Structure and Activity in the Schistosomicidal Thiaxanthone and Xanthone Derivatives

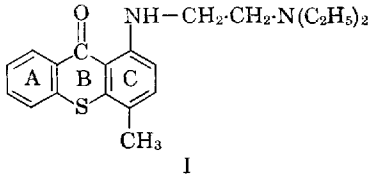
Sir:

1-(2-Diethylaminoethylamino)-4-methyl thiaxanthone (I) possesses schistosomicidal and antitumor activity. Also its analog, 6-chloro-1-(2-diethylaminoethylamino)-4-methyl xanthone (II) shows similar but less potent activity (1, 2).

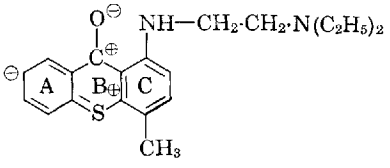
In both areas of application, the activity depends mainly upon the presence of the methyl group at the 4-position *para* to an amino side-chain at the 1-position of ring C. Changes in these groupings caused loss of activity (3).

In previous communications, it was reported that both of the groupings attached to ring C could undergo dehydrogenation through the enzymatic action of peroxidase in the presence of hydrogen peroxide (4). Also, the 4-methyl group could undergo chlorination (5) and Mannich (6) reactions under the appropriate experimental conditions.

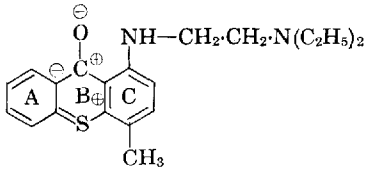
This particular reactivity may be explained by the presence of the polarizable carbonyl group adjacent to the 1-position and the heteroatom (oxygen or sulfur) neighboring the 4-position. As both heteroatoms bear 2 pairs of free electrons



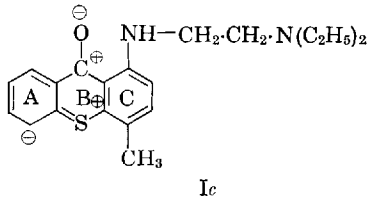
I



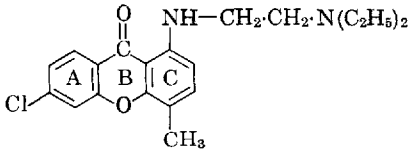
Ia



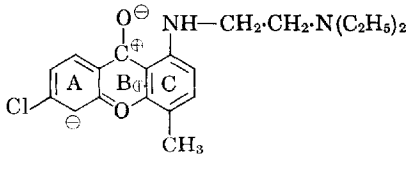
Ib



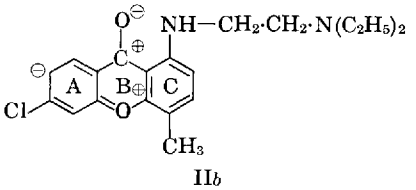
Ic



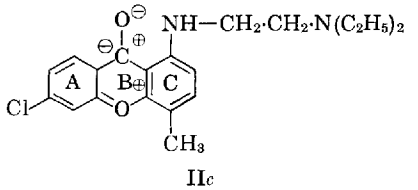
II



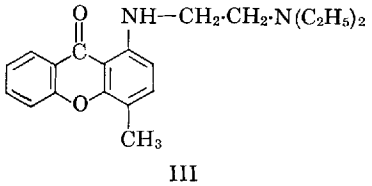
IIa



IIb



IIc



III

and the structures of both molecules (I and II) permit, to different extents, extensive delocalization of these free electrons to be involved in the resonance hybrids I, I*a*, I*b*, I*c*, and II, II*a*, II*b*, II*c* with ring A, the delocalization of the free electrons on the heteroatom preferentially extends toward ring A as ring C bears electron-donating substituents, and this would not favor the resonance hybrids to involve ring C.

This tendency is more pronounced with the sulfur present in I than with the oxygen present in II since oxygen is more electronegative than sulfur. Also, oxygen has an atomic radius of 0.66 Å., which would allow more orbital overlap with the attached carbon atom (atomic radius 0.77 Å.), and this would inhibit to an extent the electron delocalization tendency. This might explain the difference in the biological activity between I, II, and the structural analog, 1-(2-diethylaminoethylamino)-4-methyl xanthone (III) which does not show any noticeable biological activity. In II, the chlorine atom, through its inductive effect, helps to overcome the inhibiting factors of the delocalization of the electrons on oxygen. This effect is missing in III, and thus it is deprived of activity.

In these resonance hybrids, the heteroatom acquires positive charge and ring B becomes loaded with positive charges at both poles, which is electrostatically unfavorable. It tends to compensate for these positive charges by withdrawing electrons in this direction, thus increasing the acidity of the hydrogens attached to the 4-methyl group and the dissociability of that attached to nitrogen at the 1-position of the amino side-chain.

In confirmation of this hypothesis, the NMR measurements of I and II showed that the hydrogens of the 4-methyl group appeared at 7.5 τ which is at the lower part of the field. Aromatic methyl usually appears at 8 τ; thus, slight acidity is implied. In III, it appeared at 7.88 τ, which is at a higher part of the field. Also, the dipole moment of thiaxanthone itself is 5.4 *D* while that of xanthone is 3.11 *D*.

From the biological standpoint, when the carbonyl group in any of the drugs was reduced to the corresponding hydrol, then the activity was lost. In addition, when the sulfur in I was oxidized to sulfone, the drug was no longer active (3).

(1) Kikuth, W., Gonnert, R., and Mauss, H., *Naturwissenschaften*, **33**, 253(1946).
(2) Blanz, E., and French, F., *J. Med. Chem.*, **6**, 185(1963).
(3) Mauss, H., Kolling, H., and Gonnert, R., *Medizin u. Chemie*, **5**, 185(1956).
(4) Nabih, I., and ElSheikh, M., Abstracts of papers presented to the American Chemical Society, Atlantic City meeting, September 1965.
(5) Nabih, I., and ElSheikh, M., *J. Pharm. Sci.*, **54**, 1672 (1965).
(6) *Ibid.*, **54**, 1821(1965).

I. Nabih

National Research Centre
Dokki, Cairo
Egypt, United Arab Republic

Received August 17, 1965.
Accepted for publication December 10, 1965.

Role of Sulfate Formation in Biotransformation of Salicylamide in Man

Sir:

Salicylamide is eliminated in man mainly by biotransformation to the ether glucuronide and the ester sulfate (1, 2). Studies of the kinetics of salicylamide sulfate formation as a function of dose, which will be described in detail in a subsequent report (3), have shown that this process reaches a maximum rate and exhibits characteristics of apparent zero-order kinetics in the usual dose range. This preliminary report is presented in view of the theoretical and practical importance of such unusual kinetic characteristics in the elimination of a commonly used drug.

Salicylamide was administered to healthy adult males as an aqueous solution on empty stomach after an overnight fast. It was given in single doses of 150 and 1000 mg. In addition, a single dose of 1000 mg. salicylamide was given with L-cysteine which was administered every hour for 7 doses starting 3 hr. before salicylamide administration. Total urine collections were made every 0.5 hr. for 4 hr., then every hour for 4 hr., finally at convenient intervals up to 24 hr. after drug administration. Total salicylamide, salicylamide glucuronide, and salicylamide sulfate in the urine were determined by a combination of chemical and enzymatic methods (3). The results of these experiments in 2 representative subjects are shown in Table I. Essentially all of the administered drug was recovered in the urine in the form of salicylamide metabolites. About 50% was excreted as salicylamide sulfate after administration of 150 mg. of drug; this fraction decreased to about 30% when the dose was increased to 1000 mg. The maximum excretion rate of salicylamide sulfate increased