322. *The Reactions of Substituted Maleimides with Thiols.*

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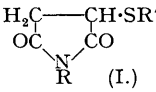
The condensation of *N*-ethyl- and *N*-phenyl-maleimide with mercaptoacetic acid and with *o*-mercaptobenzoic acid gives products of structure (I) in good yield. Desulphurisation by Raney nickel has given the expected degradation products.

It has been reported (Friedmann, Marrian, and Simon-Reuss, *Brit. J. Pharmacol.*, 1949, **4**, 105) that the mixing of equimolar neutral solutions of certain maleimides and of mercaptoacetic acid or glutathione at room temperature leads to the rapid removal of free thiol groups from solution.

Whereas it has been shown by Morgan and Friedmann (*Biochem. J.*, 1938, **32**, 733) that under similar conditions the reaction of such thiols with maleic acid is slow and incomplete (some 50% after 5 hours at 37°), the reaction of substituted maleimides with thiols is substantially complete in ½—2 minutes. In view of the interesting antimitotic activity shown by certain imides on cultures of chick fibroblasts (Friedmann, Marrian, and Simon-Reuss, *loc. cit.*) it was considered of interest to isolate and characterise some of the condensation products, especially since the thiol adducts of maleic acid still show some of the antimitotic activity of the parent unsubstituted maleic acid (*idem*, *Brit. J. Pharmacol.*, 1948, **3**, 335).

The imides used in this investigation were *N*-ethyl- and *N*-phenyl-maleimide (being more readily available than the parent compound), and the condensations with mercaptoacetic acid and with *o*-mercaptobenzoic acid were investigated in each case. Addition products of structure



(I.)

(*a*) R = Et; R′ = CH_2·CO_2H.
(*b*) R = Et; R′ = C_6H_4·CO_2H.
(*c*) R = Ph; R′ = CH_2·CO_2H.
(*d*) R = Ph; R′ = C_6H_4·CO_2H.

(I) were isolated in good yield. Raney nickel in boiling alcohol caused fission of the S–C bonds, giving a substituted succinimide and acetic or benzoic acid, although often in low yield. From (I*a*) and (I*b*) the low-melting *N*-ethylsuccinimide was identified by alkaline hydrolysis to succinic acid.

Experimental.

N-Ethylmaleimide.—An adaptation of the method of Piutti (*Gazzetta*, 1888, **18**, 483) proved reliable. *N*-Ethylmaleamic acid (10 g.) and medicinal paraffin (20 c.c.) were heated to 200° in a metal-bath. The lachrymatory distillate crystallised and was pressed on a porous plate and redistilled, to give 3·8 g. of the imide, m. p. 44°.

N-Phenylmaleimide was prepared by an adaptation of the method of Auwers (*Annalen*, 1899, **309**, 346). An intimate mixture of *N*-phenylmaleamic acid (5 g.) (Anschutz and Wurtz, *Annalen*, 1887, **239**, 140) and phosphoric oxide (5 g.) was packed into a 25-c.c. distilling flask with glass wool, attached to an air-condenser and receiver, and evacuated at the water pump. The flask was immersed in a metal-bath at 100° and heated fairly rapidly to 250°; during this operation a yellow oil distilled, which quickly solidified (2·2 g.). Larger batches gave much lower yields. The crude distillate crystallised from 50% aqueous alcohol (18 c.c.) in long thin prisms (1·45 g.), m. p. 86—88°.

N-Ethyl-α-carboxymethylthiosuccinimide.—*N*-Ethylmaleimide (1·25 g.) in water (100 c.c.) was treated with a solution of mercaptoacetic acid (0·92 g., 1 mol.), neutralised to phenolphthalein with N-sodium hydroxide (*ca.* 8 c.c.), in water (50 c.c.). After 30 minutes at room temperature, the clear solution was evaporated *in vacuo* at 60—70°, and the residual glass dissolved in water (15 c.c.), acidified to Congo-red with 5N-sulphuric acid, and extracted continuously with ether. The extract was dried (Na_2SO_4) and evaporated, finally *in vacuo* at 60°. The oily residue crystallised on treatment with a little alcohol (yield, 2·24 g., 100%). Recrystallisation from dry benzene gave colourless prisms (2·0 g.), m. p. 88—89°. For analysis, the *compound* was recrystallised from dry benzene to m. p. 90—91° (Found, in material dried at room temperature: C, 44·1, 44·3; H, 5·0, 4·6; N, 6·8, 6·9. $C_8H_{11}O_4NS$ requires C, 44·2; H, 5·1; N, 6·4%).

N-Ethyl-α-o-carboxyphenylthiosuccinimide.—*N*-Ethylmaleimide (125 mg.) and *o*-mercaptobenzoic acid (154 mg., 1 mol.) in alcohol (4 c.c.) were set aside overnight at room temperature. On gentle scratching, crystallisation ensued. The *product*, after filtration and washing with alcohol, formed

microcrystalline prisms (150 mg.; 54%), which recrystallised from methanol in almost colourless prisms, m. p. 161·5—163·5° (Found, in material dried at 80°: C, 55·7; H, 4·8; N, 5·4. $C_{13}H_{13}O_4NS$ requires C, 55·9; H, 4·7; N, 5·0%).

N-Phenyl-α-carboxymethylthiosuccinimide.—*N*-Phenylmaleimide (176 mg.), suspended in water (5 c.c.), was treated with a solution of mercaptoacetic acid (92 mg., 1 mol.) in water (1 c.c.) and N-sodium hydroxide (1 c.c.). The imide quickly dissolved when the mixture was shaken, to give a colourless solution. After 15 minutes, a trace of insoluble material was filtered off, and the filtrate acidified with 5N-sulphuric acid. A colourless crystalline solid was precipitated, which was filtered off and washed with a little water. The *product* crystallised from water (3 c.c.) in colourless microcrystalline prisms, m. p. 153·5—154·5°. For analysis, the compound was again recrystallised from water; m. p. unchanged (Found, in material dried at 80°: C, 54·1; H, 4·1; N, 5·7; equiv., 259. $C_{12}H_{11}O_4NS$ requires C, 54·3; H, 4·2; N, 5·3%; equiv., 265·3).

N-Phenyl-α-o-carboxyphenylthiosuccinimide.—This *imide*, prepared as was its *N*-ethyl analogue (above) formed colourless prisms, m. p. 179·5—182° [300 mg. (90%) from 176 mg. of phenylmaleimide]. Recrystallisation from alcohol (4 c.c.) gave colourless prisms, m. p. 179—180° (Found, in material dried at 80°: C, 62·4; H, 4·1; N, 4·1. $C_{17}H_{13}O_4NS$ requires C, 62·4; H, 4·0; N, 4·3%). The substance was prepared in lower yield by the method described for the previous compound.

Desulphurisation of N-Ethyl-α-carboxymethylthiosuccinimide.—The compound (1·0 g.), Raney nickel (" 15 c.c."), and alcohol (*ca.* 40 c.c.) were heated under reflux for 19 hours, N-sodium hydroxide added until the solution was alkaline to phenolphthalein, and the nickel filtered off through " Hyflo Supercel." The alcoholic solution was diluted with water, and the alcohol removed *in vacuo* at 60°. The residue was dissolved in a little water and continuously extracted with ether overnight. (*a*) The aqueous phase was acidified to Congo-red with 5N-sulphuric acid and, after addition of an equal volume of xylene, distilled, with the addition when necessary of equal volumes of water and xylene, until the distillate was no longer acid. 4·8 c.c. of N-sodium hydroxide was required to neutralise the distillate. The solution of the sodium salt was evaporated to dryness, dissolved in a little alcohol with the addition of a little water, clarified with charcoal, made just acid with hydrochloric acid, and heated under reflux with *p*-phenylphenacyl bromide (0·14 g.) for 2 hours. Some inorganic material separated on cooling, followed by the ester, m. p. 107—108° (40 mg.), undepressed on admixture with that of acetic acid. (*b*) The ethereal phase was dried (Na_2SO_4) and evaporated, and the residue hydrolysed by boiling 5N-sodium hydroxide (10 c.c.; 2 hours; basic fumes evolved). The aqueous solution was extracted thoroughly with ether, acidified with 10N-sulphuric acid, and extracted continuously with ether. The dried and evaporated extract gave 0·22 g. of yellow crystals which were identified, after recrystallisation from water, as succinic acid by m. p., mixed m. p., and by equivalent weight (Found: 59·9. Calc. for $C_4H_6O_4$: 59·0).

Desulphurisation of α-o-Carboxyphenyl-N-ethylthiosuccinimide.—The product of desulphurisation (performed exactly as above) was freed from the nickel by continuous extraction with hot alcohol and, after evaporation of the extract, partitioned between ether and aqueous potassium hydrogen carbonate. From the ether succinic acid was isolated after hydrolysis, and from the alkaline layer benzoic acid, which was purified by sublimation and identified by m. p. and mixed m. p.

Desulphurisation of N-Phenyl-α-carboxymethylthiosuccinimide.—This reaction was carried out as above. The ethereal extract eventually furnished a small yield of succinanil (Menschutkin, *Annalen*, 1872, **162**, 166), identified, after recrystallisation from alcohol, by its m. p. (151·5—152·5°), not depressed by an authentic specimen. The hydrogen carbonate phase gave a very slightly acid distillate with xylene, in agreement with the small yield of the other desulphurisation product.

Desulphurisation of N-Phenyl-α-o-carboxyphenylthiosuccinimide.—The reaction was carried out as above. The product was partitioned between chloroform and aqueous potassium hydrogen carbonate. From the former solvent was isolated succinanil, m. p. and mixed m. p. 151—153° after recrystallisation from alcohol, and from the latter benzoic acid, purified by sublimation, m. p. and mixed m. p. 119—120·5°.

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