

190. *A New Synthesis of 1-Amino-4-methylthioxanthone and of Miracil D.*

By D. LL. HAMMICK and D. C. MUNRO.

Previous syntheses of these compounds have been carried out *via* 1-chloro-4-methylthioxanthone as an intermediate. The preparation of the latter compound is accompanied by formation of considerable amounts of the 4-chloro-1-methyl isomer.* The synthesis described here avoids the formation of such isomers, and leads more directly to the formation of 1-amino-4-methylthioxanthone (VI), which may be readily converted into Miracil D (VII) by reaction with 2-diethylaminoethyl chloride.

THE synthesis of Miracil D (1-2'-diethylaminoethylamino-4-methylthioxanthone hydrochloride) (VII) by the method of Mauss (*Ber.*, 1948, **81**, 19) requires the intermediate 1-chloro-4-methylthioxanthone. This substance has hitherto been prepared by the condensation of *o*-mercaptobenzoic acid with *p*-chlorotoluene, and is then accompanied by the isomeric 4-chloro-1-methylthioxanthone (40%) (Ullmann and von Glenck, *Ber.*, 1916, **49**, 2491).* The conversion of 1-chloro-4-methylthioxanthone into 1-amino-4-methylthioxanthone (VI) was brought about by these authors by interaction with toluene-*p*-sulphonamide, followed by hydrolysis.

During an investigation of the reactions of Miracil D and possible biological degradation products, a synthesis of such compounds was sought which avoided the formation of structural isomers and led more directly to the formation of 1-amino-4-methylthioxanthone. We have carried out such a synthesis, based initially on the preparation of 1-aminothioxanthone by F. Meyer (*Ber.*, 1909, **42**, 3064). Our sequence is shown in the scheme on p. 1078.

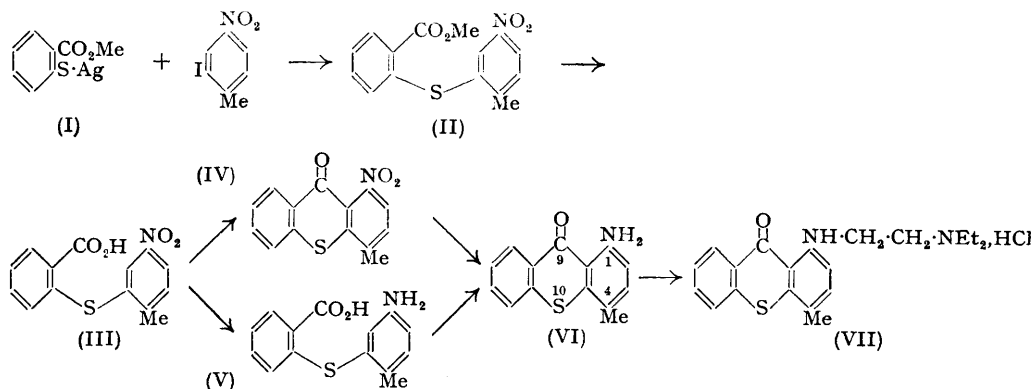
Methyl *o*-mercaptobenzoate, treated with ammoniacal silver nitrate in ethanol, readily gave an insoluble silver compound, presumably (I). This compound is stable at room temperature and is resistant to aerial oxidation in refluxing xylene. It is decomposed by concentrated hydrochloric acid. With 2-iodo-4-nitrotoluene in refluxing xylene, 2'-carbomethoxy-2-methyl-5-nitrodiphenyl sulphide (II) is formed, with elimination of silver iodide.

This reaction between 2-iodo-4-nitrotoluene and the silver compound appears to be

* *Added in Proof.*—Since this paper was submitted a synthesis of Miracil D *via* 1-chloro-4-methylthioxanthone and avoiding the formation of 4-chloro-1-methylthioxanthone has been described by Sharp (*J.*, 1951, 2961).

catalysed both by copper bronze and by cuprous iodide. Further investigations are being carried out on its applications.

The ester (II) may be hydrolysed by ethanolic sodium hydroxide below about 50°; above this temperature the formation of dark intractable material takes place.



Of three methods for the formation of the thioxanthone ring system, two were investigated for preparative purposes. The first involved ring closure of 2'-carboxy-2-methyl-5-nitrodiphenyl sulphide (III) by a Friedel-Crafts reaction using thionyl chloride and ferric chloride, subsequent reduction giving 1-amino-4-methylthioxanthone (VI). The second method, reduction of the nitro-acid to the corresponding amino-acid (V) followed by ring closure by the action of phosphoric acid was found to be more satisfactory in that the intermediate compound was more readily purified.

On being gently heated with acetic anhydride, 5-amino-2'-carboxy-2-methyldiphenyl sulphide (V) forms the normal acetyl derivative together with small amounts of 1-acetamido-4-methylthioxanthone. The former product is unchanged when heated alone or on dissolution in boiling acetic anhydride, but warm sulphuric acid causes the formation of 1-acetamido-4-methylthioxanthone.

1-Amino-4-methylthioxanthone (VI) reacts readily with 2-diethylaminoethyl chloride to form Miracid D (VII), and a convenient purification from the starting material is provided by the insolubility of the hydrochloride of 1-amino-4-methylthioxanthone in mixtures of ethanol and water, and in acetone.

EXPERIMENTAL

(All m. p.s are uncorrected.)

Methyl o-Mercaptobenzoate.—This was prepared from the acid by methanol and hydrogen chloride (Gatterman, *Ber.*, 1899, **32**, 1150), in 74% yield; it had b. p. 135—136°/15 mm.

Silver compound. The ester (20.5 g.) in ethanol (100 ml.) was added to a solution of silver nitrate (20 g.) in water (50 ml.), ammonia solution (20 ml.; d 0.880), and ethanol (200 ml.). The precipitate was filtered off, washed by stirring in ethanol (300 ml.), again filtered off, and dried in air at 100°. The silver derivative (yield, 96.5%) is a lemon-yellow powder, insoluble in water and in organic solvents, decomposed by hydrogen sulphide and by concentrated hydrochloric acid. It slowly softens with decomposition at 250° (Found: C, 34.95; H, 2.8; Ag, 39.7. $C_8H_7O_2SAg$ requires C, 34.9; H, 2.6; Ag, 39.2%).

2-Iodo-4-nitrotoluene.—2-Amino-4-nitrotoluene (30 g.) was diazotised and treated with potassium iodide (Willgerodt and Kok, *Ber.*, 1908, **41**, 2077). The crude product was taken up in ether, washed with sodium hydroxide solution and with water, and dried (Na_2SO_4). Removal of ether was followed by distillation at 15 mm. from an oil-bath at 210—230°. The distillate, b. p. 164—165°/15 mm., solidified, was washed with ether, filtered off, and dried. Further amounts were recovered from the ether after washing to remove traces of iodine, and also by exhaustive steam-distillation of the distillation residue. The yield was 40 g. (78%) and the m. p. 56° (Willgerodt and Kok give m. p. 58°). Distillation at reduced pressure enabled a tedious steam-distillation to be avoided; but attempted distillation of the crude material without the preliminary ether-treatment sometimes led to explosive decomposition.

Diphenyl Sulphide Formation.—The foregoing silver compound (40 g.), 2-iodo-4-nitrotoluene (38 g.), copper bronze (5 g.), and xylene (500 ml.) were heated under reflux for 6 hours. On cooling, the silver iodide was removed by filtration and washed with hot xylene. The xylene was removed by distillation followed by steam-distillation, and the solid residue recrystallised from benzene and ligroin (yield, 29.3 g., 67%; on 1-g. scale, 79%). After three recrystallisations from benzene and cyclohexane, 2'-carbomethoxy-2-methyl-5-nitrodiphenyl sulphide appeared as colourless prisms, m. p. 119°, soluble in benzene, less so in ligroin or cyclohexane, sparingly soluble in ethanol (Found: C, 60.0; H, 4.6; N, 4.4; S, 10.55. $C_{15}H_{13}O_4NS$ requires C, 59.5; H, 4.3; N, 4.6; S, 10.55%).

Hydrolysis. This methyl ester (32.0 g.) was dissolved in ethanol (1 l.) at 60° and cold 2% sodium hydroxide solution (300 ml.) added. After 24 hours, the liquid was decanted from unchanged ester; water (2 l.) was added and then excess of concentrated hydrochloric acid. The precipitated acid was filtered off, washed with water, and dried in air at 100°. The whole process was repeated with unchanged ester. The total yield was 29.6 g. (97%). Recrystallised three times from ethanol, the acid formed colourless plates, m. p. 187°, soluble in ethanol, benzene, glacial acetic acid, or dilute aqueous alkali (Found: C, 58.1; H, 3.8; N, 4.5. $C_{14}H_{11}O_4NS$ requires C, 58.2; H, 3.4; N, 4.5%).

5-Amino-2'-carboxy-2-methyldiphenyl cyclohexane.—The nitro-acid (20 g.) was dissolved in water (300 ml.), ethanol (140 ml.), and ammonia solution (100 ml.; d 0.880). The whole was added to a solution of ferrous sulphate hydrate (140 g.) in water (800 ml.) at 100° and stirred. After 5 minutes the suspension was filtered, and the residue washed with dilute ammonia solution. The combined filtrates were boiled to remove ethanol and ammonia, and an excess of glacial acetic acid added; the amino-acid (16 g., 89%) crystallised. This compound is soluble in acids and alkalis, readily soluble in ethanol, methanol, and benzene. Recrystallisation from *n*-propanol gave colourless prisms, m. p. 186.5° (Found: C, 64.4; H, 4.7; N, 5.7. $C_{14}H_{13}O_2NS$ requires C, 64.8; H, 5.05; N, 5.4%).

5-Acetamido-2'-carboxy-2-methyldiphenyl Sulphide.—The amino-acid (0.80 g.) was dissolved in acetic anhydride (3.0 ml.) with anhydrous sodium acetate (*ca.* 30 mg.) and heated gently on a water-bath for 10 minutes. Water (15 ml.) was added and heating continued; on cooling, an oil separated which crystallised when rubbed with ethyl acetate. After three recrystallisations from ethanol, the acetyl compound appeared as white crystals, m. p. 208°, soluble in alcohols and in dilute aqueous alkali (Found: N, 4.4. $C_{18}H_{15}O_3NS$ requires N, 4.65%).

This compound (55 mg.) was refluxed with acetic anhydride (2.5 ml.) for 3½ hours: no ring closure took place. The colourless precipitate obtained on heating with water was completely alkali-soluble.

The acetyl compound (50 mg.) dissolved in warm concentrated sulphuric acid (1 ml.) to form a carmine-red solution. After 1 minute, addition of water precipitated a yellow solid which, recrystallised from benzene, had m. p. 178° (with 1-acetamido-4-methylthioxanthone, mixed m. p. 179°).

4-Methyl-1-nitrothioxanthone.—2'-Carboxy-2-methyl-5-nitrodiphenyl sulphide (27 g.) in pure dry benzene (1.6 l.) was heated with purified thionyl chloride (30 ml.) under reflux. After 3½ hours, hydrogen chloride evolution had ceased; anhydrous ferric chloride (20 g.) was added and, after 10 minutes, heating was resumed for 5 hours. After cooling the benzene solution contained yellow crystals of 4-methyl-1-nitrothioxanthone (9.5 g.), and its evaporation gave a further 1.9 g. The tarry material remaining was boiled with glacial acetic acid, giving a brown powder. This was either purified by recrystallisation, twice from cyclohexanone and once from acetic acid, or was used directly for reduction. The total yield was 18.2 g. (72%) of pale yellow plates, m. p. 271°, sparingly soluble in benzene and glacial acetic acid, more soluble in cyclohexanone (Found: C, 62.1; H, 3.2; N, 4.5; S, 11.6. $C_{14}H_9O_3NS$ requires C, 62.0; H, 3.3; N, 5.2; S, 11.8%).

1-Amino-4-methylthioxanthone.—(a) 4-Methyl-1-nitrothioxanthone (13 g.), suspended in ethanol (30 ml.), was treated with a solution of ferrous sulphate (hydrated; 100 g.) in water (120 ml.) and heated to boiling. A solution of ammonia (50 ml.; d 0.880) in water (100 ml.) was added, and the mixture heated in boiling water for 5 hours, then filtered, and the solid residue dried at 120°. Extraction with ethanol (250 ml.) (Soxhlet), concentration, and cooling, yielded red needles, m. p. 133° (from ethanol; charcoal) (9.2 g., 79%) (Ullmann and von Glenck, *loc. cit.*, give m. p. 134°).

(b) To syrupy phosphoric acid (50 ml.; d 1.75) in a Pyrex flask at 175° 5-amino-2'-carboxy-2-methyldiphenyl sulphide (5.0 g.) was added slowly during 10 minutes, and the solution heated for a further 15 minutes. On cooling, the solution was poured into water (500 ml.), excess of

ammonia solution added, and the precipitated amine filtered off. On recrystallisation from ethanol, with charcoal, 3.83 g. (72%) were obtained.

Gaseous hydrogen chloride was passed into a hot solution of the amine in ethanol, the *hydrochloride* crystallising as colourless plates, hydrolysed by, and insoluble in, water, sparingly soluble in ethanol. Recrystallised from ethanol, this had m. p. 218° (Found: N, 5.1; S, 12.0; Cl, 13.4. $C_{14}H_{11}ONS, HCl$ requires N, 5.0; S, 11.55; Cl, 12.8%).

1-Acetamido-4-methylthioxanthone.—The amine (0.5 g.) and acetic anhydride (2.0 g.) were heated at 100° for 10 minutes, water (5 ml.) was added, and the mixture heated. The solid was filtered off, dried, and recrystallised twice from benzene, then melting at 180—181° (Ullmann and von Glenck, *loc. cit.*, give m. p. 180—181°).

Diethylaminoethyl Chloride.—Diethylaminoethanol was converted into diethylaminoethyl chloride hydrochloride by Gough and King's method (*J.*, 1928, 2436). The base was released with saturated potassium carbonate solution, ether-extracted, and distilled, and had b. p. 45°/12 mm.

Miracil D.—1-Amino-4-methylthioxanthone (2.0 g.) and diethylaminoethyl chloride (1.5 g.) were heated together in an oil-bath at 150° for 1 hour (cf. Mauss, *loc. cit.*, p. 28). The solid was dissolved in hot ethanol (25 ml.), and concentrated hydrochloric acid (25 ml.) added, followed by water (50 ml.). After 24 hours, the crystals of 1-amino-4-methylthioxanthone hydrochloride were filtered off. The filtrate was treated with sodium hydroxide solution to pH about 6 and evaporated to dryness at 30 mm. The residue was treated with ethanol (100 ml.), filtered to remove sodium chloride, and evaporated to dryness. Heating with ethanol (20 ml.), filtering, and cooling yielded crystals of Miracil D (0.77 g.). Further amounts (0.51 g.) were recovered from the mother-liquor by evaporation, treatment with acetone, filtration, evaporation, and crystallisation from ethanol. Recrystallised twice from methanol and ether, the substance appeared as a bright yellow powder, m. p. 192° (Mauss, *loc. cit.*, gives m. p. 195—196°).

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DYSON PERRINS LABORATORY, UNIVERSITY OF OXFORD.
THE ROYAL TECHNICAL COLLEGE, GLASGOW.

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