## 534. *The Synthesis of Amino-acids from Furfurylamine.*

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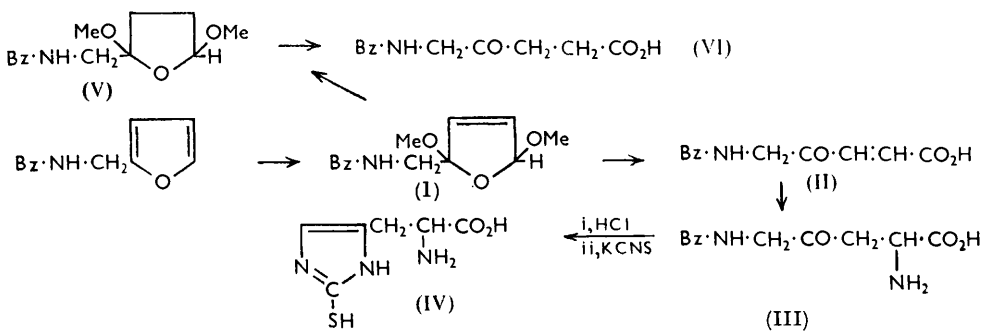
New routes to mercaptohistidine and δ-aminolævulic acid have been developed from furfurylamine.

An obvious possible intermediate for the synthesis of ergothioneine [1] is the hitherto unknown 5-amino-4-oxopent-2-enoic acid.[2] We now report the synthesis of the benzoyl derivative (II) of this compound from furfurylamine and describe its reactions.

Benzoylation of furfurylamine and electrolytic methoxylation [3] of the resulting derivative furnished the two diastereoisomers of the dihydrodimethoxyfuran (I). Treatment of these with chromium trioxide in dilute sulphuric acid resulted in fission of the hemiacetal linkages, followed by oxidation of the keto-aldehyde produced to furnish directly the crystalline 5-benzamido-4-oxopent-2-enoic acid (II). Many attempts at a preliminary hydrolysis with acid alone, in order to isolate the intermediary keto-aldehyde,




were unsuccessful. Addition of ammonia to the double bond of this compound gave the α-amino-acid (III); the position of the amino-group in this product could be confidently predicted from earlier analogous additions.[4] This orientation was confirmed by benzoylation to 2 : 5-dibenzamido-4-oxopentanoic acid and conversion of this into its methyl ester, a known degradation product of histidine.[5,6] Hydrolysis of the amino-acid (III) to 2 : 5-diamino-4-oxopentanoic acid dihydrochloride and treatment of the latter with potassium thiocyanate [6] furnished mercaptohistidine (IV).

In a synthetic approach to ergothioneine attempts were made to effect the addition of dimethylamine to the unsaturated acid (II), by using the techniques which had proved successful with ammonia. Surprisingly no pure product could be obtained. An attempt to obtain the required compound by reductive alkylation of the amino-acid (III) with formaldehyde proved equally fruitless.

Catalytic hydrogenation of the dihydrofuran (I) yielded the tetrahydrofuran (V) which, on hydrolysis and oxidation with chromium trioxide–sulphuric acid, was smoothly

[1] For a review see Bell, *Ann. Reports*, 1955, **52**, 285.
[2] For a previous attempted synthesis see Wynn and Corwin, *J. Org. Chem.*, 1950, **15**, 203.
[3] Clauson-Kaas and Tyle, *Acta Chem. Scand.*, 1952, **6**, 667.
[4] Fraser and Raphael, *J.*, 1950, 2245.
[5] Windaus, Dörries, and Jensen, *Ber.*, 1921, **54**, 2745.
[6] Heath, Lawson, and Rimington, *J.*, 1951, 2215.

converted into δ-benzamidolævulic acid; acid hydrolysis furnished the parent amino-acid hydrochloride.

## Experimental

*N-Benzoylfurfurylamine.*—Benzoyl chloride (80 g.) was added dropwise to a cooled stirred solution of freshly distilled furfurylamine (48·5 g.) in 2N-sodium hydroxide (400 ml.). After a further hour's stirring at room temperature the solid was filtered off, washed with water, and crystallised from methanol or benzene, to give the *amide* (96 g.), m. p. 104° (Found: C, 71·8; H, 5·45; N, 6·75. $C_{12}H_{11}O_2N$ requires C, 71·6; H, 5·5; N, 6·95%).

cis- *and* trans-*2-Benzamidomethyl-2 : 5-dihydro-2 : 5-dimethoxyfuran* (I).—(*a*) A solution of *N*-benzoylfurfurylamine (30·2 g.) and ammonium bromide (2·6 g.) in methanol (260 ml.) was electrolysed in the cell already described [7] for 7 hr. at −12°. The current dropped from 4·0 to 0·6 amp. and the potential difference rose from 14·0 to 16·2 v during the reaction. The cell contents were then poured into sodium methoxide solution (0·7 g. of sodium in 10 ml. of methanol), and the methanol removed under reduced pressure. The residue was triturated with warm dry ether (250 ml.) and the filtered solution allowed to evaporate slowly to small bulk. The resulting solid was filtered off and crystallised from concentrated ethereal solution, to furnish one *diastereoisomer* (I) (10·8 g.), m. p. 109—110° (Found: C, 64·2; H, 6·45; N, 5·35. $C_{14}H_{17}O_4N$ requires C, 63·85; H, 6·5; N, 5·3%). Evaporation of the ether solutions gave the other *isomer* (I) (18·9 g.) as a very viscous oil, b. p. 140°/$10^{-4}$ mm. (Found: C, 63·8; H, 6·4; N, 5·6%).

(*b*) To a stirred solution of *N*-benzoylfurfurylamine (10 g.) in dry methanol (75 ml.) and ether (40 ml.) at −25° was added dropwise a cold solution of bromine (2·8 ml.) in methanol (15 ml.) at such a rate that the temperature never rose above −20°. The mixture was stirred for 1 hr. at −20°, then cooled to −40° and treated with gaseous ammonia, the temperature being kept below −5°. The mixture was allowed to attain room temperature and stirred for a further 30 min.; dry ether (300 ml.) was then added and the precipitated ammonium bromide filtered off. The evaporated filtrate was treated as in (*a*), to yield the solid (3·6 g.) and the liquid (4·1 g.) diastereoisomer (I). The presence of potassium acetate during the addition of the bromine did not materially affect the yield.

*5-Benzamido-4-oxopent-2-enoic Acid* (II).—To a stirred solution of the mixed isomers (I) (5·2 g.) in acetone (60 ml.) at 0° was added a cold solution of chromium trioxide (10 g.) in water (30 ml.) and concentrated sulphuric acid (8·5 ml.) at such a rate that the temperature did not exceed 20°. Stirring was continued at 20° for 1 hr. and the chromium salts were then precipated by addition of acetone (250 ml.). The filtered solid was washed with dry acetone, and the combined filtrates were evaporated under reduced pressure at 20°. Crystallisation of the residue was induced by scratching and completed at 0° in 15 hr. The solid was filtered off, washed with a little ice water, dried, and recrystallised from ethyl acetate, to yield the *keto-acid* (II) (1·2 g.), m. p. 140—142° (decomp.) (Found: C, 61·9; H, 4·75; N, 6·05. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·75; N, 6·0%), $\lambda_{max.}$ 225 and 350 mμ (ε 11,900 and 5400 in EtOH), $\nu_{max.}$ (KBr disc) 690, 950, 1555, 1650, and 1750 $cm.^{-1}$. Attempted aerial oxidation of the furan (I) in the presence of cobalt acetate [8] proved fruitless, as did the action of bromine followed by silver oxide [9] on *N*-benzoylfurfurylamine.

*2-Amino-5-benzamido-4-oxopentanoic Acid* (III).—The keto-acid (II) (5 g.) was dissolved in ammonia (30 ml.; *d* 0·88) and kept at room temperature for 16 hr. The mixture was taken to dryness under reduced pressure and the residual solid triturated with ethanol. Filtration and crystallisation from ethanol–water gave the *amino-acid* (III) (1·8 g.), m. p. 178—179° (decomp.) (Found: C, 57·4; H, 5·85; N, 11·05. $C_{12}H_{14}O_4N_2$ requires C, 57·6; H, 5·65; N, 11·2%). Use of liquid ammonia produced a comparable yield. Hydrolysis with hydrochloric acid and conversion of the resulting dihydrochloride into mercaptohistidine followed exactly previous proceedings.[6] Schotten–Baumann benzoylation of the amino-acid yielded *2 : 5-dibenzamido-4-oxopentanoic acid*, m. p. 214° (from methanol) (Found: C, 64·2; H, 5·3; N, 7·6. $C_{19}H_{18}O_5N_2$ requires C, 64·4; H, 5·1; N, 7·9%). Esterification of this acid with methanolic hydrogen chloride or diazomethane furnished the known methyl ester, m. p. 173° (lit., m. p. 173° [5] and 158° [6]) (Found: C, 65·5; H, 5·5; N, 7·6. Calc. for $C_{20}H_{20}O_5N_2$: C, 65·2; H, 5·5; N, 7·6%).

[7] Clauson-Kaas, Limborg, and Glens, *Acta Chem. Scand.*, 1952, **6**, 531.
[8] McKeever, U.S.P. 2,583,112; *Chem. Abs.*, 1952, **46**, 8670.
[9] Carter, *J. Amer. Chem. Soc.*, 1928, **50**, 2299.

*2-Benzamidomethyltetrahydro-2 : 5-dimethoxyfuran* (V).—A solution of the solid isomer of the dihydrofuran (I) (4·3 g.) in methanol (50 ml.) was hydrogenated in the presence of 10% palladium–charcoal (0·5 g.). Filtration, removal of solvent, and distillation gave the *tetrahydrofuran* (V) (4·1 g.), b. p. 146°/0·1 mm. (Found: C, 63·4; H, 7·15; N, 5·3. $C_{14}H_{19}O_4N$ requires C, 63·4; H, 7·2; N, 5·3%).

*δ-Aminolævulic Acid.*—To a stirred solution of the above tetrahydrofuran (2 g.) in acetone (10 ml.) at 0° was added a solution of chromium trioxide (3·5 g.) in water (10 ml.) and concentrated sulphuric acid (2·8 ml.) at such a rate that the temperature did not rise above 20°. After a further 30 minutes' stirring at room temperature water (30 ml.) was added, the acetone removed under reduced pressure, and the residue extracted first with ether, then with ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated; the resulting solid crystallised from ethyl acetate, to give *δ-benzamidolævulic acid* (VI) (1·7 g.) as prisms, m. p. 118—119° (Found: C, 61·35; H, 5·6; N, 5·9. $C_{12}H_{13}O_4N$ requires C, 61·3; H, 5·6; N, 5·95%). The same compound was obtained by catalytic hydrogenation of the unsaturated keto-acid (II). Esterification with ethanolic hydrogen chloride furnished the known ethyl ester, prisms, m. p. 101° (from aqueous ethanol) (lit.,[5] m. p. 101°). Heating the acid for 4 hr. with concentrated hydrochloric acid gave a quantitative yield of the hydrochloride of δ-aminolævulic acid which crystallised from methanol–ether in needles, m. p. 144—147° (decomp.) as recorded.[2]

We are indebted to The Chemical Society for a Research Grant, and to the Egyptian Government for a Maintenance Award (to A. A. M.).

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THE QUEEN'S UNIVERSITY OF BELFAST.

[*Received, March 7th,* 1958.]