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The relationship between chemical structure and protective effect of dithiocarbamate derivatives against experimental hepatic injury induced by carbon tetrachloride administration in rats

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A NUMBER of substances having protective effect against experimental hepatic damage induced by CCl_4 administration have been reported by investigators. Concerning dithiocarbamates, Palma *et al.*[1] have described the antagonistic effect of 2-methylpiperazine dithioformate on various hepatic lesions induced by lipid enriched diet, pyridine and ethionine treatment and X-ray irradiation combined with CCl^4 administration in mice. Previously we found the protective effect of piperazine NN'-biscarbodithioate on liver damage induced by CCl_4[2]. This paper describes the relation of chemical structure of dithiocarbamate derivatives with their activity in protecting liver damage caused by CCl_4 in rat, as judged by plasma transaminase levels.

Male Donryu rats aged 8 weeks weighing 180–200 g were used and maintained on standard laboratory chow (CLEA CE-2). A suspension of CCl_4 in gum tragacanth was administered intraperitoneally in a dose of 0·1 ml/kg. Tested compounds were administered orally just before the injection of CCl_4. For the determination of transaminase activities, blood was collected from heart of rats under pentobarbital anesthesia 24 hr after administration of CCl_4. The plasma was obtained by centrifugation. Activities of plasma transaminases, GOT and GPT, were determined by the method of Reitman and Frankels[3] and expressed in Karmen units. Tested compounds were evaluated as being protective against hepatic injury induced by CCl_4, when the activities of plasma transaminases were reduced.

The results are summarized in Table 1 and discussed with respect to the relationship between chemical structure and protective effect. Metal salts of dithiocarbamic acid and xanthogenic acid

TABLE 1 THE REDUCTION OF PLASMA TRANSAMINASE LEVELS BY DITHIOCARBAMATE DERIVATIVES AND RELATED COMPOUNDS IN RATS INTOXICATED BY CCl_4.

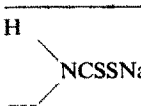
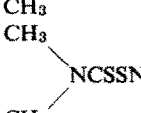
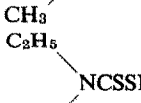
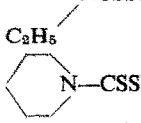
	Plasma transaminase levels (Karmen unit) GPT	GOT
	20 ± 6	93 ± 15
	13 ± 1	120 ± 32
	15 ± 4	79 ± 11
	13 ± 3	67 ± 8
	16 ± 8	136 ± 37

Table 1 continued.

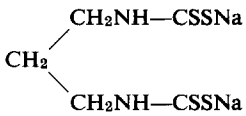
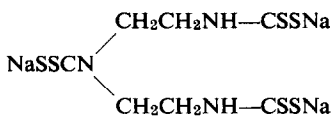
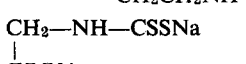
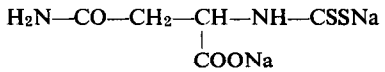
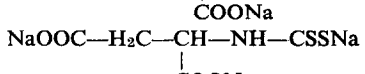
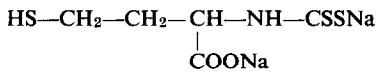
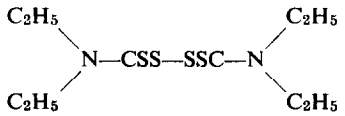
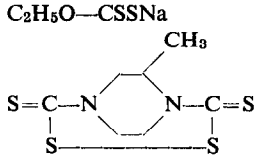
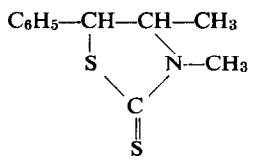
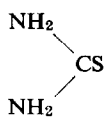
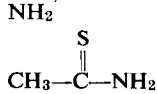
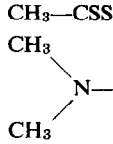
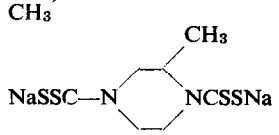
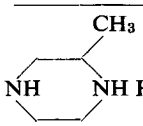
	13 ± 3	70 ± 9
	18 ± 4	94 ± 14
	18 ± 4	82 ± 9
	14 ± 4	76 ± 18
	14 ± 2	74 ± 7
$NaSO_3CH_2CH_2NH—CSSNa$	34 ± 14	165 ± 46
	16 ± 3	77 ± 13
	38 ± 14	109 ± 20
$C_2H_5O—CSSNa$	15 ± 4	70 ± 18
	878 ± 431	1592 ± 729
	1040 ± 211	2198 ± 441
CH_3COSK	677 ± 319	1424 ± 611
	452 ± 84	1075 ± 368
	474 ± 157	976 ± 271
$CH_3—CSSH$	700 ± 290	2134 ± 999
	855 ± 322	2643 ± 864
	24 ± 6	151 ± 24

Table 1 continued

	Plasma transaminase levels (Karmen Unit) GPT	GOT
	430 ± 220	780 ± 380
$Na\ SO_3\ CH_2—CH_2—NH_2$	417 ± 175	816 ± 290
$CH_3\ S—CH_2—CH_2—CH(NH_2)—COOH$	1000 ± 492	2072 ± 885
Sodium thiosulfate	1320 ± 364	3572 ± 1027
Glutathione	1234 ± 414	3296 ± 1632
B A L	2020 ± 655	5616 ± 1839
Thioctic acid	1628 ± 548	4568 ± 1979
EDTA	820 ± 251	1980 ± 580
CS_2	16 ± 4	116 ± 18
Normal rats	14 ± 4	59 ± 38
CCl_4 intoxicated rats	745 ± 400	1841 ± 1159

Figures in the tables show mean ± standard deviation.

were protective, whilst their ester and their ring forms, carbodithioate (or carbothioate) including C-CSSH (C-COSH) radical, isothiocyanate and thiourea derivatives did not show any protective effect. The corresponding compounds lacking the -CSSH radical of dithiocarbamates and some thio compounds known as detoxicating agents, namely, sodium thiosulfate, glutathione, BAL and thioctic acid had no efficiency in our experimental conditions. EDTA also had no protective effect, although its effectiveness has been reported by Calvart and Brody[4] and some other workers.[5]

From these results, it is concluded that the compounds having a -CSSH radical on the N or O atom exhibit a considerable, strong protective effect. It is likely that the effectiveness of dithiocarbamates may be attributed to the same mechanism as that of tetraethylthiuram disulfide, for it has been suggested by several workers that the latter compound may be changed into diethyl dithiocarbamate in animal bodies.[6, 7, 8] It has also been reported that CS_2 may be metabolized into dithiocarbamate in animal body.[9] It is probable, therefore, that the effectiveness of CS_2 may be due to the metabolite.

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