657. *A New Synthesis of Lucanthone (Miracil D, Nilodin).**

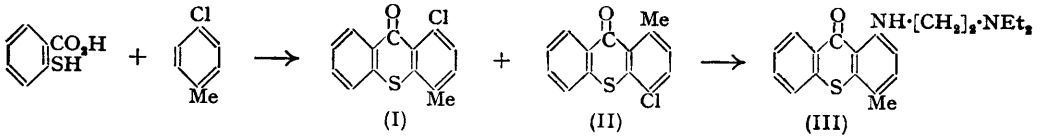
By Thomas M. Sharp.

A synthesis of lucanthone B.P. (1-2′-diethylaminoethylamino-4-methylthiaxanthone, Miracil D, Nilodin) has been developed which avoids the wasteful production of the non-reactive 4-chloro-1-methylthiaxanthone. Some variants of lucanthone with modified basic side-chains are described.

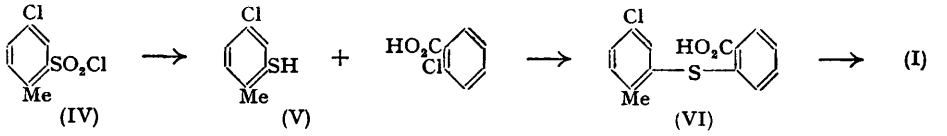
During the late war Mauss synthesized a long series of basic-substituted xanthones and thiaxanthones, some of which were found by Kikuth and Gönnert to be effective in the cure of schistosomiasis in experimental animals (*B.I.O.S. Final Report*, No. 116, Item No. 24; *C.I.O.S. Report*, Item No. 24, File No. XXV–54; Mauss, *Chem. Ber.*, 1948, **81**, 19; Kikuth, Gönnert, and Mauss, *Naturwiss.*, 1946, **33**, 253). One of the compounds, 1-2′-diethylaminoethylamino-4-methylthiaxanthone (lucanthone B.P., Miracil D, Nilodin) is now used clinically

* Patents pending.

in the treatment of human schistosomiasis caused by *Schistosoma haematobium*. For the synthesis of lucanthone, Mauss heated 2-diethylaminoethylamine with the inseparable mixture of 1-chloro-4-methyl- (I) and 4-chloro-1-methyl-thiaxanthone (II) which Ullmann and Glenck (*Ber.*, 1916, **49**, 2487) had obtained by the Davis–Smiles condensation (*J.*, 1910, **97**, 1290) of thiosalicylic acid with *p*-chlorotoluene; the labile chlorine atom in (I) was replaced while (II) remained unchanged. The process is simple but the formation of the unreactive isomeride (II) involves the waste of about half the material.



A new synthesis has now been developed in which *p*-chlorotoluene is chlorosulphonated to 5-chloro-2-methylbenzenesulphonyl chloride (IV) (anilide, m. p. 144°), identical with the compound obtained by Wynne and Bruce (*J.*, 1898, **73**, 762) *via* the sulphonic acid; this is then reduced to the thiol (V). Chien and Kuan (*J. Chinese Chem. Soc.*, 1936, **4**, 355) have described a compound, m. p. 80—81°, to which they ascribe structure (V). We find the thiol to be a liquid (b. p. 111°/17 mm.) at room temperature, quantitatively oxidized by iodine to the disulphide, m. p. 80—81°, which is clearly identical with the compound described by the Chinese workers as the thiol. The thiol (V) condenses readily with *o*-chlorobenzoic acid, to yield 2′-carboxy-5-chloro-2-methyldiphenyl sulphide (VI) which readily undergoes ring closure with sulphuric acid to 1-chloro-4-methylthiaxanthone (I). The final stage to (III) is accomplished without difficulty by the usual method.



It is interesting that the melting point of the acid (VI) is the same as that of the isomeric 2′-carboxy-2-chloro-5-methyldiphenyl sulphide obtained by Ullmann and Glenck by an unambiguous route, and that the melting point of 1-chloro-4-methyl- is the same as that of 4-chloro-1-methyl-thiaxanthone (I and II). The melting point of a mixture of the chloromethylthiaxanthones is higher than that of either individual compound, which suggests the formation of a molecular complex and perhaps explains the failure of Ullmann and Glenck to effect a separation of the isomerides by fractional crystallization.

Synthesis of the acid (VI) has also been effected by condensation of the thiol (V) with diazotized anthranilic acid (cf. Ziegler, *Ber.*, 1890, **23**, 2471).

Compounds containing a few variants of the basic side-chain of (III) have been prepared; these were found by Mr. O. D. Standen to be less active in experimental schistosomiasis than lucanthone.

Experimental.

4-Chlorotoluene-2-sulphonyl Chloride (IV) [With M. M. Coombs].—*p*-Chlorotoluene (75 g.) in dry chloroform (375 c.c.) was cooled to 10—12° in absence of moisture and stirred while chlorosulphonic acid (207 g.) was added at such a rate that the temperature did not exceed 20° (15 minutes). Stirring was continued for ½ hour at 25° and a further ½ hour at 50°. After cooling, the product was stirred on to ice (750 g.), the chloroform layer dried (Na_2SO_4), and the solvent removed. The residue was distilled under reduced pressure and the fraction, b. p. 154°/16 mm., m. p. 24°, collected; the yield was 88·7—103 g. (66·6—77·8%) (Found: S, 14·5. Calc. for $C_7H_6O_2SCl_2$: S, 14·2%). The anilide, m. p. 143—145°, is identical with that prepared by Wynne and Bruce (*loc. cit.*).

5-Chloro-2-methylthiophenol (V).—Sulphuric acid (98%; 138 g.) was added to 450 c.c. of ice-water, and molten 4-chlorotoluene-2-sulphonyl chloride (45 g.) added with vigorous stirring. The mixture was cooled rapidly to −10° to −15° and zinc dust (78·5 g.) added in portions, the temperature being kept below −5°. Stirring was continued for 2 hours at room temperature and the mixture was finally heated gently under reflux for a further 2 hours. *5-Chloro-2-methylthiophenol* was isolated by steam-distillation as a heavy colourless oil, b. p. 114—117°/17 mm. (29·9 g., 94·2%) (Found: C, 52·8; H, 4·7; S, 20·2. C_7H_7ClS requires C, 53·1; H, 4·5; S, 20·25%). 0·1558 G. required 9·8 c.c. of 0·1013N-iodine. Oxidation of 2-SH to S–S requires 9·7 c.c.; the oxidation product had m. p. 80—81°.

2′-Carboxy-5-chloro-2-methyldiphenyl Sulphide (IV) [with A. G. Turner].—(*a*) 5-Chloro-2-methylthiophenol (7·9 g.), *o*-chlorobenzoic acid (7·7 g.), anhydrous potassium carbonate (6·92 g.), benzyl

alcohol (80 c.c.), copper powder (0·5 g.), and potassium iodide (1·0 g.) were stirred and heated under reflux for 5 hours. After cooling, the solution was filtered, diluted with ether (300 c.c.), and extracted with 1% aqueous sodium hydroxide. The combined extracts were decolorized with charcoal, filtered hot, and acidified; *2′-carboxy-5-chloro-2-methyldiphenyl sulphide* separated and was filtered off from the hot solution. After crystallization from toluene it formed colourless felted needles, m. p. 195—197° (12·28 g., 87·7%) (Found: C, 60·6; H, 4·0. $C_{14}H_{11}O_2SCl$ requires C, 60·3; H, 4·0%). If a smaller quantity of potassium carbonate is used the product consists largely of the benzyl ester of the above acid.

(*b*) Anthranilic acid (2·74 g.), dissolved in hot sodium hydroxide solution (10%; 8·5 c.c.), was treated with solid sodium nitrite (1·54 g.), and the solution cooled to 5° and added slowly to 2N-hydrochloric acid (22 c.c.) at 0°. Excess of nitrous acid was removed with urea, and the cold diazo-solution added to 5-chloro-2-methylthiophenol (3·16 g.) in aqueous ammonia (*d* 0·885; 9·5 c.c.) diluted with an equal volume of water, the temperature being kept below 20°. The yellow solid formed during the addition slowly decomposed with evolution of nitrogen. After about an hour the orange solution was filtered off from a small amount of 5 : 5′-dichloro-2 : 2′-dimethyldiphenyl disulphide (m. p. 80—82°) and acidified. A light brown precipitate of 2′-carboxy-5-chloro-2-methyldiphenyl sulphide separated, which after crystallisation had m. p. 195—197°, identical with that obtained under (*a*). The yield was 50%.

1-*Chloro-4-methylthiaxanthone* (I).—2′-Carboxy-5-chloro-2-methyldiphenyl sulphide (8·2 g.) in sulphuric acid (98%; 25 c.c.) was heated on a water-bath for 75 minutes. The clear red-brown solution, after cooling, was stirred on to ice (250 g.), and the precipitated 1-*chloro-4-methylthiaxanthone* was collected, extracted with dilute ammonia, refiltered, washed, and dried. After crystallisation from alcohol it forms pale yellow needles, m. p. 143—145° (6·92 g., 90·2%) (Found: C, 64·5; H, 3·7. $C_{14}H_9OSCl$ requires C, 64·5; H, 3·5%). Ullmann and Glenck (*loc. cit.*) by distillation and fractional crystallisation of the mixture of 1-chloro-4-methyl- and 4-chloro-1-methyl-thiaxanthone obtained a substance, m. p. 150—150·5°, which they thought to be substantially pure 1-chloro-4-methylthiaxanthone. We now find that a mixture of the 1-chloro-4-methyl- (obtained above) and 4-chloro-1-methyl-thiaxanthone (obtained by treatment of Ullmann and Glenck's mixture with 2-diethylaminoethylamine as the non-reactive component) melts at 150°.

1-2′-*Diethylaminoethylamino-4-methylthiaxanthone* (III).—1-Chloro-4-methylthiaxanthone (6·92 g.), treated by Mauss's method (*loc. cit.*) with 2-diethylaminoethylamine gave a product completely soluble in dilute acetic acid, from which 8·45 g. of crude base were obtained. It formed yellow crystals from alcohol, m. p. 64—65°, and gave a hydrochloride, fine yellow needles, m. p. 196—197° in agreement with the constants recorded by Mauss. The *salicylate* forms stout prisms (from alcohol), m. p. 100—103° (Found: S, 6·7. $C_{20}H_{24}ON_2S,C_7H_6O_3$ requires S, 6·85%). The *methylenebishydroxynaphthoate* has no characteristic sharp m. p.; it decomposes from about 120° onwards (Found: C, 70·7; H, 5·8; S, 5·75. $C_{20}H_{24}ON_2S,\frac{1}{2}C_{23}H_{16}O_6$ requires C, 70·4; H, 6·0; S, 6·0%). The *methiodide*, orange needles from methanol, has m. p. 237° (decomp.) (Found: C, 52·3; H, 5·3; I, 26·2, 26·4. $C_{20}H_{24}ON_2S,CH_3I$ requires C, 52·3; H, 5·4; I, 25·2%). The *ethiodide* forms fine orange needles (from water), m. p. 210° (decomp.) (Found: C, 52·9; H, 5·4; I, 25·2. $C_{20}H_{24}ON_2S,C_2H_5I$ requires C, 53·2; H, 5·9; I, 25·6%).

1-2′-*Dimethylaminoethylamino-4-methylthiaxanthone*.—The *hydrochloride*, prepared in a similar manner from 1-chloro-4-methylthiaxanthone and 2-dimethylaminoethylamine, forms yellowish-orange needles (from alcohol), m. p. 233—235° (Found: C, 61·9; H, 5·85; S, 9·0; Cl, 10·2. $C_{18}H_{20}ON_2S,HCl$ requires C, 62·0; H, 6·1; S, 9·2; Cl, 10·2%).

1-2′-*Di*-n-*butylaminoethylamino-4-methylthiaxanthone*.—The *hydrochloride* from 1-chloro-4-methylthiaxanthone and 2-di-*n*-butylaminoethylamine (Bloom, Breslow, and Hauser, *J. Amer. Chem Soc.*, 1945, **67**, 539) forms golden needles, m. p. 167—169° (Found: C, 66·7; H, 8·1; S, 7·25. $C_{24}H_{32}ON_2S,HCl$ requires C, 66·7; H, 7·7; S, 7·4%).

4-*Methyl*-1-2′-*pyrrolidinoethylaminothiaxanthone*.—The *hydrochloride* from 1-chloro-4-methylthiaxanthone and 2-pyrrolidinoethylamine (van Alphen, *Rec. Trav. chim.*, 1939, **58**, 1105) forms small orange needles (from alcohol), m. p. 241—243° (Found: Cl, 9·4; S, 8·3. $C_{20}H_{22}ON_2S,HCl$ requires Cl, 9·5; S, 8·55%).

1-4′-*Ethylpiperazino-4-methylthiaxanthone*.—The *hydrochloride* from 1-chloro-4-methylthiaxanthone and 1-ethylpiperazine (Moore, Boyle, and Thorn, *J.*, 1929, 47) forms yellow prismatic needles (from alcohol), m. p. 297° (decomp.) (Found: Cl, 9·6; S, 8·3. $C_{20}H_{22}ON_2S,HCl$ requires Cl, 9·5; S, 8·55%).

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