, 54·9; H, 3·9; N, 11·0; OMe, 8·4; active H, 0·3. $C_{17}H_{15}O_7N_3$ requires C, 54·7; H, 4·0; N, 11·2; OMe, 8·3; 1 H, 0·3%).

erythro(?)-2 : 6-*Dichlorophenylserine Ethyl Ester Hydrochloride*.—In Part I, the parallel reaction with the methyl ester was described. The mixture of 2 : 6-dichlorobenzaldehyde (2·5 g.), glycine ethyl ester (0·7 g.), and anhydrous alcohol (10 c.c.) was refluxed for 2 hr., and ether (100 c.c.) and alcoholic 4N-hydrochloric acid (1·5 c.c.) were added. After filtration from a small precipitate and concentration of the solution, the *ester hydrochloride* crystallised. Recrystallised from alcohol–ether, it had m. p. 170° (decomp.) (Found: C, 42·0; H, 4·6; N, 4·7; Cl, 33·4. $C_{11}H_{14}O_3NCl_3$ requires C, 42·5; H, 4·5; N, 4·5; Cl, 33·2%).

threo-O-*Acetyl*-N-*dichloroacetyl*-p-*nitrophenylserine Ethyl Ester*.—This was prepared according to Huebner and Scholz (*loc. cit.*) by nitration of *O*-acetyl-*N*-dichloroacetyl-*threo*-*p*-phenylserine ethyl ester (4 g.) with fuming ntric acid (4 c.c.) and concentrated sulphuric acid (4 c.c.) (30 min.). Upon dilution with ice, an oil separated which solidified quickly. Recrystallised from 50% methanol, the ester formed shiny needles, m. p. 127—128°.

threo-N-(p-*Nitrobenzylidene*)-p-*nitrophenylserine Ethyl Ester*.—*threo*-*p*-Nitrophenylserine ethyl ester (Elphimoff-Felin, Felkin, and Welvart, *loc. cit.*) (3·7 g.) and *p*-nitrobenzaldehyde (2·2 g.) were subjected to azeotropic condensation in presence of boiling benzene (35 c.c.). After 3 hr., the solvent was evaporated and the residue triturated at 0° with methanol and a little nitromethane and recrystallised twice from *iso*propyl alcohol. It had m. p. 120°.

Ethyl 3-*Acetyl*-2 : 5-*di*-p-*nitrophenyloxazolidine*-4-*carboxylates*.—(a) threo-*Form*. The preceding substance (0·5 g.) was refluxed for 1 hr. with acetic anhydride (5 c.c.). The mixture was diluted with water, and the resulting solid triturated with methanol and recrystallised from *iso*propyl alcohol. The *ester* had m. p. 172° (Found: C, 56·2; H, 4·5; N, 9·9. $C_{20}H_{19}O_8N_3$ requires C, 56·0; H, 4·4; N, 9·8%).

(b) erythro-*Form*. The same reaction was carried out with *N*-(*p*-nitrobenzylidene)-*erythro*-*p*-nitrophenylserine ethyl ester (Part I). The *product* had m. p. 172°, but depressed the m. p. of the compound obtained as under (a) to 152° (Found: C, 56·0; H, 4·7; N, 9·9; OEt, 10·0. $C_{20}H_{19}O_8N_3$ requires C, 56·0; H, 4·4; N, 9·8; OEt, 10·5%).

The infra-red spectrum was measured in chloroform (16 mg. and 1 c.c. of solvent). The hydroxyl and the C:N bands were absent, the band of a disubstituted acetamide appeared at 1600 cm.$^{-1}$, and that of the carbethoxy-group at 1730 cm.$^{-1}$. Two bands, at 1620 and 1525 cm.$^{-1}$, respectively, are very likely due to the phenyl groups.

Azeotropic Condensations.—(*a*) *p*-Nitrobenzaldehyde (0·5 g.) and glycine ethyl ester (5·2 g.) in benzene (50 c.c.) were subjected to azeotropic distillation. After 3 hr., the solvent was distilled off and the resinous residue treated with methanolic hydrochloric acid (30 c.c.; containing 3 g. of HCl) and an excess of ether. An oil separated which solidified on standing (yield, 4·5 g., 31%). Recrystallised from amyl alcohol, the *erythro*-*p*-nitrophenylserine ethyl ester hydrochloride formed prisms, m. p. 188° (decomp.) (Bergmann *et al.*, *loc. cit.*, give m. p. 189°). The same result was obtained when half of the above quantity of ethyl ester was employed, the yield being 3·9 g. (54%).

(*b*) *m*-Nitrobenzaldehyde (7·5 g.) and glycine ethyl ester (2·6 g.) were condensed as above. With methanolic hydrochloric acid (15 c.c., containing 1·5 g. of HCl), the hydrochloride (6 g., 83%) was obtained. From 2-nitropropane it formed leaflets; when crystallisation set in, a few drops of acetone were added which prevented the product from forming an oil. *erythro*(?)-*m*-Nitrophenylserine ethyl ester hydrochloride had m. p. 182° (decomp.) (Bergmann *et al.*, *loc. cit.*, give m. p. 180—184°).

(*c*) The mixture of glycine methyl ester (2·4 g.) and *m*-nitrobenzaldehyde (8·2 g.) with benzene (50 c.c.) was subjected to azeotropic distillation, which liberated quickly 1 c.c. of water. The solution was filtered from a little insoluble material and evaporated to dryness. The residual oil, on treatment with methanolic hydrochloric acid and an excess of ether, gave a thick precipitate of erythro(?)-m-*nitrophenylserine methyl ester hydrochloride*, which crystallised from butanol in leaflets (1·1 g.), m. p. 190° (decomp.) (Found: C, 43·8; H, 4·8; N, 10·0, 9·9. $C_{10}H_{13}O_5N_2Cl$ requires C, 43·5; H, 4·7; N, 10·1%).

(*d*) 4-Methyl-3-nitrobenzaldehyde (6·3 g.) and glycine methyl ester (1·8 g.) were condensed

as above. The hydrochloride of *erythro*(?)-4-methyl-3-nitrophenylserine methyl ester which separated on addition of methanolic hydrochloric acid (15 c.c., containing 1·5 g. of HCl) and an excess of ether, formed an oil which was triturated with acetone. The crystals (0·5 g., 8%) were recrystallised from *iso*propyl alcohol, forming prisms, m. p. 179° (decomp.). The substance was identical with the ester described on p. .

(*e*) 2 : 6-Dichlorobenzaldehyde (2·5 g.), freshly distilled glycine ethyl ester (0·7 g.), and benzene (20 c.c.) were subjected to azeotropic distillation for 30 min. After cooling, anhydrous ether (100 c.c.) and alcoholic 4N-hydrochloric acid (1·5 c.c.) were added. Thus, *erythro*(?)-2 : 6-dichlorophenylserine ethyl ester hydrochloride (2 g.) was obtained; recrystallised from a little alcohol it melted at 170°. It did not depress the m. p. of the ester described before.

(*f*) 5-Nitrofurfuraldehyde (2·80 g.), glycine ethyl ester (1·0 g.), and benzene (20 c.c.) were refluxed azeotropically for 30 min. Upon cooling, *N*-(5-nitro-2-furfurylidene)-*erythro*(?)-β-(5-nitro-2-furyl)serine ethyl ester (1·0 g.) crystallised; after recrystallisation from alcohol, it melted at 134° and was identical with the Schiff base obtained as described before.

Addition of alcoholic 3N-hydrochloric acid (2·5 c.c.) to the benzene mother-liquor precipitated *erythro*(?)-β-(5-nitro-2-furyl)serine ethyl ester hydrochloride, m. p. 160° (from alcohol), identical with the hydrochloride described before.

(*g*) A different course of the azeotropic condensation was observed in the reaction between glycine methyl ester and *p*-chlorobenzaldehyde. The reaction between the ester (2·2 g.) and *p*-chlorobenzaldehyde (3·5 g.) in benzene (50 c.c.) set in at once (turbidity); the theoretical quantity of water collected in the receiver after azeotropical distillation for 30 min. The product was recrystallised from *iso*propyl alcohol and melted at 163°. The analysis pointed to the formula of N : α-*di*-p-*chlorobenzylideneglycine methyl ester*, which would imply that the *N*-(*p*-chlorobenzylidene)-*p*-chlorophenylserine ester had been formed, but had split off water, presumably during distillation (Found: C, 60·9; H, 4·1; N, 4·5; Cl, 20·9; OMe, 9·8%; *M*, 304. $C_{17}H_{13}O_2NCl_2$ requires C, 61·1; H, 3·9; N, 4·2; Cl, 21·3; OMe, 9·3%; *M*, 334).

The infra-red spectrum (0·023 g. in 1 c.c. of chloroform; cell-thickness, 0·1 mm.) showed the following bands (the most intense in *italics*): *1692*, 1609, 1577, 1476, 1430, 1297, 1103, *1084*, 1008, 978 cm.$^{-1}$. It is assumed that the strong band at 1692 cm.$^{-1}$ is due to the superposition of the ester absorption and that of the C:N double bond (Colthup, *J. Opt. Soc. America*, 1950, **40**, 397). which also absorbs at 1577 cm.$^{-1}$ (at the same wave-number as phenyl). The band at 1084 cm.$^{-1}$ is undoubtedly that of the *p*-chlorophenyl radical; it appears also in chlorobenzene, *p*-chlorotoluene, and *p*-chlorophenol (Barnes *et al.*, "Infra-red Spectroscopy," New York, 1944).

The ultra-violet spectrum (in $CHCl_3$) showed a pronounced maximum at 2715 Å and a less distinct one at 3000 Å. This substance is, therefore, less absorbent than the similar 1 : 4-diphenylbutadiene (Jones, *Chem. Reviews*, 1943, **32**, 1); this difference may be accounted for by steric inhibition of the conjugation through the esterified carboxyl group as the azlactones absorb at 3300—3600 Å (Bennett and Hoerger, *J. Amer. Chem. Soc.*, 1952, **74**, 5975; cf. Bassi, Deulofeu, and Ortega, *ibid.*, 1953, **75**, 171).

Reactions with Glycine Benzyl Ester.—(*a*) A solution of ammonia (2 g.) in chloroform (66 c.c.) was agitated for 24 hr. with glycine benzyl ester hydrobromide (13 g.) (D. Ben-Ishai and Berger, *J. Org. Chem.*, 1952, **17**, 1564). After addition of anhydrous ether (50 c.c.), the solution was filtered and evaporated *in vacuo* to dryness. The crude ester (8·2 g., 94%) was used for experiment.

(*b*) threo-p-*Nitrophenylserine benzyl ester.* When *p*-nitrobenzaldehyde (3·0 g.) and glycine benzyl ester (5 g., 1·5 mols. per mol. of aldehyde) were mixed at room temperature, an exothermic reaction set in, and the mass became a brown semi-solid. This was triturated with ether and a little acetone, and the crystalline ester filtered off (2·8 g., 44%). From *iso*propyl alcohol, the *ester* crystallised in prisms, m. p. 130° (Found: C, 60·5; H, 5·0; N, 8·8. $C_{16}H_{16}O_5N_2$ requires C, 60·7; H, 5·1; N, 8·9%).

(*c*) erythro(?)-p-*Chlorophenylserine benzyl ester hydrochloride.* To a solution of sodium methoxide (0·54 g.) in methanol (25 c.c.), there were added glycine benzyl ester hydrobromide (2·5 g.) and *p*-chlorobenzaldehyde (2·8 g.). After 48 hr. at room temperature, an oil had separated. Upon addition of 12% methanolic hydrochloric acid (6 c.c.) and an excess of ether, the oil dissolved, and a fine precipitate appeared which was recrystallised from *iso*propyl alcohol. The *ester hydrochloride* formed needles, m. p. 232° (decomp.) (Found: C, 56·0; H, 5·0; N, 4·1; Cl, 20·5; active H, 0·82. $C_{16}H_{17}O_3NCl_2$ requires C, 56·1; H, 5·0; N, 4·1; Cl, 20·7; 3 H, 0·88%).

Ethyl 3-*Methyl*-2 : 5-*di*-p-*nitrophenyloxazolidine*-4-*carboxylate* (VII).—A methanolic solution

of sarcosine ethyl ester (1·3 c.c.) (E. Fischer, *Ber.*, 1901, **34**, 452; b. p. 60°/10 mm.) and *p*-nitrobenzaldehyde (1·5 g.) was exposed to direct sunlight in a quartz vessel. Evaporation gave an oil which crystallised on trituration with methanol containing a small quantity of acetone. After recrystallisation from *iso*propanol, the *ester* had m. p. 171° (Found: C, 56·5; H, 4·7; N, 10·8; OEt, 10·9; NMe, 6·9. $C_{19}H_{19}O_7N_3$ requires C, 56·8; H, 4·7; N, 10·4; OEt, 11·2; NMe, 7·2%).

The infra-red spectrum was investigated in chloroform solution (0·025 g. in 1 c.c. of solvent; cell thickness: 0·1 mm.). Absorption in the hydroxyl region was completely lacking; at 1747 cm.$^{-1}$ the carboxyl band, and at 1606 cm.$^{-1}$ the phenyl absorption, were observed. In the oxazolidine region (E. Bergmann, Zimkin, and Pinchas, *Rec. Trav. chim.*, 1952, **71**, 168 ff.), bands appeared at 1179, 1116, 1068, and 1045 cm.$^{-1}$. The band at 1116 cm.$^{-1}$ may also be accounted for as that of the *p*-substituted benzene nucleus.

O-*Benzylserine*.—For the preparation of αβ-dibromopropionic acid, the oxidation of 2 : 3-dibromopropanol (Beilstein's "Handbuch," Vol. II, p. 258) was employed. Oxidation (of 100 g., b. p. 110—112°/15 mm.) with a mixture of concentrated (140 g.) and fuming (30 g.) nitric acid at 0° for 12 hr. and at room temperature for a further 24 hr. gave an 80% yield of αβ-dibromopropionic acid, b. p. 150—160°/23 mm., m. p. 61° (ethyl ester, b. p. 86—87°/7 mm.).

By the method of Wood and du Vigneaud (*J. Biol. Chem.*, 1940, **134**, 413), ethyl αβ-dibromopropionate (260 g.) was converted, by means of a solution of sodium (24 g.) in benzyl alcohol (500 c.c.), into ethyl β-benzyloxy-α-bromopropionate. This was isolated in crude form by evaporation of the excess of benzyl alcohol at 60°/0·1 mm., and transformed by treatment with ammonia at 100° into *β-benzyloxyalanine*. The aqueous solution obtained was repeatedly evaporated to dryness *in vacuo* and the solid product washed with cold water until the filtrate gave a negative bromide test. Recrystallisation from water gave platelets, m. p. 218° (50 g., 26%) (Found: C, 61·7; H, 6·7; N, 7·3. $C_{10}H_{13}O_3N$ requires C, 61·5; H, 6·7; N, 7·2%).

O-*Benzylserine Ethyl Ester Hydrochloride* (III).—A suspension of the amino-acid (20 g.) in anhydrous ethanol (100 c.c.) was saturated with gaseous hydrogen chloride and the mixture heated until a clear solution was obtained (5 min.). The product was evaporated to dryness *in vacuo* and the residue dissolved in a little alcohol and precipitated with dry ether. Thus, a yield of 18 g. (68%) of the *salt* (III) was obtained which had m. p. 102° (Found: C, 55·4; H, 6·8; N, 5·6. $C_{12}H_{18}O_3NCl$ requires C, 55·5; H, 7·0; N, 5·4%).

Ethyl α-Amino-α-benzyloxy-β-hydroxy-β-p-nitrophenylpropionate (IV).—At 0° the foregoing ester hydrochloride (4 g.) was stirred with chloroform (10 c.c.) which contained 2% of gaseous ammonia (Hillman, *Chem. Abs.*, 1949, **43**, 7425). The filtered solution was evaporated to dryness *in vacuo* (at 20°) and the residue dissolved in anhydrous alcohol. *p*-Nitrobenzaldehyde (3 g.) was added and the solution kept in the sun for 2 days, the desired *product* (2 g.) separating. Washing with ether and recrystallisation from *iso*propyl alcohol gave prisms, m. p. 136° [Found: C, 61·2; H, 5·7; N, 7·5; OEt, 12·0; amino-N, 3·7%; *M*, 350 (in boiling benzene). $C_{19}H_{22}O_6N_2$ requires C, 61·0; H, 5·9; N, 7·5; OC_2H_5, 12·0; amino-N, 3·7%; *M*, 374]. The infra-red spectrum (0·065 g. and 1 c.c. of chloroform; cell-thickness 0·1 mm.) of (IV) shows no band in the absorption region of the C:N double bond. The following bands have been measured and identified: 3275 (OH, hydrogen-bonded), 1731 (CO_2R), 1609 (aromatic double bond), 1349 (NO_2 in conjugation), 1183 (*para*-substituted phenyl), 1133 (ether grouping), and 1107 cm.$^{-1}$ (*para*-substituted phenyl) (cf. Randle and Whiffen, *J.*, 1952, 4153).

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