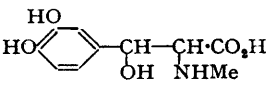
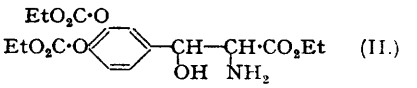
19. *The Synthesis of β-Phenylserines.*

By CHARLES E. DALGLIESH.

The synthesis of *β-4-nitro-* and *-4-amino-phenylserines* is described, and various aspects of the synthesis of *β*-phenylserine derivatives are discussed.

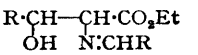
DERIVATIVES of β-phenylserine are of interest in view of their possible occurrence as precursors of adrenaline in the animal body (Dalgliesh and Mann, *J.*, 1947, 658). During the course of work primarily aimed at the synthesis of β-(3 : 4-dihydroxyphenyl)-*N*-methylserine (I) (Dalgliesh and Mann, *loc. cit.*), various other results were obtained which are here briefly presented.

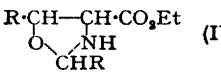
(I.) 

(II.) 

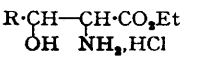
It was suggested by Dalgliesh and Mann that the preparation of the related nor-acid, 3 : 4-dihydroxyphenylserine, described by Rosenmund and Dornsaft (*Ber.*, 1919, **52**, 1734) might be improved by converting its synthetic precursor, the hydrochloride of β-(3 : 4-diethylcarbonatophenyl)serine ester (II), into the oxalate followed by hydrolysis with dilute acetic acid, the method found to be most suitable for isolating (I). This has since been found not to be so. On being heated under even mildly acid conditions derivatives of the nor-acid are rapidly transformed, paper chromatography showing the absence of the nor-acid from the derived mixture, which was not further investigated. Moreover in the initial condensation of dicarbethoxyprotocatechuic aldehyde with glycine ester to give (II), the yield has been found to be markedly dependent on the period of the reaction, decreasing rapidly after 24 hours. *Dicarbomethoxyprotocatechuic aldehyde* has also been tried in this reaction, but is much less satisfactory than the corresponding dicarbethoxy-compound.

In view of the considerable variation in the reactivities of substituted benzaldehydes in their reaction with glycine ester (Dalgliesh and Mann, *loc. cit.*) it was thought to be of interest to see whether *p*-nitrobenzaldehyde would take part in the reaction. It did, though the reaction differed from others of the same type in that the sodium appeared to act only as a surface catalyst and was not destroyed as the reaction proceeded. From the reaction mixture was isolated directly a compound (*A*) agreeing on analysis with the Schiff's *base* (III) known to be a product of this type of reaction (Erlenmeyer, *Annalen*, 1895, **284**, 36; Dalgliesh and Mann, *loc. cit.*), but not usually isolated. This changed on standing in ethanolic solution to an isomeric compound (*B*), which is suggested to be *ethyl* 2 : 5-*bis*-p-*nitrophenyloxazolidine*-4-*carboxylate* (IV). Oxazolidines are known to be very readily formed from aromatic aldehydes and phenyl-

(III.) 

(IV.) 

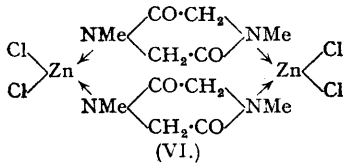
(R = *p*-$C_6H_4 \cdot NO_2$.)

(V.) 

ethanolamine derivatives, Schiff's bases of type (III) being intermediates in the reaction (*e.g.*, Meltsner, Waldman, and Kramer, *J. Amer. Chem. Soc.*, 1940, **62**, 3494). They are, moreover,

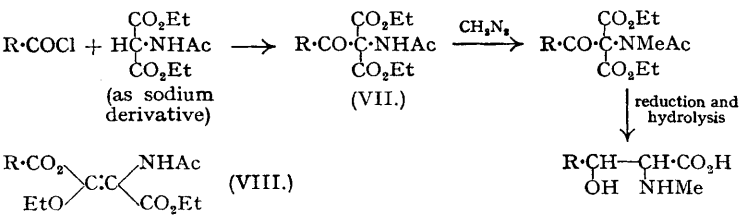
readily hydrolysed by acid, and mild acid hydrolysis of (*B*) rapidly gave β-4-*nitrophenylserine ethyl ester hydrochloride* (V). This after cold alkaline hydrolysis gave β-4-*nitrophenylserine*, hydrogenation of which gave β-4-*aminophenylserine*.

The low yields obtained in the synthesis of (I) prompted the investigation of possible alternative routes which proved unsuccessful. The possibility of some modification of the Erlenmeyer method was considered first. Condensations of this type normally give rise to an olefinic product (for an exception see Phillips, *J. Amer. Chem. Soc.*, 1945, **67**, 744), and it was hoped to convert such a product into a phenyl serine derivative by suitable addition to the double bond. In order to introduce the *N*-methyl group, attempts were made to condense veratric aldehyde and sarcosine anhydride under a variety of conditions. These failed, but in one reaction, after the reactants had been heated with anhydrous zinc chloride, there was isolated *sarcosine anhydride zincichloride*, which probably has the bimolecular structure (VI). Sarcosine and benzenesulphonylsarcosine likewise failed to condense. Similar failures of sarcosine derivatives to condense have been observed by other workers (*e.g.*, Heard, *Biochem. J.*, 1933, **27**, 54). Veratric aldehyde and glycine anhydride condensed readily to give 2 : 5-diketo-3 : 6-bis-3′ : 4′-dimethoxybenzylidenepiperazine (Deulofeu and Mendivelzua, *Z. physiol. Chem.*, 1933, **219**, 233), but this could not be methylated. When the sarcosine anhydride was replaced by *N*-methylhydantoin or creatinine, condensation with aromatic aldehydes proceeded satisfactorily. Thus 3 : 4-carbonyldioxybenzaldehyde and *N*-methylhydantoin gave 5-(3′ : 4′-*carbonyldioxybenzylidene*)-1-*methylhydantoin*, but attempts to effect suitable additions to the double bond of this compound failed. However 5-veratrylidene-creatinine (Deulofeu, *Ber.*, 1939, **72**, 1461) on treatment with cold sulphuric acid gave material in high yield which contained the elements of sulphuric acid added to the starting product, but investigation showed that sulphonation of the aromatic ring had occurred, giving 5-(3′ : 4′-*dimethoxybenzylidene*)*creatinine*-5′- or -6′-*sulphonic acid monohydrate*, which on dehydration gave the free *acid*.



(VI.)

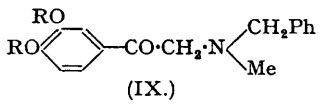
The possibility of a synthesis based on ethyl acetamidomalonate was next investigated. This intermediate has proved most successful in the synthesis of amino-acids such as phenylalanine and leucine in which the essential stage involves reaction with a primary halide (*e.g.*, Albertson and Archer, *J. Amer. Chem. Soc.*, 1945, **67**, 308), but the method does not work with secondary halides (Snyder, Shekleton, and Lewis, *ibid.*, p. 310). There appeared to be no record of its reaction with an acyl halide, and the following synthesis was therefore projected, and model experiments carried out with benzoyl chloride :



No satisfactory product could be obtained from the initial reactants in organic media, but direct action of benzoyl chloride on the free sodium derivative (which is isolable as a reasonably stable, friable white powder) readily gave an *ethyl benzoylacetamidomalonate*. This could not be induced to give a 2 : 4-dinitrophenylhydrazone; boiling methanolic sodium methoxide reconverted it into ethyl acetamidomalonate; on hydrogenation it slowly absorbed hydrogen with formation of benzaldehyde and ethyl acetamidomalonate; it gave no sodium derivative; and it was not methylated by ethereal diazomethane, either in the cold or on refluxing. The imino-hydrogen of a compound such as (VII) would be expected to be exceedingly labile, and the compound may be the *O*-benzoyl derivative (VIII). It is clearly not a suitable intermediate for the synthesis of β-phenyl-*N*-methylserine.

In considering syntheses based on known syntheses of adrenaline, 3 : 4-diacetoxyphenacyl chloride was treated with benzylmethylamine, but the product obtained was *N*-benzyl-*N*-methylacetamide. However 3 : 4-dihydroxyphenacyl chloride (chloroacetylcatechol) and benzylmethylamine gave in high yield N-*benzyladrenalone* (IX, R = H), first isolated as the

crystalline *ethanolate*. Benzylation gave the gummy *tribenzyladrenalone* (IX, R = CH_2·Ph), isolated as the glassy *hydrochloride* and *picrate* and as the crystalline *oxalate diethanolate*. Bromination of tribenzyladrenalone gave an uncrystallisable gum, and no crystalline product could be obtained after boiling with potassium cyanide. Similar difficulty with the failure of compounds of the above type to crystallise was experienced by Priestley and Moness (*J. Org. Chem.*, 1940, **5**, 355) in the synthesis of " sympathol " (2-methylamino-1-*p*-hydroxyphenylethanol).



(IX.)

In view of the isomersation of aldehydes of the type Ph·CH(OH)·CHO to Ph·CO·CH_2·OH (Evans and Parkinson, *J. Amer. Chem. Soc.*, 1913, **35**, 1770), the Strecker method of synthesis would also appear to be inapplicable to β-phenylserines.

Experimental.

3 : 4-*Dihydroxyphenylserine*.—The preparation as described by Dalgliesh and Mann was advantageously modified by the use of an excess of sodium wire, to provide as large an area of sodium surface as possible in the early stages of the reaction. Whereas a negligible yield of the required product was obtained when the mixture was worked up after standing over sodium for 40 hours, a similar preparation worked up after 26 hours gave a yield of esterified amino-acid of 9½%, and worked up after 22 hours gave a yield of 23%. The diminution of yield may be associated with the separation of a gum from the solution.

Dicarbomethoxyprotocatechuic Aldehyde.—To an ice-cooled solution of protocatechuic aldehyde (19 g.) in N-sodium hydroxide (330 ml.) was added with vigorous shaking methyl chloroformate (19·8 ml.). After a short while the copious precipitate of esterified *aldehyde* was isolated (32·3 g.; 95%) and recrystallised from methanol to give colourless crystals, m. p. 99° (Found: C, 52·1; H, 3·9. $C_{11}H_{10}O_7$ requires C, 52·0; H, 3·9%). The 2 : 4-*dinitrophenylhydrazone* had m. p. 227° (Found: N, 13·1. $C_{17}H_{14}O_{10}N_4$ requires N, 12·9%).

Dalgliesh and Mann inadvertantly attributed to the corresponding dicarbethoxyprotocatechuic aldehyde the m. p. 122°. The aldehyde is in fact an oil, and the m. p. 122° refers to the 3 : 4-carbonyldioxybenzaldehyde which was found to be formed by decomposition on large-scale distillation.

p-Nitrobenzaldehyde and Glycine Ethyl Ester.—To finely divided (" molecular ") sodium (5 g.; 2½ mol.-equivs.) was added glycine ethyl ester (7·5 g.; 1 mol.-equiv.) and *p*-nitrobenzaldehyde (22·5 g.; 2 mol.-equivs.) in dry ether (1 l.). The mixture was then set aside at room temperature under anhydrous conditions. The sodium surface almost immediately became dark, and then remained apparently unaltered. A slow reaction set in, as indicated by a stream of fine bubbles rising from the sodium, and continued at an apparently constant rate, the liquid becoming slightly cloudy after 48 hours. After 4 days a small sample of the solution was filtered and evaporated, and the residue recrystallised from ethanol to give pale yellow plates of a compound (*A*), m. p. 85°, considered to be the Schiff's *base* (III) (Found: C, 56·5; H, 4·4; N, 10·7. $C_{18}H_{17}O_7N_3$ requires C, 55·8; H, 4·4; N, 10·8%). The whole solution was then similarly treated, being left in the ethanolic mother liquors overnight. Long cream-coloured needles of m. p. 136—139° (139° after further recrystallisation from ethanol) were obtained and found to consist of an isomeric compound (*B*), considered to be the *oxazolidine* derivative (IV) (Found: C, 55·7; H, 4·7; N, 10·8. $C_{18}H_{17}O_7N_3$ requires C, 55·8; H, 4·4; N, 10·8%). When a sample of the previously recrystallised (*A*) was left in ethanol overnight it became converted into the less soluble (*B*). Total yield of (*B*), 10·8 g. (37%).

(B) was decomposed to *p*-nitrobenzaldehyde and glycine by being refluxed with 25% acetic acid for 3 hours. Therefore 3 g. of (*B*) were suspended in dry ether (100 ml.), a little alcoholic hydrogen chloride added, the whole shaken for 2 minutes and filtered, and the residue recrystallised from ethanol, giving colourless prisms of *β-4-nitrophenylserine ethyl ester hydrochloride* (V) (1·44 g.; 64%), m. p. 185° (decomp.) (Found, after 3 hours' drying at 100° in a vacuum over phosphoric oxide: C, 46·0; H, 5·1; N, 9·6. $C_{11}H_{14}O_5N_2$,HCl requires C, 45·5; H, 5·1; N, 9·6%).

To the above hydrochloride (2·18 g.) were added N-sodium hydroxide (15 ml.; 2 mol.-equivs.) and a little alcohol, and the whole was left with occasional shaking for 1 hour, after which N-hydrochloric acid (7·5 ml.) was added. The white precipitate of *β-4-nitrophenylserine* (1·64 g.; 96%) was isolated, washed with a little water, and dried. It decomposed at 188°, gave a strong ninhydrin reaction, and was readily recrystallised from water (Found: C, 48·1; H, 4·4; N, 12·4. $C_9H_{10}O_5N_2$ requires C, 47·9; H, 4·4; N, 12·3%).

The above amino-acid (0·82 g.) suspended in N-hydrochloric acid (7·26 ml.; 2 mol.-equivs.) and water (20 ml.) was hydrogenated over palladium–charcoal (0·1 g.) at room temperature. Uptake of hydrogen was complete after 2 hours, and the mixture was then filtered, the catalyst washed with a little water, N-sodium hydroxide (7·26 ml.) added to the combined filtrates, the whole evaporated to dryness, and the residue recrystallised from water to give silky needles (0·38 g.; 53%) of *β-4-aminophenylserine*. This compound is appreciably soluble in cold water, is fairly easily oxidised, gives a strong ninhydrin reaction, and decomposes at 205—207° after preliminary shrinking and darkening (Found: C, 55·5; H, 6·1; N, 14·5. $C_9H_{12}O_3N_2$ requires C, 55·1; H, 6·1; N, 14·3%). No evidence of the formation of more than one racemate of the above amino-acids was obtained.

Sarcosine Anhydride Zincichloride.—Sarcosine anhydride (3·1 g.), veratric aldehyde (8·0 g.), and anhydrous zinc chloride (9·0 g.) were dried overnight in a vacuum over phosphoric oxide, and then heated under anhydrous condition in an oil-bath at 150—160° for 1 hour. When cool, the solid residue was treated with ethanol (150 ml.), boiled, and filtered. The filtrate deposited white crystals of *sarcosine anhydride zincichloride* (VI) which after two further recrystallisations from alcohol had m. p. 348—352° (decomp.) (Found: C, 26·4; H, 3·4; N, 9·5; Cl, 25·5. $C_6H_{10}O_2N_2$,$ZnCl_2$ requires C, 25·8; H, 3·6; N, 10·0; Cl, 25·5%).

3 : 4-*Carbonyldioxybenzaldehyde and* N-*Methylhydantoin.*—The aldehyde (5·0 g.) and *N*-methylhydantoin (3·9 g.) were heated under reflux in pyridine (12 ml.) for 1 hour; the solution became deep yellow, but no solid separated. Boiling water (50 ml.) was added, and the solution made just acid with acetic acid and filtered. Yellow crystals of 5-(3′ : 4′-*carbonyldioxybenzylidene*)-1-*methylhydantoin* separated from the filtrate on cooling, and after recrystallisation from acetic acid had m. p. 298—300° (Found : C, 55·8; H, 3·5; N, 11·1. $C_{12}H_8O_5N_2$ requires C, 55·4; H, 3·1; N, 10·8%).

Sulphonation of Veratrylidenecreatinine.—Veratrylidenecreatinine (4 g.) was dissolved in concentrated sulphuric acid (30 ml.), and after 24 hours the deep orange solution poured on ice (250 g.). The yellow acicular product (4·25 g.; 81%), 5-(3′ : 4′-*dimethoxybenzylidene*)*creatinine*-5′- or -6′-*sulphonic acid monohydrate*, after recrystallisation from acetic acid had m. p. 309° (decomp.) (Found : C, 43·9; H, 4·6; N, 11·8; S, 9·3. $C_{13}H_{15}O_6N_3S,H_2O$ requires C, 43·5; H, 4·7; N, 11·7; S, 8·9%). After this had been heated for 12 hours at 80° in a vacuum over phosphoric oxide, the anhydrous *acid*, similar in appearance, m. p. 324° (decomp.), remained (Found : C, 45·6; H, 4·7. $C_{13}H_{15}O_6N_3S$ requires C, 45·7; H, 4·4%). Alkaline hydrolysis of the acid gave an aromatic compound still containing sulphur.

When veratrylidenecreatinine (2 g.) was dissolved in a mixture of concentrated sulphuric acid (7 ml.) and glacial acetic acid (7 ml.), and poured on ice (150 g.) after 24 hours, orange-red needles (1·4 g.), recrystallised from acetic acid, of 2-*acetyl*-5-(3′ : 4′-*dimethoxybenzylidene*)*creatinine*-5′- or -6′-*sulphonic acid*, m. p. 239° (decomp.), were obtained (Found : C, 47·2; H, 4·2. $C_{15}H_{17}O_7N_3S$ requires C, 47·0; H, 4·4%).

Ethyl Benzoylacetamidomalonate.—Ethyl acetamidomalonate (Snyder and Smith, *J. Amer. Chem. Soc.*, 1944, **66**, 350; 21·6 g.) was added to ethanol (300 ml.) in which sodium (2·3 g.) had previously been dissolved. The ethanol was distilled off, final traces being removed at the pump, leaving the sodium salt of ethyl acetamidomalonate as a friable white powder. To the sodium salt (20 g.) was added benzoyl chloride (9·8 ml.); considerable evolution of heat occurred, and the mixture was then heated for 15 minutes on the water-bath. After cooling, stirring with water, and decantation of the aqueous extract, the residue was recrystallised from ethanol to give long white needles (13 g.; 48%) of the *ester* (VII) or (VIII), m. p. 125° (Found : C, 59·7; H, 5·9; N, 4·4. $C_{16}H_{19}O_6N$ requires C, 59·8; H, 5·9; N, 4·4%).

N-*Benzyladrenalone* (IX, R = H).—To chloroacetylcatechol monohydrate (10·2 g.; Mannich and Hahn, *Ber.*, 1911, **44**, 1548; Hoberman, *J. Amer. Chem. Soc.*, 1935, **57**, 1382) in ethanol (25 ml.) benzylmethylamine (12·1 g.) was added, and the mixture heated on a water-bath for ½ hour. The ethanol was then distilled off, and water added to the cold residue, which on being scratched and shaken gave a copious pale yellow precipitate of N-*benzyladrenalone monoethanolate* (14·6 g.; 92%), m. p. 117—119°. This on further recrystallisation from ethanol gave colourless crystals, m. p. 121° (decomp.) (Found : C, 67·8; H, 7·2; N, 4·7. $C_{16}H_{17}O_3N,C_2H_6O$ requires C, 68·1; H, 7·2; N, 4·4%). Removal of the solvent of crystallisation at 80° in a vacuum over phosphoric oxide left the free *ketone* as a pale yellow glass (Found : C, 71·1; H, 6·5. $C_{16}H_{17}O_3N$ requires C, 70·9; H, 6·3%).

Benzylation of N-*Benzyladrenalone.*—To sodium (4·5 g.) in ethanol (300 ml.) was added *N*-benzyladrenalone monoethanolate (31 g.) followed by benzyl chloride (22 ml.), and the whole boiled under reflux with mechanical stirring for 6 hours in an atmosphere of hydrogen. The mixture was then poured into water (3 l.) and set aside overnight. The precipitated oil could not be induced to solidify, and the mixture was extracted with ether. The ethereal extract was in turn extracted with dilute hydrochloric acid, whereupon a large quantity of oil separated from the aqueous layer. This was isolated, washed by decantation, and dried in a vacuum to give *tribenzyladrenalone hydrochloride* as an uncrystallisable glass (Found : C, 73·1; H, 6·3; N, 2·6. $C_{30}H_{29}O_3N,HCl$ requires C, 73·8; H, 6·2; N, 2·8%). This was only slightly soluble in water, but an aqueous solution gave with sodium picrate solution an oil, which on isolation, washing, and drying gave the *picrate* as a glass (Found : N, 8·5. $C_{30}H_{29}O_3N,C_6H_3O_7N_3$ requires N, 8·2%). The hydrochloric acid-containing mother liquors from the extraction were made alkaline, extracted with ether, and dried (Na_2SO_4). Removal of the ether left (IX, R = CH_2·Ph) as a brown, uncrystallisable, and undistillable gum. This when dissolved in ethanolic oxalic acid deposited a precipitate which was recrystallised from ethanol to give glistening white crystals of the *oxalate diethanolate*, m. p. 191° (decomp.) (Found : C, 68·3; 68·4; H, 6·5; 7·0. $C_{30}H_{29}O_3N,C_2H_2O_4,2C_2H_6O$ requires C, 68·3; H, 6·8%).

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