The Decarboxylative Acylation of Succinic Acid Derivatives. Part I. Benzamidosuccinic Acid.

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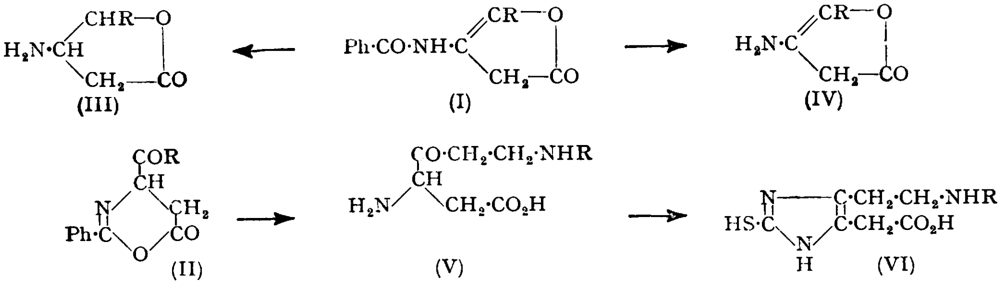
Benzoylaspartic anhydride has been submitted to decarboxylative acylation (Lawson, *J.*, 1953, 1046) by several acid anhydrides, lactones of type (I) or (II) or mixtures thereof being obtained. With aromatic acid anhydrides and nicotinic anhydride type (I) predominated, and with benzoic and *p*-acetoxybenzoic anhydrides these have been used to produce amines chemically related to sympathomimetic drugs. With β-benzamidopropionic anhydride the product was of type (II) and it was converted into the corresponding 2-mercaptohistamine derivative by hydrolysis and treatment with thiocyanate.

The reaction between benzoylaspartic anhydride and simple aliphatic acid anhydrides which gave rise to benzamido-lactones (I; R = alkyl) and ketones (II; R = alkyl) (Lawson, *J.*, 1953, 1046) has been extended to other acid anhydrides with a view to the preparation of amines of pharmacological interest. The reactions were carried out with excess of the anhydride in boiling xylene or toluene until the carbon dioxide evolution ceased. The speed of reaction varied considerably from case to case.

With benzoic anhydride, the main product was the lactone (I; R = Ph), although some ketone (II; R = Ph) was also formed, as proved by the isolation of the corresponding mercaptoglyoxaline after hydrolysis of the gum left after evaporation of the mother-liquor from (I) and treatment with thiocyanate. As with the corresponding aliphatic derivatives, hydrolysis of the lactone (I) removed the amido-group as benzoic acid and ammonium chloride, with formation of a ketone. It was, however, possible to hydrogenate the lactone by using a relatively large quantity of Raney nickel, and hydrolysis of the saturated lactone gave the amine (III; R = Ph). This substance, having a structure related to that of norephedrine, is being tested pharmacologically.



In the reaction between acetylsalicylic anhydride and benzoylaspartic anhydride carbon dioxide was evolved much more slowly. The products (I; R = Me) and (II; R = Me) corresponded to those obtained by the direct action of acetic anhydride on benzoylaspartic anhydride (Lawson, *loc. cit.*), which is not surprising when one considers the ease with which acetylsalicylic acid liberates acetic anhydride on heating.

With *p*-anisic anhydride the reaction was again relatively slow, and the small yield of the lactone (I; R = p-C_6H_4·OMe) precluded further work with it.

p-Acetoxybenzoic anhydride also reacted slowly with benzoylaspartic anhydride but, with a longer reaction time, yields of over 50% of the lactone (I; R = p-C_6H_4·OAc) were obtained. Dissolution of the product in dilute aqueous sodium hydroxide liberated the free phenol. Hydrogenation of the double bond in this substance could not be effected under the conditions used with the benzoic anhydride product; this difficulty was not surprising in view of the quaternary nature of the carbon atoms at the double bond, but the difference between the phenyl and the *p*-hydroxyphenyl derivatives is not readily understandable. At 40 atmospheres in the presence of platinum black, however, the free phenol was hydrogenated and analysis of a phenolic compound isolated in small yield indicated an uptake of six hydrogen atoms. This substance liberated its nitrogen as ammonia, and gave *cyclo*hexanecarboxylic acid on hydrolysis. It was, therefore, 3-hexahydrobenzamido-4-hydroxy-4-*p*-hydroxyphenylbut-3-enoic lactone.

Like benzamide the unsaturated lactone (I; R $= p$-C_6H_4·OAc) reacted with sodium amalgam to produce benzaldehyde, and as a result it was possible to remove the benzoyl group leaving the unsaturated amino-lactone (IV; R $= p$-C_6H_4·OH). This substance, being an αβ-unsaturated amine, was only feebly basic; it was an analogue of β-amino-α-angelicalactone (Dakin and West, *J. Biol. Chem.*, 1928, **78**, 750). On acetylation it gave an acetyl derivative, judged to contain *N*-acetyl since it showed phenolic properties.

In the reaction between *m*-acetoxybenzoic anhydride and benzoylaspartic anhydride the main product was the unsaturated lactone (I; R $= m$-C_6H_4·OAc), though in this case a small quantity of the ketone (II; R $= m$-C_6H_4·OAc) was also isolated and converted in the usual manner into the mercaptoglyoxaline. Mild hydrolytic treatment and hydrogenation of the unsaturated lactone produced substances analogous to those obtained in the *p*-series.

Phenylacetic anhydride reacted readily under the usual conditions with benzoylaspartic anhydride to give the unsaturated lactone (I; R $=$ CH_2Ph). The phenylhydrazone of a ketone $C_{18}H_{15}O_3N$ was obtained from the reaction mixture indicating the simultaneous formation of the ketone (II; R $=$ CH_2Ph).

From the reaction between nicotinic anhydride and benzoylaspartic anhydride a basic substance $C_{16}H_{12}O_3N_2$ and an amphoteric compound $C_{16}H_{14}O_4N_2$ were isolated. Apart from salt formation both substances were unaffected by boiling dilute hydrochloric acid or warm acetic anhydride, showing that a relation of substance to its anhydride probably did not apply. With concentrated hydrochloric acid both substances gave ammonium chloride, benzoic acid, and an unidentified ketone. The base $C_{16}H_{12}O_3N_2$, being analogous in formula to other products of the decarboxylative acylation of aspartic anhydride and giving similar reactions, is assigned the structure (I; R $=$ C_5H_4N). No compound analogous to $C_{16}H_{14}O_4N_2$ was isolated from the other acylations described. This substance gave a phenylhydrazone and an oxime, and was the only ketonic condensation product encountered in this work which did not give an amino-ketone on hydrolysis. Neither of the substances could be hydrogenated at one atmosphere.

β-Benzamidopropionic anhydride and benzoylaspartic anhydride in toluene gave the ketone (II; R $=$ CH_2·CH_2Bz), which was hydrolysed first to either the monobenzoyldiamino-ketone (V; R $=$ Bz) and then to the diamino-ketone (V; R $=$ H). From these two the 2-mercaptohistamines (VI; R $=$ Bz and H, respectively) were prepared by condensation with thiocyanate.

β-Phthalimidopropionic anhydride and benzoylaspartic anhydride also gave the ketone (II; R $=$ CH_2·CH_2·$C_8H_4O_2N$), which readily lost the benzoyl group on hydrolysis to give on subsequent treatment with thiocyanate 2-mercapto-4-phthalimidoethyl-5-glyoxalinylacetic acid. Removal of the phthalimido-group was not effected by prolonged boiling with hydrochloric acid.

EXPERIMENTAL

Acetoxybenzoic anhydrides and *p*-anisic anhydride were prepared in good yield by using thionyl chloride in benzene in the presence of pyridine (D.R.-P. 201,325/1907). m-*Acetoxybenzoic anhydride*, needles (from ethyl acetate), had m. p. 103° (Found: C, 63·0; H, 4·2. $C_{18}H_{14}O_7$ requires C, 63·2; H, 4·1%).

Action of Benzoic Anhydride on Benzoylaspartic Anhydride.—Benzoylaspartic anhydride (2 g.) was heated with benzoic anhydride (6 g.) in boiling xylene (30 ml.) till carbon dioxide evolution ceased (about 1 hr.). Next morning the crystalline product (2 g.) was collected. Recrystallisation from ethyl acetate gave colourless prisms of 3-*benzamido*-4-*phenylbut*-3-*enoic lactone*, m. p. 152° (Found: C, 72·5; H, 4·6; N, 5·15. $C_{17}H_{13}O_3N$ requires C, 73·2; H, 4·7; N, 5·05%). Evaporation of the xylene filtrate under reduced pressure, followed by hydrolysis with concentrated hydrochloric acid at 155° and removal of the benzoic acid by filtration and hydrochloric acid by distillation, left a small residue which on treatment with potassium thiocyanate gave 2-*mercapto*-4-*phenyl*-5-*glyoxalinylacetic acid* which, recrystallised from aqueous ethanol, had m. p. 244° (decomp.) (Found : C, 56·2; H, 4·5. $C_{11}H_{10}O_2N_2S$ requires C, 56·4; H, 4·3%).

The phenylbutenoic lactone (1 g.) was hydrogenated in ethyl acetate solution (100 ml.) with Raney nickel (5 g.). The theoretical volume of hydrogen was taken up in 2 hr. Removal of the solvent left 3-*benzamido*-4-*hydroxy*-4-*phenylbutanoic lactone*, colourless felted needles, m. p. 182°, in theoretical yield (Found : C, 72·0; H, 5·35. $C_{17}H_{18}O_3N$ requires C, 72·6; H, 5·3%). The lactone (1 g.) was hydrolysed with boiling 20% aqueous hydrochloric acid for 1 hr. and the benzoic acid removed by filtering the cooled solution. Evaporation of the filtrate left 3-*amino*-4-*hydroxy*-4-*phenylbutanoic lactone hydrochloride* (0·4 g.), needles, m. p. 234° (decomp.) (from 90% aqueous ethanol) (Found : C, 55·5; H, 5·7; N, 6·4. $C_{10}H_{12}O_2NCl$ requires C, 56·2; H, 5·6; N, 6·6%). The free base precipitated from an aqueous solution of the hydrochloride by sodium hydrogen carbonate was a wax which decomposed when kept.

Reaction with Acetylsalicylic Anhydride.—Benzoylaspartic anhydride (1 g.) and acetylsalicylic anhydride (2·5 g.) were heated in boiling xylene (20 ml.). After 5 hr. the xylene was evaporated under reduced pressure and the residue dissolved in hot benzene which was extracted with aqueous sodium hydrogen carbonate. The benzene solution after concentration gave 3-benzamido-4-hydroxypent-3-enoic lactone, m. p. 174°. The mother-liquor, on treatment with dinitrophenylhydrazine in ethanol, gave ethyl β-benzamido-γ-oxovalerate 2 : 4-dinitrophenylhydrazone, and on hydrolysis of the residue left after evaporation of the benzene, followed by treatment with potassium thiocyanate, a small amount of 2-mercapto-4-methyl-5-glyoxalinylacetic acid was obtained.

Reaction with p-*Anisic Anhydride.*—*p*-Anisic anhydride (2 g.) was heated in boiling xylene (20 ml.) with benzoylaspartic anhydride (1 g.) for several hours. After cooling and addition of benzene the solution was extracted with aqueous sodium hydrogen carbonate and then with N-sodium hydroxide. The second extract was treated with solid carbon dioxide till there was no further precipitation. The 3-*benzamido*-4-*hydroxy*-4-p-*methoxyphenylbut*-3-*enoic lactone* so obtained and recrystallised from ethanol (prisms) had m. p. 132° (Found : C, 70·0; H, 4·9; N, 4·8. $C_{18}H_{15}O_4N$ requires C, 70·0; H, 4·9; N, 4·5%).

Reaction with p-*Acetoxybenzoic Anhydride.*—Benzoylaspartic anhydride (1 g.) was mixed with *p*-acetoxybenzoic anhydride (2·6 g.) and the suspension in dry xylene (20 ml.) was boiled until evolution of carbon dioxide ceased (about 6 hr.). The solution was then kept overnight at 0°, and the product (1·2 g.) was collected. After trituration with anhydrous ether, 4-p-*acetoxyphenyl*-3-*benzamido*-4-*hydroxybut*-3-*enoic lactone* recrystallised from aqueous ethanol in colourless rosettes, m. p. 167° (Found : C, 67·4; H, 4·5; N, 4·1. $C_{19}H_{15}O_5N$ requires C, 67·6; H, 4·5; N, 4·2%). From this substance the phenol was obtained by hydrolysis, by boiling dilute hydrochloric acid for a short time or by dissolution in a small quantity of 3N-sodium hydroxide and precipitation with acid. When sodium hydroxide was used the yield of 3-*benzamido*-4-p-*hydroxyphenyl*-4-*hydroxybut*-3-*enoic lactone* was quantitative. It recrystallised from aqueous ethanol in needles, m. p. 212° (Found : C, 69·3; H, 4·4; N, 4·4. $C_{17}H_{13}O_4N$ requires C, 69·1; H, 4·4; N, 4·7%).

Attempts made to hydrogenate the acetyl derivative or the phenol under the conditions recorded above were unsuccessful but use of platinum oxide at room temperature and 40 atm. gave in 5 hr. a small yield of 3-*hexahydrobenzamido*-4-*hydroxy*-4-p-*hydroxyphenylbut*-3-*enoic lactone* (prisms from aqueous ethanol), m. p. 230° (Found : C, 67·9; H, 6·6; N, 4·6. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·3; N, 4·65%). This substance on hydrolysis with concentrated hydrochloric acid gave *cyclo*hexanecarboxylic acid, ammonium chloride, and an unidentified ketone. To remove the benzoyl group, 3-benzamido-4-hydroxy-4-*p*-hydroxyphenylbut-3-enoic lactone (1 g.), dissolved in 3N-sodium hydroxide (5 ml.), was cooled in ice-water, and 2·5% sodium amalgam (50 g.) was added with stirring during 1 hr. Benzaldehyde was identified in the solution as its dinitrophenylhydrazone. After acidification, the precipitated solid was removed and recrystallised from ethanol. 3-*Amino*-4-*hydroxy*-4-p-*hydroxyphenylbut*-3-*enoic lactone* (prisms) (0·3 g.) had m. p. 229° (decomp.) (Found : C, 62·4; H, 4·9; N, 7·6. $C_{10}H_9O_3N$ requires C, 63·0; H, 4·7; N, 7·4%). Its colour with ferric chloride was yellow, and it gave a positive Millon's test and was precipitated by mercuric sulphate and mercuric chloride solutions.

3-*Acetamido*-4-p-*hydroxyphenylbut*-3-*enoic lactone*, prepared by dissolving the amine in a few ml. of acetic anhydride containing a drop of concentrated sulphuric acid, crystallised from aqueous ethanol in prisms, m. p. 250° (decomp.) (Found : C, 61·5; H, 4·8; N, 5·9. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·7; N, 6·0%).

Reaction with m-*Acetoxybenzoic Anhydride.*—*m*-Acetoxybenzoic anhydride (1 g.) and benzoylaspartic anhydride (2·5 g.) were heated in boiling xylene (20 ml.) until CO_2 evolution had ceased (5 hr.). The gum precipitated on cooling was washed with ether and extracted with sodium hydrogen carbonate solution. The residue of impure 4-m-*acetoxyphenyl*-3-*benzamido*-4-*hydroxybut*-3-*enoic lactone* (0·9 g.) crystallised from aqueous ethanol in prisms, m. p. 135° (Found : C, 67·5; H, 4·6; N, 4·2. $C_{19}H_{16}O_5N$ requires C, 67·6; H, 4·5; N, 4·2%). The crude substance, when treated with 3N-sodium hydroxide, only partly dissolved, the small amount of insoluble residue consisting of 4-m-*acetoxybenzoyl*-4 : 5-*dihydro*-6-*oxo*-2-*phenyl*-1 : 3-*oxazine*, needles, m. p. 176° (Found : C, 67·5; H, 4·7; N, 4·2. $C_{19}H_{15}O_5N$ requires C, 67·6; H, 4·5; N, 4·2%). This substance after hydrolysis and treatment with thiocyanate gave 2-*mercapto*-4-m-*hydroxyphenyl*-5-*glyoxalinylacetic acid*, prisms (from aqueous ethanol), m. p. 300° (decomp.) (Found : C, 53·1; H, 4·0. $C_{11}H_{10}O_3N_2S$ requires C, 52·8; H, 4·0%).

Removal of the acetyl group from the unsaturated lactone was achieved as for the *p*-compound, 3-*benzamido*-4-*hydroxy*-4-m-*hydroxyphenylbut*-3-*enoic lactone* crystallising from aqueous ethanol in prisms, m. p. 201° (Found : C, 68·6; H, 4·3; N, 4·3. $C_{17}H_{13}O_4N$ requires C, 69·1; H, 4·4; N, 4·7%). This was most readily obtained directly from the xylene solution of the original reaction mixture, after extraction with sodium carbonate, by further extraction with 3N-sodium hydroxide.

Hydrogenation of the unsaturated phenol at 40 atm. with platinum black gave a small yield of 3-*hexahydrobenzamido*-4-*hydroxy*-4-m-*hydroxyphenylbut*-3-*enoic lactone*, m. p. 196° (from aqueous ethanol) (Found : C, 68·0; H, 6·1; N, 4·65. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·3; N, 4·65%).

3-*Benzamido*-4-*hydroxy*-4-*phenylpent*-3-*enoic Lactone.*—Phenylacetic anhydride (5 g.) and benzoylaspartic anhydride (2 g.) were heated in boiling xylene (20 ml.) for 2 hr. After cooling, the *lactone* (1·6 g.) was removed. Recrystallisation from ethyl acetate gave prisms, m. p. 184° (Found : C, 73·7; H, 5·1; N, 4·4. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·1; N, 4·8%).

Reaction with Nicotinic Anhydride.—Nicotinic anhydride (5 g.) (Badgett, *J. Amer. Chem. Soc.*, 1947, **69**, 2231) was heated in boiling xylene (30 ml.) with benzoylaspartic anhydride (2 g.). After 2 hr. the xylene was cooled in ice, and the crystalline precipitate filtered off, washed with ether, and treated with aqueous sodium hydrogen carbonate to remove nicotinic acid. There remained 3-*benzamido*-4-*hydroxy*-4-3′-*pyridylbut*-3-*enoic lactone* (0·8 g.) which on recrystallisation from ethanol, in which it was sparingly soluble, gave prisms, m. p. 234° (block; decomp.) (Found : C, 68·2; H, 4·5; N, 9·8. $C_{16}H_{12}O_3N_2$ requires C, 68·6; H, 4·3; N, 10·0%). The xylene filtrate (above) was extracted with 3N-hydrochloric acid, and the aqueous solution brought to pH 4 by solid sodium hydrogen carbonate. The precipitated *substance* (1·8 g.) recrystallised from aqueous ethanol in needles, m. p. 227° (block) (Found : C, 64·0; H, 4·6; N, 9·9. $C_{16}H_{14}O_4N_2$ requires C, 64·4; H, 4·7; N, 9·4%). The *phenylhydrazone* crystallised from alcohol in needles, m. p. 175° (decomp.) (Found : C, 67·9; H, 5·4; N, 14·8. $C_{22}H_{20}O_3N_4$ requires C, 68·0; H, 5·2; N, 14·4%). The *oxime*, prisms from ethanol, had m. p. 185° (Found : C, 58·6; H, 4·8. $C_{16}H_{15}O_5N_3$ requires C, 58·4; H, 4·6%). Both lactone and acid were unchanged by boiling 3N-hydrochloric acid, but hydrolysis with 20% hydrochloric acid gave benzoic acid, ammonium chloride, and an unidentified ketone.

Reaction with β-*Benzamidopropionic Anhydride.*—β-Benzamidopropionic anhydride (Barker, *J.*, 1954, 317) was crystallised from acetic anhydride–benzene. Benzoylaspartic anhydride (1 g.) was heated with the anhydride (3 g.) in boiling toluene (20 ml.) for 2 hr. and kept overnight. The sticky crystals were washed with dry ether. Extraction with aqueous sodium hydrogen carbonate removed benzoyl-β-alanine, and the 4-β-*benzamidopropionyl*-1 : 3-4 : 5-*dihydro*-6-*oxo*-2-*phenyloxazine* recrystallised from ethyl acetate as needles, m. p. 167° (1·8 g.) (Found : C, 68·0; H, 5·1; N, 8·3. $C_{20}H_{18}O_4N_2$ requires C, 68·5; H, 5·1; N, 8·0%).

This product (4 g.) was boiled with concentrated hydrochloric acid for 2 hr., then cooled, and the benzoic acid removed by filtration. On concentration of the filtrate under reduced pressure, a small amount of 3 : 6-*dibenzamido*-4-*oxohexanoic acid* separated. It crystallised from ethyl acetate in needles, m. p. 148° (Found : C, 65·3; H, 5·7; N, 7·4. $C_{20}H_{20}O_5N_2$ requires C, 65·2; H, 5·5; N, 7·6%). The mother-liquor on being evaporated *in vacuo* left a gum, which was dissolved in water and treated with potassium thiocyanate on the boiling-water bath. After an hour, crystals of 4-2′-*benzamidoethyl*-2-*mercapto*-5-*glyoxalinylacetic acid* (needles) (2·3 g.) separated. These, on recrystallisation from water, had m. p. 205° (decomp.) (Found : C, 52·5; H, 5·2; N, 12·5. $C_{14}H_{15}O_3N_3S,H_2O$ requires C, 52·0; H, 5·3; N, 13·0%). This substance on further boiling with concentrated hydrochloric acid for 2 hr. give 4-2′-*aminoethyl*-2-*mercapto*-5-*glyoxalinylacetic acid hydrochloride*, m. p. 258° (block) (Found : C, 35·8; H, 5·4.

$C_7H_{11}O_2N_3S,HCl$ requires C, 35·4; H, 5·1%). Evaporation of the mother-liquors from the benzamide gave a further quantity of the amine hydrochloride. The free *base* was obtained by adding sodium hydrogen carbonate to the hydrochloride to pH 7, and from water, in which it was rather sparingly soluble, gave prisms, m. p. 300° (decomp.; block) (Found: C, 41·9; H, 5·3; N, 20·2. $C_7H_{11}O_2N_3S$ requires C, 41·8; H, 5·5; N, 20·8%).

Reaction with β-*Phthalimidopropionic Anhydride.*—β-*Phthalimidopropionic anhydride*, prepared by the action of acetic anhydride on the acid, crystallised from benzene–ethyl acetate as prisms, m. p. 168° (Found: C, 62·3; H, 3·2; N, 6·8. $C_{22}H_{16}O_7N_2$ requires C, 62·9; H, 3·8; N, 6·7%). 4 : 5-*Dihydro*-6-*oxo*-2-*phenyl*-4-β-*phthalimidopropionyl*-1 : 3-*oxazine* was obtained in prisms (from ethyl acetate), m. p. 91°, as in the previous case (Found: C, 63·0; H, 4·7; N, 7·2. $C_{21}H_{16}O_6N_2,H_2O$ requires C, 64·0; H, 4·6; N, 7·1%). Hydrolysis with boiling hydrochloric acid for several hours removed benzoic acid, and further evaporation of the filtrate gave a small amount of felted needles consisting of 3-*benzamido*-4-*oxo*-6-*phthalimidohexanoic acid*, m. p. 216° (from ethyl acetate) (Found: C, 64·0; H, 4·4; N, 7·1. $C_{21}H_{18}O_6N_2$ requires C, 64·0; H, 4·5; N, 7·1%). The mother-liquor from this substance, on treatment as before with thiocyanate, gave 2-*mercapto*-4-2′-*phthalimidoethyl*-5-*glyoxalinylacetic acid*, m. p. 233° (decomp.) (from aqueous alcohol) (Found: C, 54·1; H, 4·2. $C_{15}H_{13}O_4N_3S$ requires C, 54·3; H, 3·9%), which resisted further hydrolysis.

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