212. *2-Mercaptoglyoxalines. Part VII.* The Preparation of Di-C-substituted 2-Mercaptoglyoxalines from Aspartic Acid.*

By Alexander Lawson.

By the action of acid anhydrides on benzoylaspartic anhydride (I; R = Ph) two series of products are obtained by acylation and loss of carbon dioxide. One corresponds to the product obtained by Dakin and West (*J. Biol. Chem.*, 1928, **78**, 745); the other comprises azlactones of β-acylamino-γ-keto-acids (III), and these undergo hydrolysis to α-amino-ketones which may be converted into 4-alkyl-2-mercapto-5-glyoxalinylacetic acids (VII). The last named on decarboxylation give the corresponding 4 : 5-dialkyl-2-mercaptoglyoxalines.

In Part VI * the preparation of 4 : 5-dialkyl-2-mercaptoglyoxalines from the simple amino-acids by the Dakin and West reaction (*J. Biol. Chem.*, 1928, **78**, 91) was described. In applying their reaction to dicarboxylic amino-acids, Dakin and West (*ibid.*, p. 745) again observed the production of ketonic products with evolution of carbon dioxide; in the case of aspartic acid, the non-crystalline product isolated was thought to consist largely of the acetyl derivative of β-amino-γ-ketovaleric acid (XIV) on the basis of the isolation of the hydrolytic products diacetyl and ammonium chloride, the former having been considered as arising from the breakdown of the intermediate β-hydroxylævulic acid.

The work now described arose out of the observation that acid anhydrides acylate benzoylaspartic acid and its anhydride with loss of carbon dioxide in the absence, as well as in the presence, of a basic catalyst such as pyridine. From the resulting benzamido-ketones disubstituted 2-mercaptoglyoxalines are readily obtained.

The structure of acylaspartic anhydrides has been discussed by Harington and Overhoff (*Biochem. J.*, 1933, **27**, 338) who on the basis of the isolation of the acid chloride of 2-methyl-oxazol-5-one-4-acetic acid from the reaction between acetylaspartic anhydride and phosphorus pentachloride favoured an oxazolone structure. Barker (*Nature*, 1951, **168**, 908), on the other hand, proved the true anhydride structure by isolation of two anilides from both acetyl- and benzoyl-aspartic anhydride (cf. also Swan, *Nature*, 1952, **169**, 826) and by absence of reaction with diazomethane and of racemisation in aqueous sodium

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acetate. He pointed out, however, that the partial racemisation in du Vigneaud and Meyer's procedure (*J. Biol. Chem.*, 1932, **98**, 295) and complete racemisation of acetylaspartic anhydride by sodium acetate and acetic anhydride may be due to the presence of the oxazolone, possibly in equilibrium with the anhydride. Further, benzoylaspartic anhydride and ammonia give benzoyl*iso*asparagine (Pauly and Weir, *Ber.*, 1910, **43**, 665) whereas acetylglutamic anhydride for which the true anhydride structure is accepted (cf. King and MacMillan, *J. Amer. Chem. Soc.*, 1952, **74**, 2859) gives acetylglutamine.

Benzoylaspartic anhydride is obtained in quantitative yield by dissolving the acid as rapidly as possible in acetic anhydride on the steam-bath and allowing the solution to cool. When the anhydride is heated in boiling acetic anhydride it rapidly dissolves and 1 mol. of carbon dioxide is evolved. The neutral crystalline product, $C_{12}H_{11}O_3N$, m. p. 94°, is unchanged by further heating with acetic anhydride in 2-picoline, which indicates the absence of an amide-hydrogen atom. It gives an immediate precipitate of a hydrazone containing an additional 2 carbon and 6 hydrogen atoms when treated with ethanolic dinitrophenylhydrazine containing a little concentrated sulphuric acid : alcoholysis of a lactone ring seems to be involved here. No ammonia is evolved when the C_{12} product is warmed with dilute sodium hydroxide solution but a ketone corresponding to the uptake of a molecule of water can then be isolated as the phenylhydrazone : this addition of water is doubtless again due to the opening of a lactone ring. Hydrolysis with 4N-hydrochloric gives benzoic acid, and the other product is an amino-ketone, since thiocyanate converts it into 2-mercapto-4-methyl-5-glyoxalinylacetic acid (VII; R′ = Me). The constitution of this substance is proved by decarboxylation to 4 : 5-dimethyl-2-mercaptoglyoxaline (VIII; R′ = Me) which on benzylation gives 2-benzylthio-4 : 5-dimethylglyoxaline hydrochloride, also prepared by an independent method (Part VI, *loc. cit.*). (4 : 5-Disubstituted mercaptoglyoxalines frequently melt above 300° so that benzylthio-derivatives serve conveniently for characterisation.)

The compound $C_{12}H_{11}O_3N$ is therefore the azlactone (III; R = Ph, R′ = Me) of β-benzamido-γ-ketovaleric acid. Compounds containing this ring have been prepared by Marrer and Miyamichi (*Helv. Chim. Acta*, 1926, **9**, 336) and by Baker and Ollis (*J.*, 1949, 345) by dehydration of acylamino-acids. The possibility that the substance $C_{12}H_{11}O_3N$, though apparently neutral, was an oxazole (XII; R = Ph, R′ = Me) was considered in view of Wiley's preparation (*J. Org. Chem.*, 1947, **12**, 43) of such compounds by vigorous dehydration of acylamino-ketones prepared from amino-acids. The oxazoles, however, resist hydrolysis by acids, the only recorded hydrolysis being that of 2 : 5-diphenyloxazole from which Gabriel (*Ber.*, 1910, **43**, 136) obtained aminoacetophenone using hydrochloric acid under pressure : 2-phenyloxazole-4-carboxylic acid, for example, can be recovered unchanged after several hours' boiling with concentrated hydrochloric acid.

A third possible structure for the compound $C_{12}H_{11}O_3N$ is (IV; R = Ph, R′ = Me) corresponding to the *N*-acetyl derivative of the β-aminoangelicalactone (Dakin and West, *loc. cit.*). Actually, this structure is realised in a product, m. p. 174°, obtained in variable yield by use of acetic anhydride in boiling acetic acid. This substance shows no ketonic reactions unless first hydrolysed with loss of nitrogen. Like Dakin and West's product it liberates ammonia in warm dilute sodium hydroxide solution. It dissolves in boiling dilute hydrochloric acid with formation of benzamide, carbon dioxide, and diacetyl.

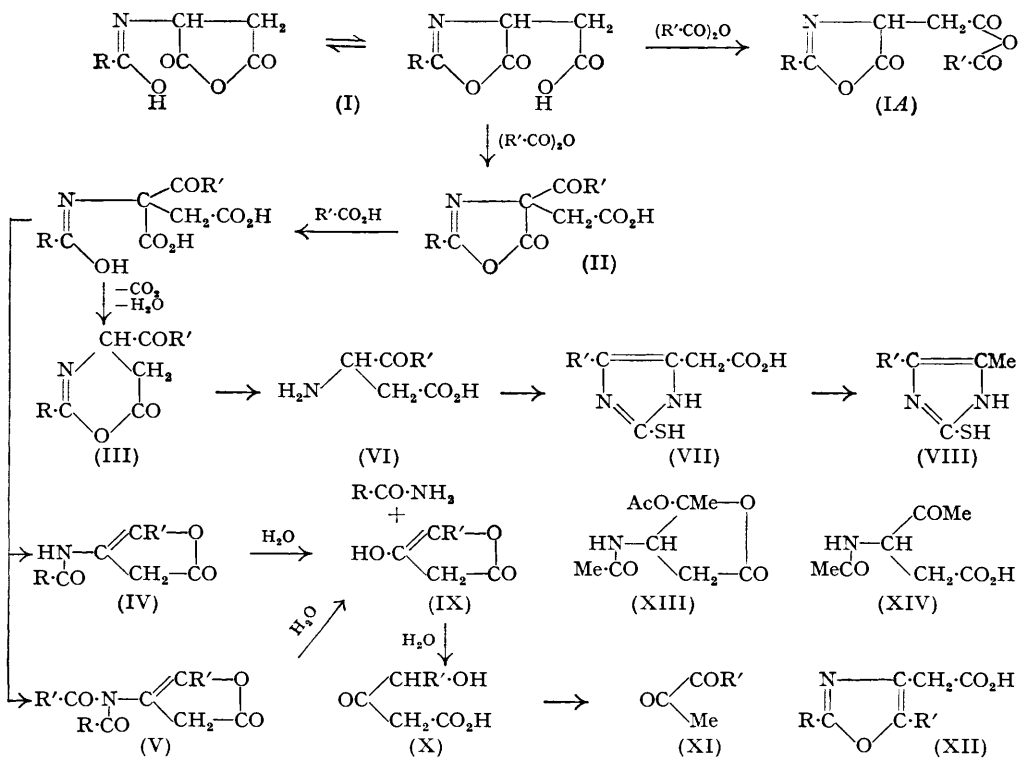
With acetic anhydride and 2-picoline at 100° benzoylaspartic anhydride rapidly gives carbon dioxide and, in almost theoretical yield, a substance $C_{14}H_{13}O_4N$. This material gives reactions similar to those of the C_{12} compound, m. p. 174°, and, in addition, acetic acid is liberated in the hydrolyses with sodium hydroxide and hydrochloric acid. It is possible to obtain after mild acid hydrolysis the phenylhydrazone of a ketone $C_5H_6O_3$ which would correspond to β-keto-γ-valerolactone (IX; R′ = Me).

Dakin and West (*loc. cit.*) suggested that the original product of the action of acetic anhydride on aspartic acid in pyridine was (XIII). On the basis of the analytical results the structure (V; R = Ph, R′ = Me) is assigned to the C_{14} product from benzoylaspartic anhydride. Such a diacylamino-structure is supported by Wiley and Borum's isolation (*J. Amer. Chem. Soc.*, 1950, **72**, 1626) of diacetylglycine ethyl ester from glycine ethyl ester and acetic anhydride in pyridine. It seems probable therefore that in the Dakin and West

reaction the first product is likewise an *N*-diacetyl derivative (V; R = R′ = Me) and that during the working up of the product one acetyl group is lost giving β-acetamidoangelicalactone (IV; R = R′ = Me) and not β-acetamido-γ-ketovaleric acid (XIV). In view of the isolation of the mercaptoglyoxaline, it appears that β-acylamino-γ-ketovaleric acids do not lose their nitrogen on hydrolysis with acid (cf. Dakin and West, *loc. cit.*). The above results, further interpreted, indicate that acids first hydrolyse the C–N linkage of the β-aminoangelicalactone structure and not the lactone ring, otherwise an amino-ketone would result.

In view of the previous work on benzoylaspartic anhydride already referred to there seem reasonable grounds for considering that in the reactions with acetic anhydride in the presence of picoline an oxazolone, generally believed to be an intermediate in the Dakin and West reaction, is the reacting form of the anhydride. In the present case the oxazolone (I) would give the acyloxazolone (II) in accordance with the views of Cleland and Niemann (*J. Amer. Chem. Soc.*, 1949, **71**, 841) and Cornforth and Elliot (*Science*, 1950, **112**, 534). It might on the other hand be argued that the similarity in structure of the benzoylaspartic oxazolone and anhydride might even allow the reaction to proceed with the latter substance.

In the reaction without picoline, however, the behaviour of benzoylaspartic acid is not so readily explained. Such a reaction, as might be expected, is also given by ethyl hydrogen acetamidomalonate, for which a successful Dakin and West reaction has already been reported (Albertson, Tullar, King, Fishburn, and Archer, *J. Amer. Chem. Soc.*, 1948, **70**, 1150), but not by benzoylglutamic anhydride or phthalimidosuccinic anhydride for which an oxazolone structure is excluded. It may be that benzoylaspartic anhydride by virtue of its close relation to the oxazolone and its having an additional carboxyl group when compared with



other oxazolones is better able to accommodate the anionic charge which is developed before acylation and therefore requires no basic catalyst. Or perhaps a mixed anhydride of the type (IA) is produced: this, after a rearrangement, could also give rise to (II). The fact that there is no reaction between acetylaspartic anhydride and acetic anhydride in the

absence of picoline may be explained by the difference in the mobility of the amide-hydrogen atom, a view which is supported by the differing degree of racemisation of benzoyl-aspartic and acetylaspartic anhydrides in du Vigneaud and Meyer's procedure (Barker, *loc. cit.*).

This common intermediate (II) from the catalysed and the uncatalysed reaction may then, after ring opening, loss of carbon dioxide, and dehydration, give either β-benzamido-γ-ketovaleric acid azlactone (III; R = Ph, R′ = Me) from which the mercaptoglyoxaline (VII; R′ = Me) is obtained, or benzamidoangelicalactone (IV; R = Ph, R′ = Me) as shown in the proposed reaction sequence above.

In the action of the higher homologues of acetic anhydride on benzoylaspartic azlactone, the presence or absence of picoline has no such clear-cut effect as in the case of acetic anhydride: products corresponding to both (III) and (IV) are formed simultaneously. Without picoline, but in boiling xylene which is a convenient solvent, propionic and butyric anhydride give crystalline products (IV; R = Ph, R′ = Et and Pr^n, respectively), from which acylamino-ketones are not obtainable. Since (IV) is more rapidly hydrolysed than (III), mother-liquors yield on hydrolysis for a short time the crystalline γ-keto-acids. In the case of the butyric anhydride derivative, the action of acetic anhydride produces isolatable amounts of the 3-benzamido-4-hydroxyhept-3-enoic lactone (IV; R = Ph, R′ = Pr^n), thus showing the close relation between the two reactions of the acyloxazolone (II). The γ-keto-acids on further hydrolysis with stronger acid lose benzoic acid, and the amino-ketonic acids produced are converted into the corresponding mercaptoglyoxalinyl-acetic acids (VII) by potassium thiocyanate.

With propionic and butyric anhydrides at 100° or the boiling point in presence of picoline benzoylaspartic anhydride gives only oils; however, hydrolysis with hydrochloric acid then enables the benzamido-keto-acids to be isolated in small yield and from these the mercaptoglyoxalines are obtained.

n-Hexanoic anhydride and benzoylaspartic anhydride in xylene give mainly a neutral non-ketonic substance $C_{16}H_{19}O_3N$, corresponding to the unsaturated lactones obtained with the lower homologues. This substance, however, is substantially unaffected by boiling 20% hydrochloric acid. Concentrated hydrochloric acid at 160° converts it into an isomeric acid which, apart from salt formation, is unaffected by sodium hydroxide solution under conditions which liberate benzoic acid from the isomer. This fact, together with the weakly basic nature of the substance, suggests that the benzoyl group is concerned in ring formation. Therefore, the acid is probably 5-*n*-amyl-2-phenyl-4-oxazolylacetic acid (XII; R = Ph, R′ = *n*-amyl). Small quantities of low-melting material encountered in the earlier experiments, particularly in those with butyric anhydride, may have been due to homologous oxazoles formed in a similar way.

Removal of solvent from the mother-liquors of the preceding neutral substance, followed by hydrolysis with concentrated hydrochloric acid, gives a benzamido-keto-acid $C_{16}H_{21}O_4N$ which on further hydrolysis loses benzoic acid to produce the amino-keto-acid from which 4-*n*-amyl-2-mercapto-5-glyoxalinylacetic acid (VII; R′ = *n*-amyl) is obtained as in the cases of the lower homologous anhydrides.

Experimental

Benzoylaspartic Anhydride.—Benzoyl-DL-aspartic acid (5 g.), finely powdered, was warmed on the steam-bath with acetic anhydride (30 ml.) and dissolution was accelerated by shaking. The solution was then filtered and cooled in ice. The anhydride which crystallised as felted needles was washed with light petroleum (yield 4 g.; m. p. 205°). Evaporation of the mother-liquor under reduced pressure gave a further quantity. To remove the last traces of acetic anhydride, which were held rather tenaciously, the product was heated at 70° *in vacuo*.

DL-β-*Benzamido-γ-ketovaleric Azlactone* (III; R = Ph, R′ = Me).—Benzoyl-DL-aspartic anhydride (2 g.) and acetic anhydride (10 ml.) were boiled under reflux till evolution of carbon dioxide ceased (12 minutes). After evaporation *in vacuo*, the sticky residue was crystallised from ethyl acetate containing a little light petroleum (b. p. 40—60°), and then from ethanol or ethyl acetate, giving the *azlactone* as prisms, m. p. 94° (1·5 g.) (Found: C, 66·0; H, 5·2; N, 6·4. $C_{12}H_{13}O_3N$ requires C, 66·4; H, 5·1; N, 6·4%). Treatment with a solution of 2 : 4-dinitrophenylhydrazine in ethanol containing a drop of concentrated sulphuric acid gave yellow needles

of *ethyl* DL-β-*benzamido-γ-ketovalerate* 2 : 4-*dinitrophenylhydrazone*, m. p. 212° (from ethanol–toluene) (Found : C, 53·6; H, 4·7; N, 15·5. $C_{20}H_{21}O_7N_5$ requires C, 54·2; H, 4·7; N, 15·8%). The azlactone dissolved in warm dilute sodium hydroxide solution; the solution was nearly neutralised with hydrochloric acid, and acetic acid and phenylhydrazine hydrochloride were added. After 15 minutes' warming on the steam-bath, β-*benzamido-γ-phenylhydrazonovaleric acid* was removed and recrystallised from ethanol–benzene as pale yellow needles, m. p. 171° (Found : C, 67·1; H, 6·0; N, 12·6. $C_{18}H_{19}O_3N_3$ requires C, 66·6; H, 5·9; N, 12·9%).

2-*Mercapto-5-glyoxalinylacetic Acid*.—β-Benzamido-γ-ketovaleric azlactone (2 g.) was boiled with 4N-hydrochloric acid (15 ml.) under reflux for 1 hour. The benzoic acid was removed from the cooled solution and the filtrate evaporated to dryness *in vacuo*. The evaporation was repeated after the addition of a little water (to remove most of the hydrochloric acid), and the residue, dissolved in water, was warmed on the steam-bath with a few crystals of potassium thiocyanate. After 1 hour the crystals of the 2-*mercapto-5-glyoxalinylacetic acid* were removed from the cooled solution and recrystallised from hot water containing a little ethanol as colourless prisms (0·9 g.), m. p. > 300° (decomp.) (Found : C, 42·0; H, 4·8; N, 16·0. $C_6H_8O_2N_2S$ requires C, 41·8; H, 4·65; N, 16·25%).

2-*Mercapto*-4 : 5-*dimethylglyoxaline*.—The above acid was decarboxylated at 200° under nitrogen (a few minutes). The 2-mercapto-4 : 5-dimethylglyoxaline had m. p. > 300° (from aqueous ethanol). When boiled for 30 minutes with a slight excess of benzyl chloride in ethanol this was converted into 2-*benzylthio*-4 : 5-*dimethylglyoxaline hydrochloride*, m. p. 172° (from alcohol–benzene) (Found : C, 56·6; H, 6·2. $C_{12}H_{15}N_2SCl$ requires C, 56·4; H, 5·9%). This had the same m. p. as, and showed no depression in m. p. when mixed with, a specimen prepared from alanine (Part VI, *loc. cit.*).

3-*Benzamido*-4-*hydroxypent*-3-*enoic Lactone* (β-*Benzamidoangelicalactone*) (IV; R = Ph, R′ = Me).—Benzoylaspartic acid (2 g.) was boiled with acetic acid (10 ml.) and acetic anhydride (10 ml.) for 15 minutes, the solution was evaporated *in vacuo*, and the gummy product dissolved in ethyl acetate. After addition of light petroleum to turbidity, and cooling, crystals of benzoylaspartic anhydride were removed and from the evaporated mother-liquor prisms of β-*benzamidoangelicalactone* gradually separated. Recrystallised from ethyl acetate or ethanol, this had m. p. 174° (Found : C, 66·6; H, 5·0; N, 5·9. $C_{12}H_{11}O_3N$ requires C, 66·4; H, 5·1; N, 6·4%). This substance was neutral in reaction. It dissolved in warm N-sodium hydroxide with the uptake of 1 equivalent of alkali. Warming it with an excess of 3N-sodium hydroxide caused evolution of ammonia and the solution became yellow and eventually blackened, presumably owing to the formation of diacetyl. The substance was dissolved in warm dilute hydrochloric acid and, after addition of water and concentration *in vacuo*, benzamide crystallised. After removal of this the distillate from the neutralised filtrate contained diacetyl as shown by the formation of the bisphenylhydrazone, m. p. 139° and bis-semicarbazone, m. p. 279°.

3-N-*Acetyl*-N-*benzamido*-4-*hydroxypent*-3-*enoic Lactone* (V; R = Ph, R′ = Me).—Benzoylaspartic anhydride (2 g.) was dissolved in acetic anhydride (10 ml.) and 2-picoline (5 ml.) on the steam-bath, carbon dioxide being evolved. After 90 minutes the solution was evaporated to dryness *in vacuo* and the crystalline residue recrystallised in prisms from ethyl acetate. The yield of N-*acetyl*-β-*benzamidoangelicalactone*, m. p. 142°, was 1·8 g. (Found : C, 65·0; H, 5·0; N, 5·45. $C_{14}H_{13}O_4N$ requires C, 64·9; H, 5·0; N, 5·4%). This substance like that above lost its nitrogen when heated with dilute acid or alkali. The solution in hot dilute hydrochloric acid, when evaporated to dryness *in vacuo*, gave the β-*phenylhydrazono-γ-valerolactone*, m. p. 148°, on appropriate treatment and crystallisation from alcohol–benzene (Found : C, 64·5; H, 5·6; N, 13·2. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9; N, 13·7%).

Action of Propionic Anhydride on Benzoylaspartic Anhydride.—Benzoyl-DL-aspartic anhydride (2 g.) was heated at the b. p. with xylene (10 ml.) and propionic anhydride (10 ml.) till evolution of carbon dioxide ceased (20 minutes). After evaporation *in vacuo*, the oily residue, on treatment with a little ethyl acetate, gave colourless crystals of 3-*benzamido*-4-*hydroxyhex*-3-*enoic lactone* (IV; R = Ph, R′ = Et) (0·4 g.). On recrystallisation from ethyl acetate this had m. p. 150° (Found : C, 67·0; H, 5·3; N, 5·9. $C_{13}H_{13}O_3N$ requires C, 67·4; H, 5·6; N, 6·0%). It was hydrolysed by boiling 4N-hydrochloric acid with loss of carbon dioxide and production of benzoic acid, ammonium chloride, and an unidentified ketone. The mother-liquor from the hexenolactone, with dinitrophenylhydrazine in ethanol containing a trace of sulphuric acid, gave yellow needles of *ethyl* DL-3-*benzamido*-4-*ketohexanoate* 2 : 4-*dinitrophenylhydrazone*, m. p. 172° after recrystallisation from ethanol (Found : C, 53·2; H, 5·0; N, 14·0. $C_{21}H_{23}O_7N_5$ requires C, 55·0; H, 5·0; N, 15·3%). Removal of the solvent from the above mother-liquor and hydrolysis of the residue with 4N-hydrochloric acid for a short time yielded

on cooling a semi-solid mixture of benzoic acid and DL-β-*benzamido-γ-ketohexanoic acid* from which the benzoic acid was removed by ether-extraction. The keto-acid recrystallised from ethyl acetate in needles, m. p. 130° (Found: C, 62·7; H, 6·1; N, 5·6. $C_{13}H_{15}O_4N$ requires C, 62·7; H, 6·0; N, 5·6%).

Hydrolysis of the last-named substance with 6N-hydrochloric acid and further treatment as described above for the corresponding acetic anhydride derivative gave 4-*ethyl*-2-*mercapto*-5-*glyoxalinylacetic acid* (VII; R′ = Et) as tufts of colourless needles, m. p. > 300° (decomp.), from water–ethanol (yield, 50% calc. on the anhydride) (Found: C, 45·9; H, 5·5; N, 14·6. $C_7H_{10}O_2N_2S$ requires C, 45·2; H, 5·4; N, 15·0%). Decarboxylation and benzylation produced 2-*benzylthio*-4-*ethyl*-5-*methylglyoxaline hydrochloride*, colourless needles (from ethanol), m. p. 153° (Found: C, 57·8; H, 6·2. $C_{13}H_{17}N_2SCl$ requires C, 58·0; H, 6·3%). Identity of this substance with that obtained by the action of benzyl chloride on 4-ethyl-2-mercapto-5-methylglyoxaline, prepared by another method, proved its constitution.

When benzoylaspartic anhydride (2 g.) was heated on the steam-bath or at the b. p. for 1½ hours with propionic anhydride (10 ml.) and 2-picoline (5 ml.) no crystallisation took place after evaporation of the solution *in vacuo*. The oily residue on hydrolysis with boiling 6N-hydrochloric acid and further treatment as described above gave 0·3 g. of 4-ethyl-2-mercapto-5-glyoxalinylacetic acid.

Action of n-*Butyric Anhydride on Benzoylaspartic Anhydride.*—Benzoyl-DL-aspartic anhydride (2 g.) was boiled with xylene (10 ml.) and *n*-butyric anhydride (10 ml.) till carbon dioxide evolution ceased (35 minutes). After evaporation *in vacuo*, there was obtained 0·3 g. of crystals which recrystallised from ethyl acetate in colourless needles, m. p. 122° (Found: C, 69·1; H, 5·9; N, 5·6. $C_{14}H_{15}O_3N$ requires C, 68·7; H, 6·1; N, 5·7%). They gave no reaction with dinitrophenylhydrazine and liberated carbon dioxide and benzoic acid with hot dilute hydrochloric acid and were therefore 3-*benzamido*-4-*hydroxyhept*-3-*enoic lactone* (IV; R = Ph, R′ = Pr^n). A small sample of the non-crystalline material from this reaction on treatment with dinitrophenylhydrazine in ethanol containing a trace of sulphuric acid gave *ethyl* DL-3-*benzamido*-4-*ketoheptanoate* 2 : 4-*dinitrophenylhydrazone* as yellow needles (from ethanol), m. p. 163° (Found: C, 55·3; H, 5·4; N, 14·7. $C_{22}H_{23}O_7N_5$ requires C, 55·7; H, 5·3; N, 14·8%. The bulk of the non-crystalline material was heated with boiling 4N-hydrochloric acid for 30 minutes and cooled. The insoluble oily layer solidified and was removed. Extraction of the benzoic acid left a crystalline residue (0·8 g.) of DL-β-*benzamido*-γ-*keto*-n-*heptanoic acid*, needles (from ethyl acetate), m. p. 146° (Found: C, 63·6; H, 6·3; N, 5·1. $C_{14}H_{17}O_4N$ requires C, 63·9; H, 6·5; N, 5·3%). The last-named substance on hydrolysis with 6N-hydrochloric acid for 3 hours and further treatment as described above for the lower homologue gave 2-*mercapto*-4-n-*propyl*-5-*glyoxalinylacetic acid* (VII; R′ = Pr^n), m. p. 264° (after sintering at 240°), prisms from aqueous ethanol (0·4 g. from 0·5 g. of the keto-acid) (Found: C, 48·0; H, 5·9; N, 14·0. $C_8H_{12}O_2N_2S$ requires C, 48·0; H, 6·0; N, 14·0%). When the reaction between *n*-butyric anhydride and benzoylaspartic anhydride was carried out in 2-picoline as previously described an oil was obtained, which afforded β-benzamido-γ-keto-*n*-heptanoic acid and 2-mercapto-4-*n*-propyl-5-glyoxalinylacetic acid. Decarboxylation of the last substance at 240° in nitrogen gave 2-*mercapto*-5-*methyl*-4-n-*propylglyoxaline*, prisms (from aqueous ethanol), m. p. 267° (Found: C, 53·7; H, 7·6. $C_7H_{12}N_2S$ requires C, 53·8; H, 7·7%).

Action of n-*Hexanoic Anhydride on Benzoylaspartic Anhydride.*—Benzoyl-DL-aspartic anhydride (2 g.) was boiled with xylene (15 ml.) and *n*-hexanoic anhydride (15 ml.) till carbon dioxide evolution ceased (45 minutes). After evaporation under reduced pressure, the solution crystallised and 3-*benzamido*-4-*hydroxynon*-3-*enoic lactone* (1·5 g.) (IV; R = Ph, R′ = *n*-amyl) was collected. This substance, recrystallised from ethyl acetate in colourless needles, had m. p. 135° (Found: C, 69·7; H, 7·1; N, 5·4. $C_{16}H_{19}O_3N$ requires C, 70·4; H, 7·0; N, 5·1%). It was neutral and was hardly affected by boiling concentrated hydrochloric acid for 6 hours. Concentrated hydrochloric acid at 160° (4 hours) converted it almost quantitatively into an isomeric *acid* which, being soluble in the hydrochloric acid, was obtained after evaporation *in vacuo*. This acid was recrystallised from ethyl acetate–light petroleum or aqueous ethanol as felted needles, m. p. 96° (Found: C, 69·8; H, 7·0; N, 4·9. $C_{16}H_{19}O_3N$ requires C, 70·4; H, 7·0; N, 5·1%). It gave no ketonic reactions, was unaffected by boiling 2N-sodium hydroxide, and was recovered unchanged by distillation at 1 mm. after having been heated to 240° in nitrogen.

The excess of hexanoic anhydride in the mother-liquor from the nonenolactone above was removed by distillation at 1 mm. The oily residue on treatment with dinitrophenylhydrazine in ethanol gave yellow needles of *ethyl* DL-β-*benzamido*-γ-*keto*-n-*nonanoate* 2 : 4-*dinitrophenylhydrazone*, m. p. 155° (from ethanol) (Found: C, 57·0; H, 5·6. $C_{24}H_{29}O_7N_5$ requires C, 57·7;

H, 5·8%). After hydrolysis of the oily residue with boiling 20% hydrochloric acid and cooling, the crystalline material obtained was collected and after treatment with sodium carbonate and reprecipitation with acid recrystallised from ethyl acetate–light petroleum, giving colourless needles of DL-β-*benzamido-γ-keto*-n-*nonanoic acid*, m. p. 127° (0·7 g. from 2 g. of benzoylaspartic anhydride) (Found: C, 66·4; H, 7·3. $C_{16}H_{21}O_4N$ requires C, 66·1; H, 7·2%). The benzoyl group was removed by hydrolysis with concentrated hydrochloric acid at 160° for 4 hours, and treatment with potassium thiocyanate as described above gave colourless plates of 4-n-*amyl*-2-*mercapto*-5-*glyoxalinylacetic acid*, m. p. 174° (decomp.) (from aqueous ethanol) (60%) (Found: C, 52·8; H, 7·0; N, 12·3. $C_{10}H_{16}O_2N_2S$ requires C, 52·7; H, 7·0; N, 12·3%). Decarboxylation of the acid at 175° gave smoothly 4-n-*amyl*-2-*mercapto*-5-*methylglyoxaline*, prisms (from aqueous ethanol), m. p. 228° (Found: C, 58·9; H, 8·7. $C_9H_{16}N_2S$ requires C, 58·7; H, 8·7%).

Phthalimidosuccinic Anhydride.—King and Kidd's method (*J.*, 1949, 3315) for glutamic acid was followed. DL-Aspartic acid (3·0 g.), phthalic anhydride (3·1 g.), and pyridine (12 ml.) were boiled under reflux for 2 hours, filtered, and concentrated *in vacuo* to a thick syrup. Boiling this with acetic anhydride for 3 minutes and then cooling gave DL-*phthalimidosuccinic anhydride* (3·8 g., 69%), m. p. 227° (from acetic anhydride) (Found: C, 58·9; H, 3·0. $C_{12}H_7O_5N$ requires C, 58·8; H, 2·9%).

Reaction between Acetic Anhydride and Ethyl Hydrogen Acetamidomalonate.—Ethyl hydrogen acetamidomalonate (1 g.) was dissolved rapidly in acetic anhydride (10 ml.) at 100° and the solution concentrated *in vacuo*. On cooling, *ethyl hydrogen* NN-*diacetylaminomalonate* (0·4 g.) crystallised in plates, m. p. 119° (decomp.) (Found: C, 46·5; H, 5·6. $C_9H_{13}O_6N$ requires C, 46·8; H, 5·6%). When the above reactants were refluxed, carbon dioxide was evolved and the oily residue obtained after evaporation *in vacuo* was boiled for 30 minutes with 3N-hydrochloric acid containing potassium thiocyanate. Crystals of ethyl 2-mercapto-4-methylglyoxaline-5-carboxylate which came down on concentration of the solution were recrystallised from aqueous ethanol and then had m. p. 237° (decomp.).

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