[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RESEARCH DIVISION, SHARP AND DOHME, INC.]

β-m-Hydroxyphenylserine and β-p-Hydroxyphenylserine[1]

BY WILLIAM A. BOLHOFER

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The preparation of *threo-* and *erythro-β-m*-hydroxyphenylserine and *erythro-β-p*-hydroxyphenylserine is described. *erythro-β-m*-Hydroxyphenylserine (XIV) was synthesized from ethyl *m*-benzyloxybenzoylacetate (V). Thionyl chloride treatment of one of the intermediates, *erythro*-N-acetyl-*β-m*-hydroxyphenylserine ethyl ester (XI), resulted in an inversion of configuration and acid hydrolysis of the reaction mixture yielded *threo-β-m*-hydroxyphenylserine (XVI). An attempt was made to prepare *erythro-β-p*-hydroxyphenylserine (XXIII) from ethyl *p*-benzyloxybenzoylacetate (VI) using the same reactions as in the meta-hydroxy series. However, some changes were necessary because certain of the intermediates showed a strong tendency to form cinnamic acid type compounds (XVII). Extensive decomposition prevented the preparation of *threo-β-p*-hydroxyphenylserine from *erythro*-N-acetyl-*β-p*-hydroxyphenylserine ethyl ester (XII) by an inversion of the configuration with thionyl chloride.

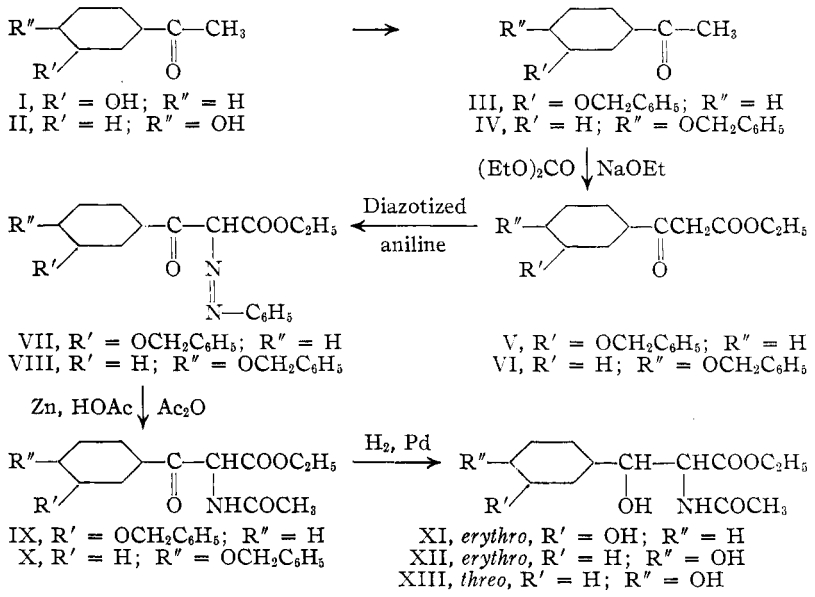
The concept that β-phenylserine and hydroxylated β-phenylserines serve as precursors in the biosynthesis of the hypertensive agents norepinephrine and epinephrine was first proposed in 1919 by Rosenmund and Dornsaft.[2] They synthesized β-*p*-hydroxyphenylserine and β-3,4-dihydroxyphenylserine, both of which hold a prominent position in the postulated biological synthesis. These compounds, prepared by other investigators,[3] have been tested for biological activity[4,5] with somewhat inconclusive results.

In a review article,[5] Beyer pointed out that the discrepancies may be due to the presence of varying quantities of stereoisomers in the samples with which the various investigators worked. Since the β-phenylserines possess two asymmetric centers, two diastereoisomeric modifications are possible, one of which would presumably be preferentially utilized in a reaction occurring in physiological systems.

In order to make available both diastereoisomeric modifications of some mono- and di-hydroxylated β-phenylserines, a synthetic program was launched with the preparation of pure isomers as its goal. The synthesis of both isomers of the parent compound, β-phenylserine, by a new method has already been reported[6] and the present paper reports the results obtained when this method was applied to the synthesis of the diastereoisomers of β-*m*-hydroxyphenyl- and β-*p*-hydroxyphenylserine.

The *threo-* and *erythro-β-m*-hydroxyphenylserine (XVI, XIV) were prepared from ethyl *m*-benzyloxybenzoylacetate (V) in the same manner that *threo-* and *erythro-β*-phenylserine were prepared from ethyl benzoylacetate.[6]

Ethyl *m*-benzyloxybenzoylacetate (V) was allowed to react with diazotized aniline in an emulsion of ethyl alcohol, benzene and aqueous sodium acetate. Reduction of the phenylazo compound VII with zinc dust in acetic acid gave ethyl α-acetamido-*m*-benzyloxybenzoylacetate (IX) mixed with acetanilide. Purification of the product by recrystallization was unsuccessful but a satisfactory separation was made by repeated water extraction of a benzene solution of the mixture.



Catalytic reduction of ethyl α-acetamido-*m*-benzyloxybenzoylacetate (IX) was carried out with palladium catalyst in glacial acetic acid. Hydrogenolysis of the benzyl group occurred prior to reduction of the ketone group, but no attempt was made to isolate the intermediate phenolic-ketone as was done in the para-hydroxy series (XIX). The product, N-acetyl-*β-m*-hydroxyphenylserine ethyl ester (XI), appeared to be a single isomer and it was assigned the *erythro* configuration since it was shown in the first paper of this series[6] that N-acetyl-β-phenylserine ethyl ester prepared by this method was exclusively in the *erythro* form.

In cases where an α-amino alcohol can exist in

(1) Presented at the Miniature Meeting of the Philadelphia Section of the American Chemical Society, January 29, 1953.

(2) K. W. Rosenmund and H. Dornsaft, *Ber.*, **52**, 1734 (1919).

(3) M. Guggenheim, "Die Biogenen Amine," 3rd ed., A. Karger, Basel and New York, 1940, p. 431; F. G. Mann and C. E. Dalgliesh, *Nature*, **158**, 375 (1946); C. E. Dalgliesh and F. G. Mann, *J. Chem. Soc.*, 658 (1947); W. H. Hartung, unpublished.

(4) H. Blaschko, P. Holten and G. H. S. Stanley, *Brit. J. Pharmacol.*, **3**, 315 (1948); K. H. Beyer, H. Blaschko, J. H. Burn and H. Langemann, *Nature*, **165**, 926 (1950); C. G. Schmiterlow, *Brit. J. Pharmacol.*, **6**, 127 (1951).

(5) K. H. Beyer, Advances in Chemistry Series, No. 2, "Chemical Factors in Hypertension," American Chemical Society, 1950, p. 45.

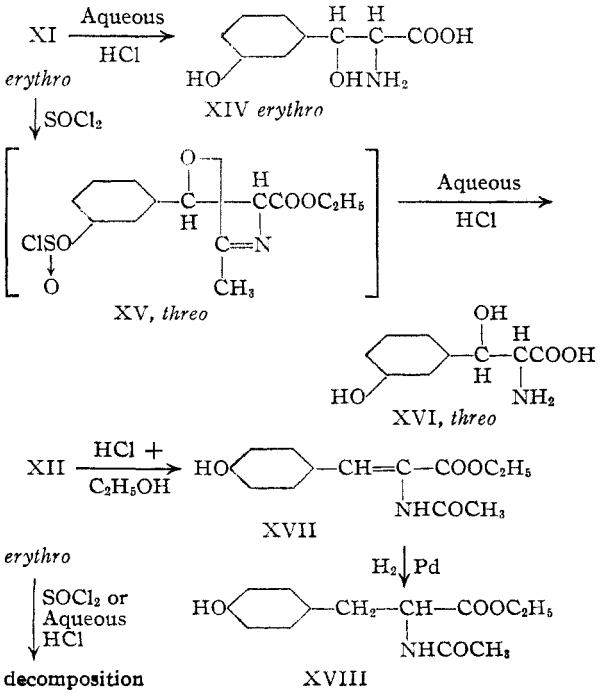
(6) W. A. Bolhofer, THIS JOURNAL, **74**, 5459 (1952).

two diastereoisomeric modifications, a single diastereoisomer usually predominates in the amino alcohol product prepared by catalytic reduction of the corresponding α-amino ketone. It is logical that similar amino alcohols prepared by catalytic reduction would all possess the same configuration.

Although *erythro*-N-acetyl-β-*m*-hydroxyphenylserine ethyl ester (XI) did not yield a crystalline oxazoline hydrochloride on treatment with thionyl chloride, acid hydrolysis of the reaction mixture gave *threo*-β-*m*-hydroxyphenylserine (XVI) in good yield. The high yield and ease of inversion constitutes further proof that the N-acetyl-β-*m*-hydroxyphenylserine ethyl ester (XI) has the *erythro* configuration as it has already been shown[6] that facile inversion is characteristic only of the *erythro* structure. *erythro*-β-*m*-Hydroxyphenylserine (XIV) was prepared by direct acid hydrolysis of the *erythro*-N-acetyl ester (XI). This product was more soluble in water and had a much lower melting point than the *threo* isomer. Both isomers were obtained in a white, analytically pure state. Paper chromatography in the organic phase of the system water (5 vol.), *n*-butyl alcohol (4 vol.), acetic acid (1 vol.) showed that both isomers had an R_F value of 0.33–0.35 (phenylalanine 0.58) and both gave the typical red-brown β-phenylserine color with ninhydrin.

Due to extensive decomposition it was not possible to esterify β-*m*-hydroxyphenylserine with alcoholic hydrogen chloride. Likewise, treatment of the N-acetyl ester XI with cold alcoholic hydrogen chloride yielded only oily products.

In the para-hydroxy series, the reactions paralleled those in the meta-hydroxy series up to the hydrolysis of N-acetyl-β-*p*-hydroxyphenylserine ethyl ester (XII). The compounds in the para series were usually higher melting and less soluble than their corresponding meta analogs. These differences in physical properties made the isolation and purification of the products in the para-hydroxy series easier than in the meta series.



Complete reduction of ethyl α-acetamido-*p*-benzyloxybenzoylacetate (X) in alcohol with palladium catalyst yielded N-acetyl-β-*p*-hydroxyphenylserine ethyl ester (XII, XIII) as a mixture of isomers. After fractional crystallization, 90% of the mixture was found to consist of an isomer which melted at 127–128°. Since this was by far the predominant isomer, it was assigned the *erythro* structure in analogy with results obtained in the β-phenylserine and β-*m*-hydroxyphenylserine series. The higher melting (208–210°) *threo* isomer XIII constituted not more than 5–10% of the mixture and since it was obtained in such small amounts it was not used for preparative work. Both isomers gave satisfactory analyses and identical ultraviolet absorption spectra.

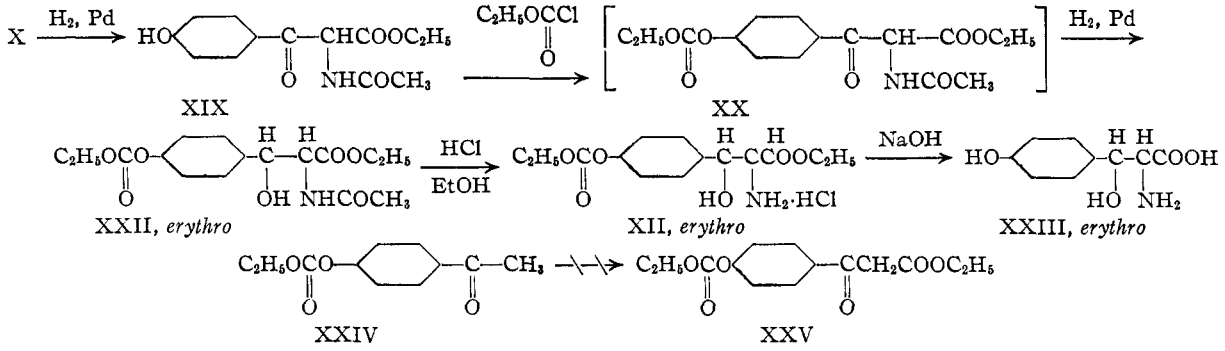
Aqueous acid hydrolysis of *erythro*-N-acetyl-β-*p*-hydroxyphenylserine ethyl ester (XII) was unsatisfactory. The solution became very dark and no product could be isolated. Little if any β-*p*-hydroxyphenylserine could be identified in the dark solution by paper chromatography. This behavior was very different from that observed in the meta-hydroxy series. When *erythro*-N-acetyl-β-*p*-hydroxyphenylserine ethyl ester (XII) was treated with alcoholic hydrogen chloride, an unsaturated product, ethyl α-acetamido-*p*-hydroxycinnamate (XVII), was isolated. This product was identified by hydrogenating it to form the known[7] N-acetyl-DL-tyrosine ethyl ester (XVIII).

From the work of Rosenmund and Dornsaft[2] it was known that N-(*p*-carbethoxyoxybenzylidene)-β-*p*-carbethoxyoxyphenylserine ethyl ester could be treated with alcoholic hydrogen chloride to form β-*p*-carbethoxyoxyphenylserine ethyl ester hydrochloride (XXII). This result indicated that the acetyl group in N-acetyl-β-*p*-hydroxyphenylserine ethyl ester (XII) could be cleaved with alcoholic hydrogen chloride if the para-hydroxy group were protected by conversion to a para-carbethoxyoxy group. This was done by an indirect route.

Ethyl α-acetamido-*p*-hydroxybenzoylacetate (XIX) was obtained from ethyl α-acetamido-*p*-benzyloxybenzoylacetate (X) by catalytic hydrogenolysis of the benzyl group. The phenolic ketone XIX was treated with ethyl chlorocarbonate and ethyl α-acetamido-*p*-carbethoxyoxybenzoylacetate (XX) was obtained as an oil. Reduction of the oil was carried out in ethanol using palladium on charcoal catalyst and crystalline *erythro*-N-acetyl-β-*p*-carbethoxyoxyphenylserine ethyl ester (XXI) was obtained. The compound was assigned the *erythro* structure in accordance with the results obtained in the β-phenylserine and the β-*m*-hydroxyphenylserine series.

The acetyl group was removed by an acid-catalyzed alcoholysis and crystalline *erythro*-β-*p*-carbethoxyoxyphenylserine ethyl ester hydrochloride (XXII) (m.p. 187–188) was obtained. It appeared to be a single isomer and is apparently identical with the compound (m.p. 181°) reported by Rosenmund and Dornsaft.[2] The ethyl ester hydrochloride

(7) C. Niemann and G. E. McCasland, THIS JOURNAL, 66, 1870 (1944).



XXII on alkaline hydrolysis gave *erythro*-β-*p*-hydroxyphenylserine (XXIII). These results indicate that the β-*p*-hydroxyphenylserine synthesized by Rosenmund and Dornsaft possessed the *erythro* configuration, a conclusion also reached by Holland and co-workers[8a] who prepared both diastereoisomers of β-*p*-hydroxyphenylserine from the corresponding isomers of β-*p*-aminophenylserine. Bergmann and associates[8b] have synthesized β-*p*-carbethoxyoxyphenylserine ethyl ester hydrochloride and β-*p*-hydroxyphenylserine by a new method but the structural configurations of these products are not known.

An attempt was made to prepare ethyl *p*-carbethoxyoxybenzoylacetate (XXV) for use as the starting compound in the synthesis of *erythro*-β-*p*-hydroxyphenylserine. However, treatment of *p*-carbethoxyoxyacetophenone (XXIV) with sodium ethoxide and ethyl carbonate yielded *p*-hydroxyacetophenone (II) as the sole product.

Inversion of the configuration of *erythro*-N-acetyl-β-*p*-hydroxyphenylserine ethyl ester (XII) by oxazoline formation with thionyl chloride was not successful. The thionyl chloride caused extensive decomposition similar to the acid-catalyzed decomposition described above. No crystalline oxazoline was obtained and paper chromatography of acid and alkaline hydrolyzates of the reaction mixture demonstrated the absence of any β-*p*-hydroxyphenylserine.

Experimental[9]

m-Benzyloxyacetophenone (III).—This compound was prepared by the benzylation procedure of Suter and Ruddy.[10] The product (84.7%) had a m.p. of 29–30° and a b.p. of 165–170° at 0.5 mm. Bass and van Duzee[11] report a b.p. of 184–188° at 3 mm.

Ethyl *m*-Benzyloxybenzoylacetate (V).—Sodium (9.4 g., 0.4 mole plus 2.5% excess) was dissolved in 150 ml. of absolute alcohol in a three-necked flask fitted with a stirrer, thermometer, nitrogen inlet and a condenser for distillation. The condensate receiver was protected from atmospheric moisture by a calcium chloride drying tube. Most of the alcohol was removed by distillation and 80 ml. of dry xylene was added. Distillation was continued until the vapor temperature reached 139°, leaving a pasty mass of crystalline sodium ethoxide which was not allowed to go to dryness. A slow stream of dry nitrogen was passed through the apparatus at all times.

The sodium ethoxide was cooled to room temperature and 250 ml. of distilled ethyl carbonate and 90.4 g. (0.4 mole) of *m*-benzyloxyacetophenone was added. The temperature was increased slowly and at 110° distillation commenced. In about 15 minutes 70 ml. of distillate was collected. This distillate appeared to be an azeotrope of ethyl alcohol and ethyl carbonate. The volume of upper layer obtained on dilution of the distillate with an equal volume of water gave, by difference, a fair measure of the quantity of alcohol produced in the reaction.

After distillation of the azeotrope, the temperature was increased and held at 140° for ten minutes. The reaction mixture was cooled and added to a well-stirred, cold mixture of 550 ml. of ether and 1375 ml. of 2 *N* acetic acid. After removal of the organic layer, the aqueous raffinate was extracted with two 300-ml. portions of ether, and the combined extracts were washed with 500 ml. of water. The ether solution was dried (Na_2SO_4) and the ether and diethyl carbonate were removed by vacuum distillation.

The crude product, which was an oil, was dissolved in 1375 ml. of ethyl alcohol at 50° and the solution was added with vigorous stirring to a solution of 110 g. of copper acetate in 1375 ml. of water at the same temperature. A dark oil quickly separated which crystallized to gummy green crystals on standing overnight. After thorough washing with ethyl alcohol and hexane, a green powder resulted which melted at 133–134°. Recrystallization from chloroform yielded a pure salt melting at 147–148°.

Decomposition of the copper salt was effected by dissolving it in a mixture of 850 ml. of 2 *N* sulfuric acid and 1000 ml. of ether. The liquids were separated and the ether solution was washed, dried (Na_2SO_4) and concentrated to an oil weighing 112.2 g. (68.5%). By evaporative distillation at 150° and one micron pressure, a colorless oil was obtained which crystallized very slowly to a waxy solid, m.p. 39–41°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.33; H, 6.22.

Ethyl α-Phenylazo-*m*-benzyloxybenzoylacetate (VII).—Aniline was diazotized by adding an ice-cold solution of 22.7 g. (0.33 mole) of sodium nitrite in 110 ml. of water to a mixture of 30.7 g. (0.33 mole) of aniline, 145 ml. of concentrated hydrochloric acid and 350 g. of ice. The diazonium salt solution was added over a 30-minute period to a mixture of 270 g. of sodium acetate (hydrate) in 180 ml. of water, 1080 ml. of ethyl alcohol and 89.4 g. (0.30 mole) of ethyl *m*-benzyloxybenzoylacetate in 360 ml. of benzene. Two phases were formed and vigorous stirring was necessary to obtain proper mixing. The temperature was maintained at 0° and, after the addition of the diazonium salt, stirring was continued for one hour longer. More water (1080 ml.) and benzene (270 ml.) were added, the phases were separated, and the aqueous raffinate was extracted with 300 ml. and 150 ml. of benzene. The combined benzene extracts were washed with three 250-ml. portions of water and the solvent was removed by concentration under vacuum. The residue was an oil (122 g.) which was dissolved in 244 ml. of *n*-butyl ether and allowed to crystallize at 0°. After being washed with cold *n*-butyl ether and hexane, the product weighed 109 g. (86.5%) and melted at 83–85°. (This compound was initially obtained in a form melting at 50–51.5° but on standing it changed over to the higher-melting polymorphic form.)

Anal. Calcd. for $C_{24}H_{22}O_4N_2$: C, 71.63; H, 5.51. Found: C, 71.67; H, 5.63.

Ethyl α-Acetamido-*m*-benzyloxybenzoylacetate (IX).—A solution of 90.5 g. (0.225 mole) of ethyl α-phenylazo-*m*-

(8) (a) D. O. Holland, P. A. Jenkins and J. H. C. Nayler, *J. Chem. Soc.*, 273 (1953); (b) E. D. Bergmann, H. Bendas and W. Taub, *ibid.*, 2673 (1951).

(9) All melting points are uncorrected. The microanalyses were carried out by Mr. Kermit Streeter and his staff.

(10) C. M. Suter and A. W. Ruddy, THIS JOURNAL, **66**, 747 (1944).

(11) S. L. Bass and E. M. van Duzee, U. S. Patent 2,109,458 (1938).

benzyloxybenzoylacetate in 170 ml. of glacial acetic acid was added to a well-stirred mixture of 101 g. of zinc dust, 337 ml. of acetic acid and 79 ml. of acetic anhydride as rapidly as the temperature could be maintained at 20–25° by external ice cooling (*ca.* 45 min.). The mixture was stirred for 30 minutes at room temperature and then the zinc acetate and unreacted zinc were removed by filtration and washed thoroughly with glacial acetic acid. The filtrate and washings were combined and concentrated under reduced pressure to remove most of the acetic acid and anhydride. The residual oil (169.2 g.) was dissolved in 900 ml. of benzene and the solution was extracted fifteen times with 900-ml. portions of water. Each water extract was passed through a separatory funnel containing 360 ml. of benzene before being discarded. This procedure removed all of the acetanilide from the product. The combined benzene solutions were concentrated under vacuum to an oil (85.4 g.) which was dissolved in 256 ml. of warm *n*-butyl ether. On cooling, an oil separated but with vigorous stirring this changed into powdery crystals and the mixture was held at 0° for 18 hours. The product (64.3 g., 81.0%), after being washed with cold *n*-butyl ether and hexane, melted at 70.5–72°. A sample, recrystallized from *n*-butyl ether, melted at 72–73°.

Anal. Calcd. for $C_{20}H_{21}O_5N$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.74; H, 6.03; N, 3.94.

***erythro*-N-Acetyl-β-*m*-hydroxyphenylserine Ethyl Ester (XI).**—A solution of 45.0 g. (0.127 mole) of ethyl α-acetamido-*m*-benzyloxybenzoylacetate in 225 ml. of glacial acetic acid containing 9.8 g. of 5% palladium on charcoal catalyst was hydrogenated at atmospheric pressure and temperature. In 5.5 hours, the compound absorbed 6,500 ml. of hydrogen (theory 6,220 ml.) and then the reduction ceased. After filtration, the acetic acid was removed by a vacuum concentration. The residue was dissolved in 100 ml. of hot chloroform and crystallization occurred at 0°. The product (32.0 g., 94.7%) melted at 139–141° and a recrystallization from water yielded material melting at 141–142°.

Anal. Calcd. for $C_{13}H_{17}O_5N$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.61; H, 6.54; N, 5.26.

***erythro*-β-*m*-Hydroxyphenylserine (XIV).**—A solution of 10.0 g. of *erythro*-N-acetyl-β-*m*-hydroxyphenylserine ethyl ester in 100 ml. of 2.5 *N* hydrochloric acid was heated under reflux for 30 minutes. The solution was concentrated almost to dryness and the residue was placed in a vacuum desiccator over sodium hydroxide pellets. A light yellow powdery hydrochloride (9.1 g., theory 8.75 g.) was obtained which was dissolved in 10 ml. of water. The solution was neutralized with 2 *N* sodium hydroxide and, after standing at 0° for 24 hours, 4.5 g. (61.0%) of a white crystalline product was collected. This product was recrystallized from 15 ml. of boiling water and 2.3 g. of pure, chloride-free material was obtained. After being dried for one hour at 80° *in vacuo*, it decomposed with gas evolution at 175°.

Anal. Calcd. for $C_9H_{11}O_4N$: C, 54.82; H, 5.62; N, 7.11. Found: C, 54.67, 54.75; H, 5.71, 5.69; N, 7.04, 7.06.

***threo*-β-*m*-Hydroxyphenylserine (XVI).**—Ten grams of *erythro*-N-acetyl-β-*m*-hydroxyphenylserine ethyl ester was added to 30 ml. of thionyl chloride at 0°. A clear yellow solution resulted and the excess thionyl chloride was removed under reduced pressure below 45°. Carbon tetrachloride (50 ml.) was added to the residue and, after half had been distilled under reduced pressure, 70 ml. of water was added with external ice cooling. Concentrated hydrochloric acid (30 ml.) was then added, the remaining carbon tetrachloride was removed by concentration under reduced pressure, and the remaining aqueous solution was heated under reflux for two hours. The solution was concentrated to a small volume, 50 ml. of water was added and the *p*H adjusted to 6–7 with 20% sodium hydroxide. The product (4.7 g., 73.7%) was very insoluble in water. Recrystallization was effected by dissolving it in 50 ml. of 0.7 *N* sodium hydroxide and then neutralizing the solution with concentrated hydrochloric acid. After drying at 80° for 1 hour *in vacuo*, the product (3.4 g.) decomposed with gas evolution at 230°.

Anal. Calcd. for $C_9H_{11}O_4N$: C, 54.82; H, 5.62; N, 7.11. Found: C, 54.67, 54.77; H, 5.81, 5.76; N, 7.07, 7.08.

***p*-Benzyloxyacetophenone (IV).**—This compound was prepared from *p*-hydroxyacetophenone in the same manner that *m*-benzyloxyacetophenone was prepared from *m*-hydroxyacetophenone. The product (96.9%) melted at 91–92°. Priestly and Moness[12] report 93° for the m.p. of *p*-benzyloxyacetophenone.

Ethyl *p*-Benzyloxybenzoylacetate (VI).—This compound was prepared in the same manner with the same quantities of reactants as ethyl *m*-benzyloxybenzoylacetate. After distillation of the ethyl carbonate–ethyl alcohol azeotrope, the mixture was heated at 125–130° for 30 minutes. As the solution was cooling down, 400 ml. of hexane was added slowly enough so that crystallization occurred without oiling out. After being cooled in an ice-bath for two hours, the slurry of sodium salt was added to 1.5 liters of hexane and the powder was filtered and washed thoroughly with hexane. Preparation of a copper complex for purification was unnecessary when the sodium salt was isolated in this manner.

The product (almost hexane free) was added to a mixture of 600 ml. of ether and 1 liter of 2 *N* acetic acid. When the powder dissolved, the layers were separated and the aqueous layer was extracted with 200 ml. of ether. The combined extracts were washed with water and sodium bicarbonate solution and then dried. Vacuum concentration was carried out until the temperature reached 100° at 0.3 mm. The residue (92.5 g., 77.6%) crystallized and melted at 50–55°. It was pure enough for the next reaction. Repeated recrystallization from ether yielded white crystals, m.p. 58–59°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.53; H, 6.12.

Ethyl α-Phenylazo-*p*-benzyloxybenzoylacetate (VIII).—This compound was prepared in the same manner with the same quantities of reactants as ethyl α-phenylazo-*m*-benzyloxybenzoylacetate. The oil (120 g.) from the benzene extracts was crystallized by dissolving it in 180 ml. of isopropyl ether and allowing the solution to stand at 0° for 48 hours. The product weighed 92.0 g. (76.5%) and melted at 76–78°. Recrystallization of a sample from isopropyl alcohol gave a product melting at 82–83°.

Anal. Calcd. for $C_{24}H_{22}O_4N_2$: C, 71.63; H, 5.51. Found: C, 71.56; H, 5.60.

Ethyl α-Acetamido-*p*-benzyloxybenzoylacetate (X).—This compound was prepared in the same manner with the same quantities of reactants as ethyl α-acetamido-*m*-benzyloxybenzoylacetate. After removal of the acetic acid and anhydride, the residual oil was dissolved in 560 ml. of benzene. This solution was extracted twice with water, once with saturated sodium bicarbonate and then the benzene was removed by concentration under vacuum. The residue was dissolved in 260 ml. of isopropyl alcohol and crystallization was allowed to take place at 0° (acetanilide remained in solution). The product weighed 68.0 g. (85.0%) and melted at 116–118°. A sample, recrystallized from isopropyl alcohol, melted at 117–118°.

Anal. Calcd. for $C_{20}H_{21}O_5N$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.72; H, 6.07; N, 3.92.

N-Acetyl-β-*p*-hydroxyphenylserine Ethyl Ester (XII, XIII).—A solution of 35.5 g. (0.10 mole) of ethyl α-acetamido-*p*-benzyloxybenzoylacetate in 200 ml. of ethyl alcohol at 70° was hydrogenated at atmospheric pressure using 1.8 g. of 5% palladium on charcoal catalyst. The benzyl group was cleaved rapidly (*ca.* 2 hr.) and, since the intermediate hydroxy ketone is soluble in alcohol, the temperature was allowed to fall to 25°. Reduction of the ketone group was slow and it was necessary to twice replace the catalyst. The complete reduction took about 2.5 days with a total of 4,560 ml. of hydrogen being consumed (theory 4,920 ml.). The catalyst was removed and the solution was concentrated to an oil which was dissolved in 100 ml. of hot chloroform. After standing at 0° for 18 hours, the crystalline product was collected by filtration. The product was a mixture of isomers melting over the range 124–129°.

Fractional crystallization of the product from ethyl acetate yielded 2.2 g. of a very insoluble substance melting at 170–185° and 21.3 g. (80.0%) of the major product melting at 123–127°. Recrystallization of a sample of the latter material first from isopropyl alcohol and then from ethyl acetate gave a product having a constant m.p. of 127–128.5°.

Anal. Calcd. for $C_{13}H_{17}O_5N$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.76; H, 6.51; N, 5.23.

(12) H. M. Priestly and E. Moness, *J. Org. Chem.*, **5**, 355 (1940).

Recrystallization of the high melting isomer from 125 ml. of water yielded 1.0 g. of crystals melting at 200–205°. Three recrystallizations of this substance from absolute ethyl alcohol yielded a product having a constant m.p. of 208–210°.

Anal. Calcd. for $C_{13}H_{17}O_5N$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.57; H, 6.46; N, 5.20.

Ethyl α-Acetamido-p-hydroxycinnamate (XVII).—To 50 ml. of absolute ethyl alcohol approximately half saturated with hydrogen chloride there was added 10 g. of N-acetyl-β-*p*-hydroxyphenylserine ethyl ester. After standing at room temperature for 24 hours, the solution was concentrated under vacuum to about 20 ml., 15 ml. of water was added, and the solution was further concentrated to about 10 ml. The aqueous solution was oily but crystallization was rapid at 0° and 5.3 g. (56.9%) of product melting at 158–161° was obtained. Recrystallization from water gave a sample melting at 159–161°.

Anal. Calcd. for $C_{13}H_{15}O_4N$: C, 62.65; H, 6.07; N, 5.62; C_2H_5O–, 18.08. Found: C, 62.94; H, 6.00; N, 5.64; C_2H_5O–, 17.77, 17.94.

N-Acetyl-DL-tyrosine Ethyl Ester (XVIII).—One-half gram of ethyl α-acetamido-*p*-hydroxycinnamate was dissolved in 10 ml. of ethyl alcohol and hydrogenated at atmospheric pressure and temperature using 0.1 g. of 5% palladium on charcoal catalyst. After four hours, 52 ml. of hydrogen was taken up (theory 49.2 ml.) and the reaction stopped. The ethyl alcohol was removed by vacuum concentration and the residue was crystallized from 10 ml. of water. The product (0.35 g.) melted at 128–130° (reported 133–134°).[7]

A sample of the product was hydrolyzed by heating it with 2 *N* hydrochloric acid for two hours. Chromatographic adsorption of the hydrolysate on paper in the organic phase of the mixture *n*-butyl alcohol (4), water (5), acetic acid (1) yielded a single zone with ninhydrin at R_F 0.30. Tyrosine, chromatographed simultaneously, showed an identical result.

Ethyl α-Acetamido-p-hydroxybenzoylacetate (XIX).—A warm solution of 28.4 g. (0.08 mole) of ethyl α-acetamido-*p*-benzyloxybenzoylacetate in 160 ml. of ethyl alcohol containing 1.40 g. of 5% palladium on charcoal catalyst, was hydrogenated at atmospheric pressure. It was necessary to keep the solution warm at first to prevent crystallization of the benzyl ether compound. When hydrogen consumption decreased suddenly from 9 ml./min. to 1 ml./min., the reduction was stopped, although only about 85% of the theoretical quantity of hydrogen had been taken up. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was stirred vigorously with 60 ml. of xylene and, after cooling at 0° for two hours, the product was collected by filtration. It weighed 22.0 g. (theory 21.2 g.) and melted at 119–123°.

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 59.92; H, 6.01; N, 4.84.

(This compound could not be purified by crystallization from common solvents. Judging from the quantity of hydrogen consumed, the yield, and the analyses, the impurity would appear to be about 10% of the starting material. It does not interfere with the next reaction.)

***erythro*-N-Acetyl-β-p-carbethoxyoxyphenylserine Ethyl Ester (XXI).**—To a stirred solution of 17.0 g. (0.064 mole) of ethyl α-acetamido-*p*-hydroxybenzoylacetate in 18 ml. of pyridine, 6.3 ml. (0.066 mole) of ethyl chlorocarbonate was added dropwise with cooling. The slurry of product and pyridine hydrochloride was added to a mixture of 150 ml. of chloroform and 100 ml. of water. The chloroform layer was washed with three 100-ml. portions of 1 *N* hydrochloric acid and then with water. After drying and removal of the chloroform by vacuum concentration, 18.5 g. (86%) of ethyl α-acetamido-*p*-carbethoxyoxybenzoylacetate (XX) remained as a light yellow oil. A solution of the oil in 185 ml. of ethyl alcohol was hydrogenated at atmospheric pressure using 1.85 g. of 5% palladium on charcoal catalyst (it was necessary to add a fresh portion of catalyst during the course of the reduction). A total of 1,400 ml. of hydrogen was taken up in 11 hours. The catalyst was removed and the solution was concentrated to an oily residue which was crystallized by adding 45 ml. of absolute ether. When crystallization was fairly complete, 45 ml. of hexane was slowly added with agitation and the mixture was allowed to stand at 0° for 18 hours before the product was collected. The product weighed 16.4 g. and melted at 81–83°. Recrystallization from a mixture of carbon tetrachloride (85%) and ethyl acetate (15%) yielded a sample melting at 92–94°.

Anal. Calcd. for $C_{16}H_{21}O_7N \cdot {}^1/_2H_2O$: C, 55.16; H, 6.08; N, 4.02. Found: C, 55.07, 54.96; H, 6.01, 6.04; N, 4.05, 4.06.

***erythro*-β-p-Carbethoxyoxyphenylserine Ethyl Ester Hydrochloride (XXII).**—A solution of 4.0 g. of *erythro*-N-acetyl-β-*p*-carbethoxyoxyphenylserine ethyl ester in 16 ml. of absolute ethyl alcohol approximately half saturated with hydrogen chloride was allowed to stand overnight at room temperature. The product crystallized and after filtration it was washed with alcohol. It weighed 1.27 g. (32.2%) and decomposed at 187–188° with gas evolution. (The compound obtained by Rosenmund and Dornsaft[2] melted at 181° dec.)

Anal. Calcd. for $C_{14}H_{20}O_6NCl$: C, 50.38; H, 6.04; N, 4.19. Found: C, 50.28; H, 6.31; N, 4.20.

***erythro*-β-p-Hydroxyphenylserine (XXIII).**—A solution of 1.0 g. of *erythro*-β-*p*-carbethoxyoxyphenylserine ethyl ester hydrochloride in 13 ml. of 1.0 *N* (4 equivalents) sodium hydroxide was allowed to stand at room temperature for one hour. The solution was neutralized with 9.7 ml. of 1.0 *N* hydrochloric acid and 0.48 g. (59.0%) of white, chloride-free crystals were obtained. After one recrystallization from 50 ml. of water, the product (dried at 80° *in vacuo*) melted with decomposition and gas evolution at 215–220°. (β-*p*-Hydroxyphenylserine prepared by Rosenmund and Dornsaft[2] melted at 217°.)

Anal. Calcd. for $C_9H_{11}O_4N$: C, 54.82; H, 5.62; N, 7.11. Found: C, 54.61, 54.76; H, 5.71, 5.76; N, 7.06, 7.08.

***p*-Carbethoxyoxyacetophenone (XXIV).**—A suspension of 50 g. (0.368 mole) of *p*-hydroxyacetophenone in 400 ml. of water was cooled to 0°. One-quarter of a solution of 14.7 g. (0.368 mole) of sodium hydroxide in 70 ml. of water was added and then one-quarter (9 ml.) of the ethyl chlorocarbonate (total 36 ml., 0.38 mole) was slowly added with stirring. This process was repeated until all the reactants had been added. The final reaction mixture was neutral and filtration yielded 60.0 g. of a brown solid. A recrystallization from 50 ml. of absolute ether gave 51.0 g. (66.7%) of a light yellow product, m.p. 39–40°. Repeated recrystallization from ether yielded a pure white sample melting at 44–45°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.46; H, 5.81. Found: C, 63.14; H, 5.85.

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