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 In addition, when the sulfur in I was oxidized to sulfone, the drug was no longer active (3).

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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

TABLE I.—EFFECT OF DOSE AND CYSTEINE ADMINISTRATION ON SULFATE CONJUGATION OF SALICYLAMIDE

	Subject 1			Subject 2		
Dose, mg.	150	1000	1000 + Cysteine	150	1000	1000 + Cysteine
Urinary recovery, % of dose	101	97	99	99	92	98
Per cent excreted as sulfate[a]	53	28	52	49	32	49
Max. sulfate excretion rate, mg./hr.[b]	43	109	268	45	121	241

[a] Per cent of amount recovered in urine. [b] Expressed in terms of salicylamide; based on 0.5 hourly urine collection.

less than threefold despite the 6.7-fold increase in the administered dose. The peak excretion rate of salicylamide sulfate after administration of 1000 mg. salicylamide represents a maximum which is not increased by use of larger doses and apparently reflects the maximum capacity of the body for this conjugation process. Coadministration of L-cysteine with 1000 mg. of salicylamide had a pronounced effect on the formation of the sulfate conjugate. The fraction excreted in the form of this metabolite increased to the value found with the lower dose, and the maximum excretion rate became essentially proportional to the administered dose when compared to the lower dose. Apparently, L-cysteine serves as a precursor for sulfate and thereby increases the capacity of the process responsible for salicylamide sulfate synthesis in the body. The results of these experiments show that man has a limited capacity for salicylamide sulfate formation and suggest that the limiting factor is the availability of sulfate.

Some important implications of these findings are: (*a*) the relative rate of salicylamide elimination decreases with dose, (*b*) pharmaceutical dosage form characteristics which affect the absorption rate of salicylamide will also affect the metabolic fate of this drug, (*c*) studies of salicylamide metabolism for which unusually large doses are employed for assay convenience yield quantitative results which do not apply to lower doses, (*d*) the elimination rate of salicylamide in high doses may be increased by administration of L-cysteine (and probably by absorbable sulfate or other sulfate precursors).

Until recently, ethanol was the only drug known to be metabolized in man by apparent zero-order kinetics in the therapeutic dose range. Salicylate (4) and salicylamide (specifically, glycine conjugation of the former and sulfate formation of the latter) can now be added, and there is preliminary evidence that at least 1 other type of biotransformation process exhibits saturation kinetics in man (5). The general implications of these findings, particularly as reflected in items (*a*) to (*c*) in the preceding paragraph, require therefore serious consideration.

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