158. *The Retardation of Chemical Reactions. Part IX. The Stabilisation of Perchloroethylene for Medicinal Purposes.*

By Kenneth C. Bailey.

The photochemical oxidation of perchloroethylene may be retarded by thymol, ether, alcohol, thiourea, sodium thiosulphate, and other compounds. Thymol is especially effective, giving considerable protection when present in a concentration as low as two parts in a million.

THE administration of perchloroethylene for hook-worm disease in tropical countries has been attended, in certain cases reported to the author, by unpleasant results. These have been traced to the fact that the compound had suffered atmospheric oxidation, with production of the poisonous carbonyl chloride.

It has been found that when pure perchloroethylene is used, oxidation is very much less than with the commercial product, which has been employed on occasions. The most serious dangers can therefore probably be readily avoided. It seemed worth while, however, to examine the photochemical oxidation of the pure compound with a view to retarding it by added substances.

When perchloroethylene was shaken with air in the dark at 280 r.p.m. for 30 hours, no oxidation whatever could be detected, but when it was exposed to sunlight or artificial light, oxidation took place fairly rapidly. The extent of oxidation in all experiments was determined by adding 25 c.c. of water, shaking, allowing the mixture to stand until all the carbonyl chloride had been hydrolysed to carbon dioxide and hydrochloric acid, and estimating by titration (phenolphthalein indicator) the total acid produced. In some experiments 0·1 c.c. of water was added initially per 20 c.c. of perchloroethylene. The velocity of oxidation was not drastically affected by its presence. The initial oxidation of the moist sample was a little less vigorous, but its later oxidation was more rapid, than that of the sample to which no water had been added. In the quantitative experiments of Tables I—III, water was added in all cases.

In a set of preliminary experiments, perchloroethylene, with and without possible retarders, was exposed to summer sunlight in ordinary glass bottles for 4 weeks. The unprotected sample was extensively oxidised. Oxidation was accelerated by iodine, very slightly retarded by quinol, fairly well retarded by butyl and *iso*butyl alcohols, turpentine, benzaldehyde, resorcinol, diphenylamine, α- and β-naphthylamines, α- and β-naphthols, and sulphur, and well retarded by alcohol, ether, thymol, *o*-toluidine, sodium thiosulphate, and thiourea. In certain cases (quinol, benzaldehyde, resorcinol, diphenylamine, the naphthylamines, and the naphthols) the retarding agent caused development of colour.

The action of sodium thiosulphate and thiourea (both of which are good retarders of the oxidation of alkaline sodium salicylate solutions; Hilton and Bailey, J., 1938, 631) is interesting, since the solubility of each in perchloroethylene is very low. A saturated solution of thiourea (approximately 1 part in 70,000 of the solvent), free from solid, was oxidised at about half the rate of untreated perchloroethylene, but a saturated solution of sodium thiosulphate (less than 1 part in 120,000 of solvent), free from solid, was oxidised almost as rapidly as perchloroethylene alone. In each case, however, when the latter was left in contact with the powdered solid, the velocity of oxidation was very greatly reduced. The solid presumably dissolves continuously, so as to replace oxidised material and maintain a saturated solution.

Alcohol, ether, and thymol seemed to be the most suitable retarders for the purpose. In the experiments the results of which are summarised in Table I, the perchloroethylene (20 c.c., with 0·1 c.c. of water) was contained in glass flasks (vol. = 350 c.c.) placed around a 100-watt electric bulb so that the distance from the surface of the bulb to the nearest surface of the flask was 5 inches.

TABLE I.

Inhibitor.	Parts of C_2Cl_4 to 1 part of inhibitor (D).	N/10-NaOH, c.c., required to neutralise total acid.						
		0·1.	0·2.	0·3.	0·4.	1.	2.	5.
		Time (in days) required to produce acid.						
None	—	2·75	4·5	5·6	6·6	10·5	13·5	18·3
Alcohol	20,000	2·0	3·5	4·5	5·5	9·0	13·8	23·5
,, ...	2000	8·0	12·75	16·75	20·0	—	—	—
,, ...	500	17·0	29·0	37·5	—	—	—	—
Ether	75,000	3·0	5·5	7·3	9·1	16·0	22·8	—
,, ...	2000	10·0	20·5	28·0	—	—	—	—
Thymol	500,000	18·0	31·5	—	—	—	—	—
,, ...	50,000	45·0	68·5	—	—	—	—	—

The following was adopted as a basis of comparison of the efficiencies of the three retarders at various dilutions. The number of days needed for the development of a given acidity in a retarded solution is divided by the number of days for the unretarded liquid, and the ratio is termed R. The number of parts of perchloroethylene to 1 part of retarder (*i.e.*, the dilution) is termed D. The product RD then increases with the efficiency of the retarder.

TABLE II.

		N/10-NaOH, c.c., required.					
		0·1.	0·2.	0·3.	0·1.	0·2.	0·3.
Inhibitor.	*D.*		*R.*			$RD \times 10^{-3}$.	
Alcohol	2000	2·9	2·8	3·0	5·8	5·6	6·0
,,	500	6·2	6·4	6·7	3·1	3·2	3·35
Ether	75,000	1·1	1·2	1·3	82·5	90·0	97·5
,,	2000	3·6	4·5	5·0	7·2	9·0	10·0
Thymol	500,000	6·5	7·0	—	3250	3500	—
,,	50,000	16·4	15·2	—	820	760	—

It will be seen that, in each case, the specific efficiency of the retarder diminishes with increasing concentration, that thymol is much more efficient than ether, and ether decidedly more efficient than alcohol.

In a second series of experiments, ultra-violet light illumination was used (Hanovia quartz lamp, 1·3 amps., 220 volts). 15 C.c. of perchloroethylene (with 0·1 c.c. of water) were contained in each of several clear quartz flasks (vol. = 350 c.c.), two of which were exposed at a time. The distance from the plate of the lamp to the surface of the liquid in the flask was 4·6 inches. The results obtained are in Table III, the times of oxidation being measured in hours instead of days.

TABLE III.

		N/10-NaOH, c.c., required to neutralise total acid.										
	Parts of C_2Cl_4 to 1 part of inhibitor (*D*).	0·1.	0·2.	0·3.	0·4.	1·0.	0·1.	0·2.	0·3.	0·1.	0·2.	0·3.
Inhibitor.		Time (hrs.) required to produce acid.						*R.*			$RD \times 10^{-3}$.	
None	—	2·6	4·6	6·5	8·2	15·5	—	—	—	—	—	—
Alcohol	2000	6·2	11·0	15·3	19·0	—	2·4	2·4	2·4	4·8	4·8	4·8
Ether	2000	21·0	38·0	—	—	—	8·1	8·3	—	16·2	16·6	—
Thymol	50,000	19·0	36·0	—	—	—	7·3	7·8	—	365	390	—

The order of efficiency of the retarders is the same. Protective power greater than that of thymol for perchloroethylene has rarely been recorded in experiments on atmospheric oxidation. It seems as if perchloroethylene treated with 2—5 parts of thymol per million can safely be kept in colourless glass bottles with no precaution against casual exposure to light, although persistent exposure to bright sunlight would doubtless lead ultimately to oxidation of the retarder and failure of protection. It seems unlikely that such a minute proportion of a relatively harmless substance would affect the therapeutic properties of the perchloroethylene.

The nature of the oxidation products has not yet been fully investigated. The titration value of the acid after hydrolysis is slightly lower with methyl-orange as indicator than when phenolphthalein is used, doubtless owing to the presence of carbonic acid. The silver titration value for hydrochloric acid, however, is only about two-thirds of the total acid, as estimated with methyl-orange as indicator. The evidence suggests the production of some other acid, in addition to the hydrochloric acid obtained by the hydrolysis of carbonyl chloride. Investigation of this point is contemplated.

I am much indebted to Mr. J. V. Collins, Government Analyst of Ceylon, for information about the problem.

TRINITY COLLEGE, DUBLIN. [*Received, March* 14*th*, 1939.]