

TABLE I

Lattice parameters of potassium acetate (Relative accuracy : $\pm 0.005 \text{ \AA}$; absolute accuracy : 0–5%)

Temperature °C	$a \text{ \AA}$	$c \text{ \AA}$	β°	Temperature °C	$b \text{ \AA}$
23.0	9.103 $\times 2$	4.048	100.8	25.0	5.825 $\times 4$
36.1	9.139 $\times 2$	4.040	100.5	50.0	5.808 $\times 4$
55.2	9.234 $\times 2$	4.049	100.1	60.5	5.811 $\times 4$
72.0	9.298 $\times 2$	4.041	99.6	67.4	5.810 $\times 4$
73.6	9.306 $\times 2$	4.025	99.3	68.3	5.820 $\times 4$
75.7	9.317	4.024	99.2	70.6	5.822 $\times 4$
86.0	9.365	4.022	98.2	86.0	5.816
95.3	9.384	4.017	98.5	126.7	5.780
105.0	9.432	4.009	97.9	152.7	5.762
113.3	9.478	4.005	97.5	161.4	5.758
124.0	9.510	4.006	96.8	198.5	5.748
135.0	9.565	3.994	95.7		
147.6	9.645	3.993	94.0		
150.2	9.698	3.991	93.1		
155.0	9.744	3.991	90.0		
160.0	9.744	3.991	90.0		
247.0	9.853	4.021	90.0		

(Note : The values of the lattice constants ' a ' and ' b ' are to be multiplied by 3 and 4 respectively because of the appearance of the superlattice in form III. Thermal expansion has been calculated on the basis of the constants of the original lattice. The absolute accuracy of β is about one degree but the relative accuracy is $\pm 0.1^\circ$.)

to slide over them for closest packing. The penetration of the methyl group in between the other two ions separates them to some extent, so that this model accounts for both the contraction of a and expansion of b , on cooling in form II. The form III has not been investigated in detail; but from space group consideration and examination of diffraction patterns, it has been speculated to be a modulated structure obtained from form II structure.

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INFLUENCE OF PHENOBARBITONE ON SALICYLATE METABOLISM IN CARBON TETRACHLORIDE TREATED RATS

THE identification of the event that triggers the reaction of the liver to carbon tetrachloride has so far eluded investigators. Damage to mitochondria and endoplasmic reticulum¹⁻⁴, sympathoadrenal discharge and subsequent hepatic hyposia⁵ and peroxidative decomposition of cytoplasmic membrane lipids^{6,7} have been implicated. Racknagel⁸ has reviewed the relative importance of these and other factors. There is evidence to suggest that (carbon tetrachloride) induce inhibition of hepatic activity is due to the accumulation of catecholamines after its administration. Catecholamines exert profound lipolytic activity to the extent that the hepatic cells are unable to cope up with the increased need of lipid metabolism. Beta adrenergic agents are known to prevent liver damage caused by carbon tetrachloride⁹. It is well known that phenobarbitone can enhance hepatic microsomal activity¹⁰. One may therefore consider the possibility of antagonism between the influences of phenobarbitone and carbon tetrachloride on the drug metabolising capacity of liver. In the present report it was considered worthwhile examining whether phenobarbitone can be

of any use when drug metabolism is impaired due to such exogenous causes.

Experimental

Albino rats (Haffkine strain) of either sex weighing between 200–250 g were divided in groups of five. Food was withdrawn six hours prior to the commencement of the experiments. All the rats had free access to water throughout the experiments.

One group received only sodium salicylate (equivalent to 40 mg/kg of salicylic acid dissolved in 0.5 ml of distilled water) intraperitoneally and served as a

and total salicylate (TSA). The procedure described by Smith *et al.*¹¹ and modified by Levy and Procknal¹² was employed. These experiments were performed in triplicates to allow statistical analysis. The data was analysed to demonstrate significant results using student's *t*-test.

Results

The average per cent urinary excretion of FSA, SU, SG and TSA after 24 and 48 hours of salicylate administration in various groups of rats is shown in Table I.

TABLE I

The average per cent urinary excretion of FSA, SU, SG and TSA after 24 and 48 hours of salicylate administration in various groups

METABOLITE	Group	A		B		C		D		E	
	Time	24	48	24	48	24	48	24	48	24	48
	in hours										
Free Salicylic acid	Mean	35.05	46.84	36.62	48.38	34.59	45.77	36.75	48.54	38.19	47.73
	S.E.	± 2.51	± 2.20	± 0.72	± 1.08	± 1.48	± 1.76	± 2.72	± 1.69	± 1.23	± 2.30
Salicyluric acid	Mean	11.76	15.66	8.61	12.06	5.52	6.71	8.51	11.40	11.92	16.02
	S.E.	± 0.88	± 1.24	± 0.58	± 1.15	± 0.38	± 0.55	± 0.46	± 1.16	± 0.87	± 0.93
Salicyl glucuronide	Mean	11.08	16.28	8.35	11.93	3.80	5.53	9.78	12.02	11.48	16.08
	S.E.	± 1.29	± 2.85	± 0.84	± 1.76	± 0.53	± 1.01	± 0.65	± 0.72	± 0.50	± 1.71
Total salicylate	Mean	59.30	78.77	53.58	72.39	44.27	58.01	55.99	73.97	61.60	79.84
	S.E.	± 4.52	± 5.73	± 2.22	± 3.82	± 2.54	± 2.40	± 1.14	± 1.37	± 0.20	± 2.75

A. Sodium salicylate alone.

B. Carbon tetrachloride was given 24 hours prior to sodium salicylate.

C. Coadministration of carbon tetrachloride and phenobarbitone 24 hours prior to sodium salicylate.

D. Carbon tetrachloride was given 24 hours prior to concomitant administration of phenobarbitone and sodium salicylate.

E. Coadministration of phenobarbitone and sodium salicylate.

control. The animals of the another group were treated with 0.5 ml/kg of carbon tetrachloride (I.P.) 24 hours prior to administration of sodium salicylate. Carbon tetrachloride and phenobarbitone (1 mg/kg I.P.) were administered conjointly to another group 24 hours prior to administration of sodium salicylate while to another group sodium salicylate and phenobarbitone were administered 24 hours after the administration of carbon tetrachloride. One group received only phenobarbitone and salicylate simultaneously.

Urine samples were collected from 24 h prior to and 48 h after the administration of sodium salicylate. All the urine samples were analysed for free salicylate (FSA), salicyluric acid (SU), salicyl glucuronide (SG)

The excretion of FSA remained unaffected when salicylate was given with carbon tetrachloride or phenobarbitone individually or conjointly. The excretion of SU ($P > 0.05$) and SG ($P > 0.10$) was significantly lowered in carbon tetrachloride treated rats. However, administration of phenobarbitone along with sodium salicylate did not produce any appreciable change in the excretory pattern of administered salicylate. The excretion of SU and SG was drastically reduced ($P < 0.05$) by simultaneous administration of phenobarbitone with carbon tetrachloride.

Alteration in time schedule of administration of phenobarbitone along with sodium salicylate 24 hours after the treatment of carbon tetrachloride produced similar results as that of carbon tetrachloride alone.

Discussion

The excretion of SU and SG in carbon tetrachloride treated rats seems to have been reduced presumably due to inhibition of their biosynthesis, by carbon tetrachloride induced inhibition of hepatic microsomal system which is responsible for conjugation of drugs with glycine and/or glucuronic acid. Phenobarbitone is known to enhance metabolism of salicylamide in human by hepatic microsomal enzyme induction¹³. It however failed to alter in any way the metabolic rate of sodium salicylate in normal rats. Yaffe *et al.*¹³ have also reported similar observation. The difference in the effect of phenobarbital on the glucuronide conjugation of salicylamide and salicylate is of considerable interest. There have been other reports of similar differences. Remmer¹⁴ found that phenobarbital increased the rate of glucuronide conjugation of sulfadimethoxine in rats but he did not obtain a similar barbiturate effect with salicylate and salicylamide¹⁵. Catz and Yaffe¹⁶ found that sodium barbital enhanced the glucuronide conjugation of bilirubin in mice but had no effect on the conjugation of phenolphthalein and ortho-aminophenol. The reason for these selective effects is not known at present. They may be due to the existence of more than one glucuronide-forming enzyme system¹⁷, each with its own substrate specificity and differing in their response to barbiturates.

Phenobarbitone, when given with carbon tetrachloride, failed to antagonise the inhibitory effect of carbon tetrachloride on salicylate metabolism. Conversely there was further decrease in urinary excretion of salicylate conjugates. Such potentiation of carbon tetrachloride effect is difficult to explain. It is however possible that this effect has relation with the depressant effect of phenobarbitone or its actions on metabolism.

Phenobarbitone is known to inhibit autonomous ganglion and also the cholinergic impulses. The studies on the effect of barbiturates on sympathetic neurotransmission are scant but are indicative of catecholamine release from synapses after barbiturate administration¹⁸. Such processes will have additive effect to carbon tetrachloride's hepatotoxic action which is believed to be predominantly due to catecholamine release. Miller¹⁹ has also reported that barbiturates enormously sensitize to the toxicity of carbon tetrachloride.

Thus, the potentiation of carbon tetrachloride-hepatotoxicity by phenobarbitone resulting in reduced rates of salicylate metabolism and elimination would elevate salicylate blood levels and consequently lead to salicylate toxicity.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF AMIDINE SULPHIDES

Introduction

HIGH local anaesthetic activity and low toxicity have been claimed¹ for a group of pseudothiuronium salts. Sulphur substituents in these salts included 2-aminoethyl, 2-(1-piperidyl) and 2-(4-morpholinyl). Numerous 2-alkyl pseudothiourea hydrochlorides showed marked activity² against *Staphylococcus aureus* and