330. *A Synthesis of Acylamidomalondialdehydes.*

By J. W. Cornforth, (Miss) E. Fawaz, L. J. Goldsworthy, and Sir Robert Robinson.

Oxazole-4-aldehydes are converted by aqueous alkali into acylamidomalondialdehydes, which are intermediates in certain schemes for the synthesis of penicillins.

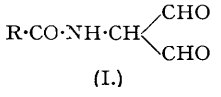
It is noteworthy that penicillin syntheses, by which term we mean not only the proved synthesis of benzylpenicillinic acid, but also the production of traces of biologically active material destroyed by penicillinase, have been demonstrated only by way of an oxazolone. For example, the various claims that penicilloic acids have been dehydrated to penicillins are of doubtful validity.

There is even no evidence that inactivated penicillin can be activated *in vivo*. In considering possible alternative last stages of the biogenesis of penicillin, an oxidative process is attractive. Thus a four-membered ring containing :N–CH(OH)– might be initially produced from :NH OCH–, more easily than is :N–CO– from :NH CO_2H–, and then suffer oxidation.

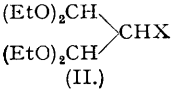
An attempt to realise this scheme led to the present work.

Attempts to prepare acylamidomalondialdehydes (I) by application of conventional methods were uniformly unsuccessful. For example, hippuraldehyde could not be formylated, and the halogen atom in *chloromalondialdehyde tetraethyl acetal* (II; X = Cl) proved to be too little reactive for smooth replacement by amines, though *benzylaminomalondialdehyde tetraethyl acetal* (II; X = CH_2Ph·NH) could be prepared in low yield, and some indication of formation of amino-acetal (II; X = NH_2) was found after heating it with alcoholic ammonia to a high temperature.

Earlier work at Oxford (see "The Chemistry of Penicillin," Chap. XXI) had made 2-substituted oxazole-4-aldehydes (III) readily available. An examination of these aldehydes led to the rather surprising discovery that on warming them with dilute alkali the oxazole ring underwent fission with formation of acylamidomalondialdehydes in excellent yield.



(I.)



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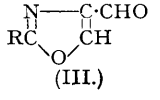
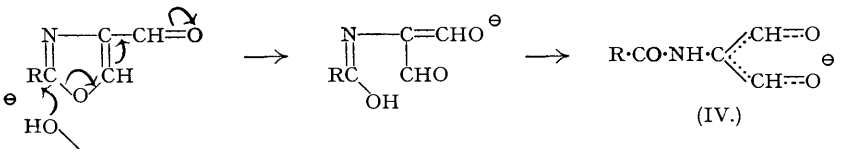


(III.)

The oxazole ring usually has great stability towards alkali; 4-phenyl-2-methyloxazole, for example, resists the action of alcoholic potassium hydroxide at 200° and can be distilled unchanged over hot soda-lime (Lewy, *Ber.*, 1888, **21**, 924). The ready fission of these aldehydes probably involves attack on C_2 by a hydroxyl ion, the driving force of the reaction being derived from the "resonance" stabilisation of the symmetrical malondialdehyde anion (IV). The process is analogous to a rearrangement of certain oxazoles described elsewhere ("The Chemistry of Penicillin," Chap. XXI) and thought to involve fission and recyclisation at C_2.



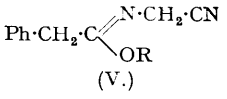
(IV.)

Oxazole-4-aldehydes are available from the corresponding carboxylic acid chlorides and nitriles by the Rosenmund and the Stephen reduction, respectively. A synthesis of 4-cyano-oxazoles has already been described (Cornforth and Huang, *J.*, 1948, 1969). Oxazole-4-carboxlic

acids can be made by analogous procedures (Cornforth and Cornforth, *J.*, 1947, 96) or alternatively by rearrangement of 4-hydroxymethyleneoxazolones (*op. cit.*, Chap. XXI).

Phenylacetimido methyl ether and the related ethyl ether reacted with aminoacetonitrile to give 1-*methoxy-* and 1-*ethoxy*-2-*phenylethylideneaminomethyl cyanide* (V). These product were formylated with ethyl formate–potassium ethoxide, and the resulting potassium salts (VI) added to boiling acetic acid, giving 4-*cyano*-2-*benzyloxazole* (VII). The condensation with aminomethyl cyanide was more satisfactory with phenylacetimido ethyl ether, but formylation of (V; R = Me) was easier, the potassium salt crystallising much more readily.

The potassium salt (VI; R = Me) reacted with ammonium sulphate to form 4-*cyano*-2-*benzylglyoxaline* (VIII) (cf. Cornforth and Cornforth, *loc. cit.*). This substance was amphoteric, ionisation of the imino-hydrogen atom being evidently favoured by the electron-attracting cyano-group.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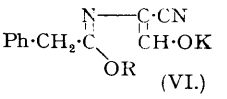
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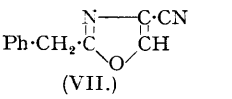
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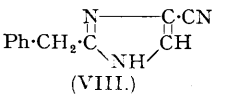
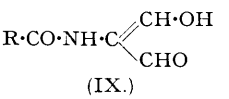

(VIII.)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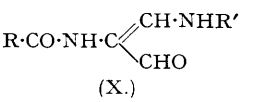
(X.)

Reduction of the cyanide (VII) to 2-*benzyloxazole*-4-*aldehyde* (III; R = CH_2Ph) by Stephen's method proceeded smoothly, though it was necessary to decompose the aldimine stannichloride with sodium hydrogen carbonate.

Reduction of 2-phenyloxazole-4-carboxyl chloride by Rosenmund's technique gave 2-*phenyloxazole*-4-*aldehyde* (III; R = Ph), and the same method was used to prepare 2-benzyloxazole-4-aldehyde from 2-*benzyloxazole*-4-*carboxyl chloride* (or its 5-chloro-derivative).

Alkaline fission of the appropriate oxazole-aldehyde gave *benzamido-*, *phenylacetamido-*, and *hexamido-malondialdehydes* (I or IX; R = Ph, CH_2Ph, or n-C_5H_{11}). These substances were crystalline solids and could be kept for long periods without deterioration. They resembled known malondialdehydes in most properties and reactions. The ultraviolet light absorption of phenylacetamidomalondialdehyde indicated that the enol form (IX; R = CH_2Ph) was predominant. Condensation of the dialdehydes with primary amines gave derivatives (X) of αβ-diaminoacraldehyde.

Condensation of the acylamidomalondialdehydes, especially the phenylacetamido-derivative, with D-penicillamine and its methyl ester was studied in a preliminary way at Oxford and the bisthiazolidine derivative was isolated without difficulty. In experiments giving variable results, indications of antibiotic activity, partly destroyed by penicillinase, were obtained.

These findings are not described in the present paper because the investigation has been transferred to Hampstead, and it is hoped that one of us (J. W. C.) will be able to carry the matter a stage further.

Experimental.

Chloromalondialdehyde.—The process follows the indications given by Prins [D.R.-P. 261689 (1913)]. 1 : 1 : 2 : 3 : 3-Pentachloropropane (54 g.; *Rec. Trav. chim.*, 1935, **54**, 307) was stirred and treated below 20° with a solution of potassium hydroxide (15 g.) in ethanol (100 c.c.), added during one hour. After a further ½ hour, water (500 c.c.) was added, and 1 : 2 : 3 : 3-tetrachloropropene (45 g.) was isolated by means of ether; b. p. 54°/15 mm. Tetrachloropropene (25 g.) was mixed with sulphuric acid (75 c.c.; *d* 1·84) and stirred rapidly at 40—50° until evolution of hydrogen chloride ceased (8 hours). The mixture was poured into ice and water (100 c.c.), and the precipitate (8 g.) collected. Continuous extraction of the filtrate with ether (10 hours) gave a further 2 g. Recrystallisation of the whole product from benzene containing a few drops of acetone gave chloromalondialdehyde in colourless prisms, m. p. 145—146°. A further quantity could be obtained from the aqueous mother-liquor by precipitation as the anil and hydrolysis of this with alcoholic potash (cf. Dieckmann and Platz, *Ber.*, 1904, **37**, 4638).

Chloromalondialdehyde Tetraethyl Acetal.—The dialdehyde (5·4 g.) was dissolved in dry ethanol (15 c.c.) which had previously been heated under reflux for one hour with ammonium chloride (0·5 g.). Ethyl orthoformate (16 g.) was added and the mixture kept in a closed flask for 5 days. Ether (100 c.c.) was added, and then enough dilute aqueous ammonia to dissolve the ammonium chloride. Distillation of the ethereal layer gave the *acetal* (II; X = Cl), b. p. 116—120/12 mm. A twice-distilled specimen was analysed (Found: C, 51·7; H, 9·1; Cl, 13·8. $C_{11}H_{23}O_4Cl$ requires C, 52·0; H, 9·0; Cl, 13·8%).

Reaction of the Acetal (II; X = Cl) *with Benzylamine.*—The acetal (10 g.) was heated under reflux for 12 hours with benzylamine (20 c.c.). After dilution with ether (200 c.c.) and separation of benzylamine hydrochloride, ether and benzylamine were removed by distillation at low pressure. The residue, dissolved in ether (100 c.c.), was shaken at 0° with dilute sulphuric acid (2 × 15 c.c.), which was separated, quickly neutralised with sodium carbonate, and extracted repeatedly with ether. The

ether-soluble product (3 g.) was distilled, and the fraction, b. p. 80—85°/0·5 mm., containing *benzylaminomalondialdehyde tetraethyl acetal* (II; X = Ph·CH_2·NH), collected and redistilled (Found: C, 66·0; H, 9·5; N, 4·8. $C_{18}H_{31}O_4N$ requires C, 66·4; H, 9·5; N, 4·3%). The picrate could not be purified. The acetal with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid gave, after neutralisation, a product, probably *benzylaminomalondialdehyde mono-2 : 4-dinitrophenylhydrazone*, which had m. p. 211—213° (decomp.) after crystallisation from ethanol (Found: C, 54·1; H, 3·7. $C_{16}H_{15}O_5N_5$ requires C, 53·8; H, 4·1%).

Reaction of the Acetal (II; X = Cl) *with Ammonia.*—The acetal (6·3 g.), dry methanol (100 c.c.), and dry ammonia (28 g.) were heated in an autoclave at 150° for 10 hours. The mixture was concentrated to 50 c.c., 5% potassium hydroxide (10 c.c.) added, and evaporation continued until the vapour no longer burned. The supernatant oil, consisting largely of unchanged acetal, was separated. Extraction of the aqueous liquor, after saturation with sodium chloride, for ten hours with ether gave an oil (0·5 g.) which gave a precipitate with picric acid in ethanol. The oil (0·59 g.) obtained from a similar experiment conducted at 200° was distilled in bulbs. One fraction appeared to contain the desired *aminomalondialdehyde tetraethyl acetal* (II; X = NH_2) (Found: C, 55·7; H, 10·9; N, 5·0. $C_{11}H_{25}O_4N$ requires C, 56·2; H, 10·6; N, 5·9%).

1-*Methoxy- and* 1-*Ethoxy-2-phenylethylideneaminomethyl Cyanide* (V; R = Me and Et).—(i) Phenylacetimido methyl ether (90 g.) was added to a chilled mixture of saturated aqueous sodium hydrogen carbonate (500 c.c.) and ether (100 c.c.). After swirling and separating, the aqueous layer was extracted with ether (50 c.c.) both before and after being made alkaline to phenolphthalein. The ethereal extracts were dried at −10° (K_2CO_3) and distilled, giving phenylacetimido methyl ether (61·5 g.; 85%). On cooling, this crystallised in large prisms, m. p. 32°.

Aminomethyl cyanide hydrogen sulphate (20 g.) in water (10 c.c.) was neutralised to methyl-orange with concentrated potassium hydroxide solution. A further 5 g. of the sulphate was then added, followed by a solution of phenylacetimido methyl ether (25 g.) in ether (125 c.c.). The mixture was cooled in ice and stirred vigorously for half an hour; the ether was separated, washed with a little water, and dried quickly ($MgSO_4$). After removal of ether at room temperature, the residue was distilled. A fraction (10·8 g.) boiling below 80°/0·1 mm. was methyl phenylacetate containing some unchanged imido-ether. The main fraction (13·8 g.), a colourless oil, b. p. 100°/0·1 mm., was the desired 1-*methoxy-2-phenylethylideneaminomethyl cyanide* (V; R = Me). It was fairly stable in closed vessel at −10°, but quickly reddened at room temperature (Found: C, 69·5; H, 6·5. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·3%).

In the preparation of aminomethyl cyanide hydrogen sulphate (Anslow and King, *J.*, 1929, 2465) a mixture of acid and neutral sulphates was often obtained. When this happened, the composition was determined by titration with alkali, after which the weight of salt and the degree of neutralisation necessary could be calculated.

(ii) Phenylacetimido ethyl ether (7 g.) was diluted with a little ether, cooled to −10° and added to a similarly-cooled, concentrated solution of aminomethyl cyanide hydrochloride (4 g.) in water. After being shaken for 2½ hours and kept at 0° over-night, the ethereal layer was separated, and the aqueous layer extracted with ether. Isolation of the product then followed as above; the colourless oily product (6·3 g.), 1-*ethoxy-2-phenylethylideneaminomethyl cyanide* (V; R = Et), had b. p. 125°/0·5 mm. (Found: C, 70·8; H, 7·1; N, 13·7. $C_{12}H_{14}ON_2$ requires C, 71·3; H, 6·9; N, 13·9%).

4-*Cyano-2-benzyloxazole.*—Potassium (1·05 g.) was dissolved in alcohol (4 c.c.) and ether (15 c.c.). The solution was diluted with ether to 100 c.c., cooled to −10°, and treated with a mixture of 1-methoxy-2-phenylethylideneaminomethyl cyanide (5 g.) and ethyl formate (3 c.c.). After being kept at <0° for two hours and then overnight in a refrigerator, the crystalline, hygroscopic potassium salt (VI; R = Me) was collected, washed quickly with ether, and dried in a vacuum (yield, 5·6 g.). It showed with alcoholic ferric chloride the colour changes characteristic of its class (Cornforth and Cornforth, *loc. cit.*).

The salt was added to boiling acetic acid (15 c.c.) during five minutes. Water and alkali were added and the product extracted with ether. On distillation, 4-*cyano-2-benzyloxazole* (VII) (3·3 g.), b. p. 120°/0·2 mm., was obtained; it had a tendency to remain supercooled, but eventually solidified. Crystallisation from ether gave colourless prisms, m. p. 59° (Found: C, 71·4; H, 4·2; N, 15·6. $C_{11}H_8ON_2$ requires C, 71·1; H, 4·3; N, 15·2%).

The formylation of 1-ethoxy-2-phenylethylideneaminomethyl cyanide was carried out in similar fashion, but the potassium salt separated more slowly and tended to be gelatinous.

4-*Cyano-2-benzylglyoxaline.*—A crude sample of the potassium salt (VI; R = Me) was dissolved in water and an excess of ammonium sulphate was added. After several hours the mixture was neutralised to litmus and extracted with ethyl acetate, which was then extracted with dilute hydrochloric acid. Neutralisation of the chilled acid extract, and crystallisation of the precipitate from water (charcoal), gave the *glyoxaline* (VIII) in long colourless needles, m. p. 192·5—194° (Found: C, 71·9; H, 4·8; N, 22·8. $C_{11}H_9N_3$ requires C, 72·1; H, 4·9; N, 22·9%). The substance was soluble in dilute acids (including acetic) and also in dilute sodium hydroxide, but not in cold aqueous sodium carbonate.

2-*Benzyloxazole-4-carboxyl Chloride.*—The synthesis of 2-benzyloxazole-4-carboxylic acid from phenylacetimido ethyl ether was reported, without details of procedure, by Merck and Co. "The Chemistry of Penicillin, Chap. XXI). Ethyl 1-ethoxy-2-phenylethylideneaminoacetate was prepared from the imido-ether and glycine ethyl ester hydrochloride, using the technique described above for the condensation of the same imido-ether with aminomethyl cyanide hydrochloride; the ester (20 g. from 16·5 g. of imido-ether) was a colourless oil, b. p. 130—135°/0·5 mm. (Found: C, 68·1; H, 7·6. Calc. for $C_{14}H_{19}O_3N$: C, 67·5; H, 7·6%). Formylation in the usual manner and cyclisation of the resulting potassium salt with hydrogen chloride in alcohol–ether gave ethyl 2-benzyloxazole-4-carboxylate, m. p. 74—75°. This was hydrolysed by boiling under reflux for 10 minutes with a 10% excess of 15% aqueous potassium hydroxide. The cooled solution was stirred and treated dropwise with the calculated amount of N-sulphuric acid. The precipitated 2-benzyloxazole-4-carboxylic acid was collected; m. p. 156—158°.

A solution of thionyl chloride (5·5 c.c.) in pure chloroform (33 c.c.) was added to a suspension of the acid (8·9 g.) in the same solvent (22 c.c.). After the mixture had been heated under reflux for two hours

and evaporated at low pressure, the product was crystallised from light petroleum (b. p. 60—80°). 2-*Benzyloxazole-4-carboxyl chloride* (9 g.) formed long prisms, m. p. 62° (Found: C, 59·6; H, 3·7; N, 6·3. $C_{11}H_8O_2NCl$ requires C, 59·6; H, 3·6; N, 6·3%).

2-*Benzyloxazole-4-aldehyde*.—(i) Hydrogen was bubbled through a boiling solution of 2-benzyloxazole-4-carboxyl chloride (2·4 g.) in xylene (8 c.c.), containing palladised barium sulphate (0·65 g.) in suspension. The evolution of hydrogen chloride was substantially complete after 2½ hours. Catalyst and solvent were removed, and the residue was crystallised from light petroleum (b. p. 60—80°). The *aldehyde* (1 g.), thin prisms, had m. p. 70—71°, raised to 72° by recrystallisation (Found: C, 70·4; H, 4·6; N, 7·9. $C_{11}H_9O_2N$ requires C, 70·6; H, 4·8; N, 7·5%). The 2 : 4-*dinitrophenylhydrazone*, prepared by shaking a solution of the aldehyde in ether with one of the hydrazine in 2N-hydrochloric acid, crystallised from benzene in microscopic, orange-yellow needles, m. p. 224° (Found: C, 56·0; H, 3·5; N, 19·9. $C_{17}H_{13}O_5N_5$ requires C, 55·6; H, 3·5; N, 19·1%).

(ii) A suspension of stannous chloride (20 g.; anhydrous) in ether (100 c.c.) was saturated with hydrogen chloride. 4-Cyano-2-benzyloxazole (10 g.) was melted, diluted with a little ether, and added quickly to the mixture with vigorous stirring, which was continued until the lower layer became too viscous (about 30 minutes). More hydrogen chloride was passed in, and the whole kept overnight. The upper layer was decanted, and the remaining viscous gum added gradually to an excess of aqueous sodium hydrogen carbonate. The crude aldehyde (8·85 g.) was recovered by ether extraction, using a centrifuge to separate the layers; it crystallised on removal of the ether. A portion, recrystallised from ether and sublimed at 60°/0·05 mm., had m. p. 71° (Found: C, 70·8; H, 4·9%).

2-*Phenyloxazole-4-aldehyde*.—2-Phenyloxazole-4-carboxylic acid (10 g.) was boiled gently under reflux with an excess of thionyl chloride for two hours. The residue after removal of thionyl chloride was recrystallised from light petroleum (b. p. 60—80°). The *acid chloride* formed colourless plates (9 g.), m. p. 108—109° (Found: C, 57·8; H, 3·1. $C_{10}H_6O_2NCl$ requires C, 58·0; H, 2·9%). This chloride (5 g.) in xylene (25 c.c.) with palladised barium sulphate (2 g.) and thiourea (10 mg.) was boiled under reflux with occasional shaking while hydrogen was passed in. After 10 hours, 75% of the theoretical quantity of hydrogen chloride had been evolved. The catalyst was removed and washed with ether; the filtrate was shaken with sodium hydrogen sulphite solution (40 c.c.; saturated). After 30 minutes at 0° the crystalline adduct was collected, dissolved in a minimum of water, and decomposed by addition of sodium carbonate. The precipitated 2-*phenyloxazole-4-aldehyde* was recrystallised from light petroleum (b. p. 60—80°), giving 3 g., m. p. 94° (Found: C, 68·9; H, 4·3; N, 8·3. $C_{10}H_7O_2N$ requires C, 68·3; H, 4·0; N, 8·0%). The orange 2 : 4-*dinitrophenylhydrazone* had m. p. 209° after recrystallisation from ethanol (Found: C, 54·4; H, 3·5; N, 19·2. $C_{16}H_{11}O_5N_5$ requires C, 54·4; H, 3·1; N, 19·8%). The aldehyde, in a little alcohol, was treated with a slight excess of aniline; after 6 hours water was added and the *anil* collected; recrystallisation from alcohol gave yellowish prisms, m. p. 123° (Found: C, 77·3; H, 5·4; N, 11·6. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·8; N, 11·3%).

Phenylacetamidomalondialdehyde (I or IX; R = CH_2Ph).—2-Benzyloxazole-4-aldehyde (2·93 g.) was boiled with N-sodium hydroxide (50 c.c.) for 10 minutes, clarified with charcoal, cooled, and treated with N-hydrochloric acid (50 c.c.). The *dialdehyde* (2·35 g.) was collected; m. p. 108°. A further small amount could be recovered from the filtrate by ether extraction.

The crude product from the Stephen reduction of 4-cyano-2-benzyloxazole (above) was hydrolysed in similar fashion to give the same dialdehyde (5·6 g. from 8·85 g.). A by-product of this process was 2-*benzyloxazole-4-carboxyamide* which separated on cooling the alkaline liquor and had m. p. 168—169° after crystallisation from alcohol (Found: N, 13·6. $C_{11}H_{10}O_2N_2$ requires N, 13·9%); on alkaline hydrolysis it gave ammonia and 2-benzyloxazole-4-carboxylic acid.

The dialdehyde crystallised from light petroleum in long needles, m. p. 108° (Found: C, 64·5; H, 5·6; N, 6·6; equiv., 205. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4; N, 6·8%; equiv., 205). The equivalent weight was determined by titration with standard barium hydroxide (phenolphthalein). The substance was easily soluble in aqueous sodium hydrogen carbonate and, to some extent, in aqueous sodium acetate. It gave a purple colour with ferric chloride. The ultraviolet-light absorption curve (substance dissolved in 0·02N-sodium hydroxide) showed a maximum at 2670 A. (log ε 4·41) and a minimum at 2350 A. (log ε 3·45). When 50% aqueous methanol was the solvent, the maximum was at the same wave-length; when this solution was made 0·04N. with respect to hydrochloric acid, absorption in this region became weaker and less selective ($\lambda_{max.}$ 2480 A., log ε 4·08).

The *mono*-2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in minute, brick-red, torpedo-shaped crystals, m. p. 187—190° (dependent on rate of heating) (Found: C, 53·2; H, 4·0; N, 17·7. $C_{17}H_{15}O_6N_5$ requires C, 53·0; H, 3·9; N, 18·2%). An aqueous solution of the dialdehyde was treated with aniline sulphate; next day the precipitate was recrystallised from ethanol giving *β-anilino-α-phenylacetamidoacraldehyde* (X; R = CH_2Ph; R′ = Ph), yellowish prisms, m. p. 235—237° (Found: C, 73·3; H, 5·9; N, 10·0. $C_{17}H_{16}O_2N_2$ requires C, 72·9; H, 5·7; N, 10·0%), which gave a red coloration with ferric chloride in ethanol.

Benzamidomalondialdehyde (I or IX; R = Ph).—2-Phenyloxazole-4-aldehyde (2 g.) was boiled with 2N-sodium hydroxide (20 c.c.) until dissolution was complete (2 minutes). After cooling and acidification of the mixture, the product was collected and recrystallised from light petroleum (b. p. 60—80°). The dialdehyde (2 g.) formed colourless prisms, m. p. 76—77° (Found: C, 62·6; H, 4·9; N, 7·3. $C_{10}H_9O_3N$ requires 3, 62·8; H, 4·7; N, 7·3%). It was acidic, gave a blood-red colour with ferric chloride, and strongly reduced Tollens's reagent. On addition of benzylamine to the dialdehyde (0·5 g.) in ether (20 c.c.), a *benzylamine* salt separated; m. p. 136—137°, after recrystallisation from ethanol (Found: C, 68·5; H, 6·2. $C_{10}H_9O_3N,C_7H_9N$ requires C, 68·4; H, 6·0%). This was melted in a vacuum over phosphoric anhydride. When frothing ceased the residue was recrystallised from ethanol to give *β-benzylamino-α-benzamidoacraldehyde* (X; R = Ph, R′ = CH_2Ph) as colourless plates, m. p. 61—62° (Found: C, 72·4; H, 5·9; N, 10·6. $C_{17}H_{16}O_2N_2$ requires C, 72·9; H, 5·7; N, 10·0%), which gave a red colour with ferric chloride. Aniline sulphate was added to a solution of the dialdehyde (0·5 g.) in water (200 c.c.); after 12 hours the yellow solid was recrystallised from ethanol; *β-anilino-α-benzamidoacraldehyde* (X; R = R′ = Ph) formed needles (0·54 g.), m. p. 152—153°; it gave an almost

black dinitrophenylhydrazone, but no colour with alcoholic ferric chloride (Found: C, 71·9; H, 5·4. $C_{16}H_{14}O_2N_2$ requires C, 72·2; H, 5·2%).

Condensation of Phenylacetamidomalondialdehyde with Penicillamine and Penicillamine Methyl Ester.—A series of experiments on the condensation of phenylacetamidomalondialdehyde with varying amounts of penicillamine or its methyl ester gave amorphous products, formed by the condensation of one molecule of the dialdehyde with two molecules of penicillamine or its ester. In condensations involving the use of less than two molecular proportions of penicillamine or its ester, unchanged dialdehyde has been recovered from the product of the reaction. All attempts to obtain pure crystalline substances from the product failed. The following is a description of a typical experiment. To a suspension of phenylacetamidomalondialdehyde (51 mg.) in *iso*propyl ether (1 c.c.) and ethanol (0·5 c.c.) was added a solution of D-penicillamine hydrochloride (88 mg.; slightly less than 2 mols.) in water (0·5 c.c.). Sodium acetate crystals (66 mg.) were added, and the mixture was shaken at room temperature. After 2 hours the reaction mixture still gave a blue coloration with ferric chloride, but there was no coloration at the end of 5 hours. The mixture was evaporated to dryness *in vacuo* at room temperature, and the residue was triturated with excess of a saturated solution of sodium hydrogen carbonate. The solution was filtered, the filtrate extracted with ether, and the extract, found to contain only 3 mg. of dissolved solid material, was discarded. On acidification to pH 2 with N-hydrochloric acid, a white precipitate (40 mg.) was formed. This was collected, and a further quantity (22 mg.) of the white substance was obtained by extracting the filtrate with ether. When heated, this amorphous product started to soften at about 120° and gradually melted, with decomposition and evolution of gas, at 140—150°. Attempts to obtain a pure crystalline substance from this product by manipulation with solvents were unsuccessful (Found: C, 54·2; H, 6·4; N, 8·6. $C_{21}H_{29}O_5N_3S_2$ requires C, 54·0; H, 6·2; N, 9·0%).

Another specimen of the condensation *product*, prepared in a similar way, had equiv. 235·6. A dicarboxylic acid, $C_{21}H_{29}O_5N_3S_2$, requires equiv. 233·5.

D-Penicillamine methyl ester also yielded a bisthiazolidine derivative.

Many further experiments were made, but, for the reason already mentioned, need not be described at this stage.

Hexamidomalondialdehyde (I or IX; R = *n*-C_5H_{11}).—2-Amyloxazole-4-aldehyde was hydrolysed with N-sodium hydroxide as described in the other examples. The *dialdehyde* separated from light petroleum (b. p. 60—80°) in colourless needles, m. p. 66—67° (Found: C, 58·2; H, 8·1; N, 7·9. $C_9H_{15}O_3N$ requires C, 58·4; H, 8·1; N, 7·6%). It dissolved in aqueous sodium hydrogen carbonate and gave a blood-red colour with ferric chloride.

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