91. *Catalytic Toxicity and Chemical Structure. Part III. The Influence of Various Factors on the Toxicity of Sulphur Compounds.*

By Edward B. Maxted and Herbert C. Evans.

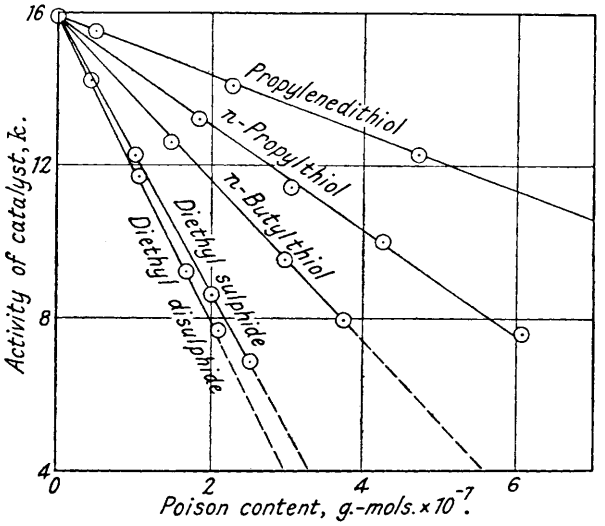
The principal point of interest in the present work is that the addition of a second terminal sulphur atom to a hydrocarbon chain of given length decreases rather than increases the toxicity per g.-mol. It is considered that this is due to the restriction imposed on the mobility, since the decrease in toxicity does not occur if the sulphur atoms are adjacent to one another.

In Parts I and II (J., 1937, 603, 1004), the development of toxic properties in normally non-toxic hydrocarbon chains by enforced proximity to a catalytic surface—by virtue, for instance, of the permanent attachment of one end of the chain to the surface by a terminal sulphur atom—has been examined for hydrocarbon chains of various lengths.

A point of considerable interest arises if the hydrocarbon chain contains two terminal sulphur atoms in place of one. In the case of a single sulphur anchor, the chain as a whole is free, save for its permanent attachment at one end; and the maximum surface area over which there is a time-probability of adsorption is a circle of radius equal to the chain length. It should be possible, however, to restrict this mobility, and consequently to diminish the area of influence, by providing a second sulphur anchor at the other end of the chain, in a manner analogous to the effect of two anchors, in place of one, in restricting the area of possible drift of a boat. Accordingly, if the explanation of induced toxicity which has been developed in previous papers is correct, the molecular toxicity of a hydrocarbon-chain compound terminated at each end by a catalytically poisonous element or group should, in spite of its possessing twice the content of sulphur or other poisonous element, be considerably less than that of a chain of similar length containing only a single terminal sulphur atom. This point has now been verified experimentally, in that the molecular toxicity of propylenedithiol, $SH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}SH$, was found, in spite of its greater sulphur content, to be considerably less than that of either *n*-propylthiol, $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}SH$, or of *n*-butylthiol, $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}SH$, with which latter compound the dithiol is perhaps more nearly comparable from the standpoint of chain length owing to the inclusion of the extra sulphur atom. If, on the other hand, the two sulphur atoms, instead of occupying terminal positions, are adjacent to one another, little change in toxicity would be expected: thus, diethyl disulphide, $(C_2H_5)_2S_2$, does not differ greatly

in molecular toxicity from diethyl sulphide, $(C_2H_5)_2S$, again in spite of its doubled sulphur content. The relevant data are given in Table I.

Other points which have been investigated include the effect of a double bond and of a branching chain. It would perhaps be expected that a hydrocarbon chain, anchored to a surface at one end and containing an unsaturated bond, would be less toxic than a compound containing a saturated chain of equal length, by reason of the probable greater adsorbed life, and consequently the lesser mobility, of the unsaturated group, accompanied by a less effective cover of the total surface within the range of the chain. The inclusion of a double bond was, however, found on trial to have little influence on the poisoning power, in that there is little difference between the molecular toxicity of *n*-propyl and of allyl sulphide. The relative toxic effectiveness of an anchored branching hydrocarbon chain, compared with that of a straight chain containing the same number of carbon atoms, has been studied for *n*-propyl and *iso*propyl sulphides. Here the normal chain, probably by reason of its greater length, is somewhat more toxic than the *iso*-compound; but the difference is not great. It is probable that the restriction in the range brought



about by the shorter chain is not compensated by the greater effectiveness of cover which would be expected within this restricted range by virtue of the greater area of the chain ends. The relative toxicities are shown in Table II.

Measurements were also made of the toxic effect of an anchored hydrocarbon ring, in place of a chain. Three cases, representing progressive stages in the removal of the ring from the poisonous atom proper, were examined, *viz.*, thiophen, in which the sulphur anchor is contained in the ring itself, thiophenol, in which it is adjacent to this, and β-phenylethylthiol, $C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}SH$, in which the ring is connected with the anchor by means of a short chain. Thiophenol, as would be expected from its six- in place of five-membered ring, together with its increased range by virtue of the extra-cyclic sulphur atom, was more toxic than thiophen; but β-phenylethylthiol—probably by reason of the greater distance of removal of the benzene ring from the catalyst surface and consequently the less favourable position of the ring for preferential adsorption—showed an effective toxicity intermediate between those of thiophen and thiophenol (see Table III).

Finally, some work was done on the toxicity of substituted thioureas and certain related substances. This group seemed at first sight an easily obtained series, in which the influence of chain length and molecular complexity could be studied in a similar manner to that already carried out for long-chain thiols and sulphides. Unfortunately, however, the thioureas are capable of ready isomerisation; and there is difficulty in determining the isomeric form or forms in which the poison is acting.

Experimental.

The general technique and the method of expressing toxicity were as described in previous papers and are not repeated here. A uniform stock of supported platinum was used throughout, and the standard reaction employed for measuring the activity of the catalyst at various stages of poisoning was, as before, the hydrogenation of crotonic acid at 27°. Each charge consisted of 5 c.c. of 2N-crotonic acid in acetic acid solution, to which was added a further 5 c.c. of acetic acid containing a known quantity of poison, and 0·05 g. of the standard catalyst.

Influence of a Second Sulphur Atom.—The poisoning graphs for *n*-propylenedithiol, *n*-propylthiol and *n*-butylthiol under similar conditions are summarised in the figure, and the results show the relationship described on p. 455. With a hydrocarbon chain containing two terminal sulphur atoms, full extension across the catalytic surface is not probable, the mean occurring position being probably that in which the terminal sulphur anchors are attached in positions such that the chain is in a state of least strain; and rotary movement of the chain loop thus formed, about a horizontal axis passing through the terminal sulphur atoms, should be possible, the range of possible obstructive cover of potential adsorbing surface being however far less than for a chain of similar length anchored at one end only.

On calculating the values of α by means of the expression, $k_c = k_0 (1 - \alpha c)$, the values given in Table I are obtained.

Table I.

Inhibitant.	$\alpha \times 10^{-5}$.	Rel. toxicity per g.-mol. of inhibitant.	Inhibitant.	$\alpha \times 10^{-5}$.	Rel. toxicity per g.-mol. of inhibitant.
n-Propylthiol	8·7	0·65	Diethyl sulphide	22·7	1·00
n-Butylthiol	13·3	1·00	Diethyl disulphide ...	25·0	1·10
Propylenedithiol	5·1	0·38			

Propyl, iso*Propyl, and Allyl Sulphides.*—

Table II.

Inhibitant.	$\alpha \times 10^{-5}$.	Rel. toxicity per g.-mol. of inhibitant.
n-Propyl sulphide	19·8	1·00
Allyl sulphide	20·6	1·04
*iso*Propyl sulphide	17·6	0·89

Miscellaneous Ring Compounds.—The relative toxicities of these compounds are given in Table III.

Table III.

Inhibitant.	$\alpha \times 10^{-5}$.	Rel. toxicity per g.-mol. of inhibitant.
Thiophen	9·9	1·00
Thiophenol	16·1	1·63
β-Phenylethylthiol	12·0	1·21

An interesting case of unexpected toxicity was given by β-thionaphthol, which showed a toxicity only approximately equal to that of thiophenol ($\alpha \times 10^{-5} = 15{\cdot}1$, on the same scale as in Table III). This was checked by duplicate determinations both with thiophenol and with thionaphthol. It is possible that this seeming anomaly, which is the first that has been encountered, may be due to the lesser mobility of the larger ring system, this factor compensating—from the standpoint of the degree of effectiveness of obstructive cover of the total surface within range—for the certainly greater maximum range of the larger ring.

Toxicity of Derivatives of Thiourea.—Owing to the possibilities of isomerism in these compounds, the observed effective toxicity, unlike that of stable poisons such as those previously studied (the toxicities of which are independent of the solvent used), changes with the conditions and with the solvent. It was not considered worth while in such cases to investigate further the conditions of equilibrium between possible products, since, from the present standpoint, a definite molecular form is desirable for correlation with the toxicity; and the figures in Table IV are merely given for purposes of record, as an indication of the effective toxicity exerted at 27° in acetic acid and in alcoholic solution respectively. It will be seen that only thioacetamide appears to retain its structure, and consequently has the same toxicity, in acetic acid and in alcohol.

TABLE IV.

Inhibitant.	$a \times 10^{-5}$. In HOAc.	$a \times 10^{-5}$. In EtOH.	Relative effective toxicity per g.-mol. of inhibitant ($H_2S = 1$). In HOAc.	Relative effective toxicity per g.-mol. of inhibitant ($H_2S = 1$). In EtOH.
Thiourea	13·5	20·5	5·9	9·0
s-Diphenylthiourea	16·6	25·1	7·3	11·1
s-Diphenylthiocarbazide	26·5	15·9	11·7	7·0
Thiosinamine	7·3	18·4	3·2	8·1
Thioacetamide	8·3	8·25	3·66	3·64

UNIVERSITY OF BRISTOL.

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