



L-CYSTINE DERIVATIVES. SYNTHESIS OF T-BUTYL AND BENZHYDRYL ESTERS OF NN'-BIS- PHTHALOYL-L-CYSTINE

The preparations of NN'-bis-phthaloyl-L-cystine bis-t-butyl ester and NN'-bis-phthaloyl-L-cystine bis-benzhydryl ester are described. Removal of the N-protecting group from the t-butyl ester gave L-cystine bis-t-butyl ester, but attempts to remove the N-protecting groups from the benzhydryl ester were unsuccessful.

The possibility of preparing *L*-cystine bis-*t*-butyl ester and *L*-cystine bis-benzhydryl ester by removing the *N*-phthaloyl group from the corresponding fully protected derivatives of *L*-cystine has been investigated. *NN'*-Bis-phthaloyl-*L*-cystine bis-*t*-butyl ester has been synthesized by the procedure described by TASCHNER *et al.* [1] for other amino-acids which involves treatment of the *N*-protected amino-acid with *t*-butyl acetate and aqueous perchloric acid. The *N*-phthaloyl group was removed by the action of hydrazine in excess at room temperature, as described in the literature [2] for other derivatives, and *L*-cystine bis-*t*-butyl ester was obtained. *NN'*-Bis-phthaloyl-*L*-cystine bis-benzhydryl ester has been prepared by the procedure applied by HISKEY *et al.* [3] to the synthesis of *N*-phthaloylglycine benzhydryl ester. Attempts to remove the *N*-phthaloyl group from this cystine derivative were unsatisfactory; an excess of hydrazine at room temperature failed to react with the compound which was recovered unchanged while hydrazine in boiling methanol appeared to cause strong decomposition of the compound.

EXPERIMENTAL

The purity of all compounds was confirmed by t.l.c. on kieselgel 60 F₂₅₄, usually in the two systems benzene-chloroform-ethanol (12:12:1) and chloroform-methanol (9:1). Compounds were revealed by the (NH₄)₂SO₄—H₂SO₄ method [4]. Evaporations and concentrations were all carried out under reduced pressure with a rotary evaporator. Extracts were dried over magnesium sulphate. Optical rotations were measured with a Bellingham and Stanley Pepol 66 polarimeter. N.m.r. spectra were recorded at 33 °C with a Perkin-Elmer R32 90 MHz spectrometer. The microanalyses were carried out by Dr. Ilse Beetz (Kronach, Germany).

NN'-Bis-phthaloyl-*L*-cystine was prepared by the procedure of NEFKENS *et al.* [5], using a 5 % excess of *N*-ethoxycarbonylphthalimide and *NN'*-dimethylformamide to improve the solubility of the *L*-cystine.

NN'-Bis-phthaloyl-*L*-cystine bis-*t*-butyl ester. To a suspension of *NN'*-phthaloyl-*L*-cystine (1.00 g; 0.002 mol) in *t*-butyl acetate (20 ml) was added aqueous 60 % perchloric acid (0.086 g; 0.0005 mol). The clear solution obtained was kept at room temperature with occasional stirring for three days. After addition of ethyl acetate (40 ml), the solution was washed (1M aqueous sodium hydrogen carbonate and water), dried, and evaporated,

yielding an oil which solidified on trituration with light petroleum (40–60 °C). Crystallisation from methanol gave a solid material (0.5 g) which by chromatographic analysis was shown to be a mixture of two components. Chromatography on a column of silica gel (7.0 g) and elution with chloroform yielded the diester chromatographically homogeneous (0.36 g; 29 %), m.p. 129–131 °C, $[\alpha]_D^{20}$ –286.4° (c 1.00 in CHCl_3), τ (CDCl_3) 1.90–2.60 (8H, complex, C_6H_4), 4.60–5.00 (2H, t, CH), 6.39–6.70 (4H, d, CH_2), 8.30–8.70 (18H, s, Bu^t) (Found: C, 58.5; H, 5.7; N, 4.4; S, 10.1. $\text{C}_{30}\text{H}_{32}\text{N}_2\text{O}_8\text{S}_2$ requires C, 58.8; H, 5.3; N, 4.6; S, 10.5).

L-Cystine bis-t-butyl ester. *NN'*-bis-phthaloyl-*L*-cystine bis-*t*-butyl ester (0.612 g, 0.001 mol) was dissolved in ethanol (2.5 ml) containing hydrazine hydrate (0.125 g; 0.0025 mol). The yellow solution was stirred at room temperature for 18 h during which time the phthalazine precipitated out. The solid was filtered and the filtrate was evaporated to dryness. The oily residue obtained was dissolved in a mixture of ether (15 ml) and aqueous 1*M*-sodium hydrogen carbonate (5 ml). The organic layer was washed with saturated aqueous sodium chloride, dried and evaporated to yield a chromatographically homogeneous oil (0.15 g; 43 %) which was chromatographically identical with a sample of *L*-cystine bis-*t*-butyl ester obtained by direct esterification of *L*-cystine [6].

NN'-Bis-phthaloyl-*L*-cystine bis-benzhydryl ester. To a solution of benzhydrol (1.93 g; 0.0104 mol) in dry benzene was added *NN'*-bis-phthaloyl-*L*-cystine (2.50 g; 0.005 mol) and *p*-toluenesulfonic acid monohydrate (0.09 g; 0.0005 mol). The mixture was refluxed for 24 h under a Dean-Stark trap. A small precipitate was filtered and the cooled filtrate was extracted successively with aqueous 0.1*M* — sodium hydrogen carbonate and saturated aqueous sodium chloride, dried, and evaporated to dryness. The residue was triturated with light petroleum

(b.p. 40–60 °C), giving a solid (2.8 g; 67 %) m.p. 76 °C (softening from 64 °C). Two recrystallisations from ethyl acetate-light petroleum (b.p. 40–60 °C) followed by another two from ethyl acetate-ethanol, gave the pure ester, m.p. 112–114 °C (2.1 g; 55 %), $[\alpha]_D^{20}$ –210.0° (c 1.00 in CHCl_3), τ (CDCl_3) 2.20–2.40 (8H, complex, C_6H_4), 2.40–2.78 (20H, complex, Ph), 3.10–3.20 (2H, s, CH), 4.42–4.80 (2H, t, CH), 6.30–6.60 (4H, d, CH_2) (Found: C, 68.7; H, 4.4; N, 3.5; S, 7.6. $\text{C}_{48}\text{H}_{36}\text{N}_2\text{O}_8\text{S}_2$ requires C, 69.2; H, 4.4; N, 3.4; S, 7.7).

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