Chlorination and Condensation Reactions at the 4-Methyl Group of Lucanthone and Oxalucanthone

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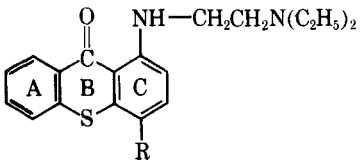
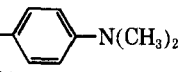
The schistosomicidal agents lucanthone (I) and oxalucanthone (II) reacted with gaseous chlorine to give chloromethylated products (III) and (IV) which, with diethylamine, gave 1-(2-diethylaminoethylamino)-4-diethylaminomethylthioxanthone (VII) and 1-(2-diethylaminoethylamino)-4-diethylaminomethyl-6-chloroxanthone (VIII), respectively. I and II condensed with aromatic aldehydes, while III and IV failed to do so.

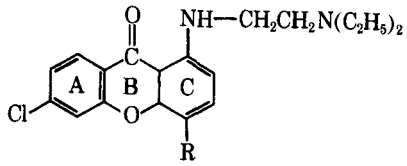
LUCANTHONE, 1-(2-diethylaminoethylamino)-4-methylthioxanthone (I), and its analog, 1-(2-diethylaminoethylamino) - 4 - methyl - 6 - chloroxanthone (II), referred to here as oxalucanthone, are used as oral schistosomicidal agents (1). Recently, they found application as antitumor agents (2).

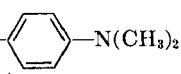
In both areas of application, their chemotherapeutic activity depends upon the presence of a methyl group at the position *para* to the amino group of ring C (3). Replacement of the methyl group at the 4-position with ethyl or methoxy caused a loss in biological activity.

A study of the structure-activity of the 4-methylated compounds might throw light on the biological mechanism of action of both drugs.



I, R = CH_3
III, R = CH_2Cl
V, R = CH=CH—  —$N(CH_3)_2$
VII, R = $CH_2N(C_2H_5)_2$



II, R = CH_3
IV, R = CH_2Cl
VI, R = CH=CH—  —$N(CH_3)_2$
VIII, R = $CH_2N(C_2H_5)_2$

DISCUSSION

I and II were separately subjected to the action of gaseous chlorine in presence of an acid binding material, a technique which was initially developed for the chlorination of the methyl group in picolines and quinaldines (4) in the presence of alkali metal acetate, which neutralizes the hydrochloric acid formed during the reaction (5) and also acts as a catalyst (6). This technique has been modified recently by dissolving the starting material in chloroform or carbon tetrachloride in presence of anhydrous sodium carbonate at a temperature of about 60° (7). When applied to α-picolines and quinaldines, it gave a yield of 65% of monochloromethylated product.

In our work, the latter technique was applied for the chlorination of I and II in chloroform solution, and the mono-chloromethylated products 1-(2-diethylaminoethylamino) - 4 - chloromethylthioxanthone (III) and 1-(2-diethylaminoethylamino)-4-chloromethyl-6-chloroxanthone (IV) were isolated in 80 and 71% yields, respectively. III showed a positive halogen test. Infrared analysis of both products showed stretching absorption at 750–700 $cm.^{-1}$, which corresponds with compounds having one single chlorine atom (8), (C—Cl). Furthermore, when I and II reacted separately with an aromatic aldehyde (*e.g.*, *p*-dimethylaminobenzaldehyde) in the presence of zinc chloride, condensation took place to give V and VI, similar to the aldehyde condensation in α-picoline (9) and quinaldine (10), where it involved the methyl group.

When this condensation reaction was applied on the chlorinated products III and IV under the same conditions, no reaction occurred and both reactants were recovered unchanged.

When III and IV reacted with diethylamine, replacement of chlorine took place, and the product from III gave a negative halogen test. 1-(2-Diethylaminoethylamino) - 4 - diethylaminomethylthioxanthone (VII) and 1-(2-diethylaminoethylamino)-4-diethylaminomethyl-6-chloroxanthone (VIII) were obtained.

EXPERIMENTAL

All melting points were taken in open capillary tubes and corrected.

Preparation of Lucanthone (I) and Oxalucanthone (II).—Both were prepared according to the procedure described by Mauss (11).

1 - (2 - Diethylaminoethylamino) - 4 - chloromethylthiaxanthone (III).—To a solution of 1.7 Gm. (0.005 mole) of I in 15 ml. of chloroform, was added 0.6 Gm. of anhydrous sodium carbonate. A constant stream of dry chlorine gas was passed into the solution for 6 hr. with stirring, during which time the reaction mixture was kept at 60°. When brought to room temperature, 15 ml. of distilled water was added to dissolve inorganic salts. The pH of the solution was 6; 25 ml. of 2 *N* sodium hydroxide was added to raise the pH to 9. The chloroform layer was then separated and the water layer extracted twice with more chloroform. The

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combined chloroform extracts were dried over anhydrous sodium sulfate, the solvent distilled, and the remaining viscous material was treated with ether to induce crystallization. The product was recrystallized from 70% ethyl alcohol to give 1 5 Gm. (80% yield) of light yellow crystals, m.p. 158°.

Anal.—Calcd. for $C_{20}H_{23}ClN_2OS$: C, 64.07; H, 6.18; Cl, 9.46. Found: C, 63.69; H, 5.92; Cl, 9.18.

1 - (2 - Diethylaminoethylamino) - 4 - diethylaminomethylthioxanthone (VIII).—A mixture of 1.87 Gm. (0.005 mole) of III and 3.65 Gm. (0.005 mole) of diethylamine was refluxed for 6 hr. Then the mixture was poured with stirring into 60 ml. of 10% sodium hydroxide solution. Cooling yielded a solid product which was recrystallized from ethyl alcohol to give 1.2 Gm. (58% yield) of VII, m.p. 245°.

Anal.—Calcd. for $C_{24}H_{33}N_3OS$: C, 67.57; H, 8.08; N, 10.21. Found: C, 67.39; H, 7.83; N, 10.09.

1-2(-Diethylaminoethylamino)-4-chloromethyl-6-chloroxanthone (IV).—Into a solution of 1.79 Gm. (0.005 mole) of II, 20 ml. of chloroform, and 0.7 Gm. of anhydrous sodium carbonate, a constant stream of chlorine gas was passed for 6 hr. While being stirred, the solution temperature was kept at 60°. After cooling to room temperature, the reaction product was extracted as described for III, and the isolated product (IV) was recrystallized from 70% ethyl alcohol, m.p. 179°. Yield, 1.4 Gm. (71%).

Anal.—Calcd. for $C_{20}H_{22}Cl_2N_2O_2$: C, 61.07; H, 5.64; Cl, 18.03. Found: C, 60.82; H, 5.48; Cl, 17.79.

1 - (2 - Diethylaminoethylamino) - 4 - diethylaminomethyl-6-chloroxanthone (VIII).—A mixture of 1.93 Gm. (0.005 mole) of IV and 3.65 Gm. (0.005 mole) of diethylamine was refluxed for 5 hr. The product was extracted as described in the preparation of VIII. The isolated product was recrystallized from ethyl alcohol, m.p. 212°. Yield, 1.5 Gm. (53%).

Anal.—Calcd. for $C_{24}H_{32}ClN_3O_2$: C, 67.01; H, 7.50; N, 9.77. Found: C, 66.84; H, 7.33; N, 9.62.

Condensation of I with p-Dimethylaminobenzaldehyde.—A mixture of 1.75 Gm. (0.005 mole) of I and 0.75 Gm. (0.005 mole) of *p*-dimethylaminobenzaldehyde, and a few crystals of fused zinc chloride was heated in an oil bath at 150° for 6 hr. Cooling gave a solid product. It was triturated with boiling water. The insoluble material was recrystallized from hot acetic acid, m.p. 295°. Yield, 1.85 Gm. (78%) of V.

Anal.—Calcd. for $C_{29}H_{33}N_3OS$: C, 73.81; H, 7.05; N, 8.90. Found: C, 73.62; H, 6.83; N, 8.73.

Condensation of II with p-Dimethylaminobenzaldehyde.—A mixture of 1.79 Gm. of (0.005 mole) of II, 0.75 Gm. (0.005 mole) of *p*-dimethylaminobenzaldehyde, and a few crystals of fused zinc chloride was heated to 170° for 7 hr. Cooling gave a solid product. It was triturated with boiling water. The insoluble material was recrystallized from acetic acid, m.p. 147°. Yield, 1.75 Gm. (71.4%) of VI.

Anal.—Calcd. for $C_{29}H_{32}ClN_3O_2$: C, 71.04; H, 6.58; N, 8.37. Found: C, 71.53; H, 6.45; N, 8.62.

Attempted Condensation of III and IV with p-Dimethylaminobenzaldehyde.—Both products were subjected to the condensation reaction with *p*-dimethylaminobenzaldehyde in the presence of zinc chloride and applying the same procedure already described for I and II. No reaction occurred and both products were recovered unchanged (no depression in mixed melting points).

CONCLUSION

Thus, in these reactions—namely, the chlorination with gaseous chlorine and the condensation with aromatic aldehydes—the reactivity of the methyl group in lucanthone and oxalucanthone showed a similarity to that of the methyls in α-picolines and quinaldines.

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