Trichloroethyl Carbonate I. Synthesis, Physical Properties, and Pharmacology

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Trichloroethyl carbonate was prepared from trichloroethanol and phosgene. It is a tasteless, crystalline solid with limited solubility in water. Pharmacological comparisons of trichloroethyl carbonate and trichloroethanol reveal that these compounds are about equitoxic and equipotent in decreasing spontaneous motor activity in mice after oral administration. These observations suggest that this carbonate is a prodrug of trichloroethanol.

CHLORAL HYDRATE which was used as a sedative by Liebreich (1) as early as 1869 is still one of the least toxic and most beneficial sedatives and hypnotics available (2). A hypnotic dose produces drowsiness within 15 to 30 min. and physiological sleep, which lasts for 6 to 8 hr., soon follows, and no hangover reaction is observed. However, the usefulness of the drug has been restricted by certain undesirable properties; it has a penetrating odor, and it possesses a bitter taste. Furthermore, it frequently causes stomach irritation, and it may produce nausea and vomiting at high doses. These factors, in addition to the popularity of the barbiturates, may account for the neglect of this drug. Chloral hydrate is rapidly converted in the body to trichloroethanol (3–5), which is also a potent sedative and hypnotic. Mackay and Cooper (3) studied this conversion in detail and showed chloral hydrate to be a potent hypnotic agent of short duration, and that the long duration of action observed was due to the metabolite trichloroethanol. Thus, the pharmacological effects noted after administration of chloral hydrate are chiefly due to its metabolite trichloroethanol.

While trichloroethanol has long been known to possess these pharmacological properties and has been studied at length in humans (6, 7), it has nonetheless been neglected as a therapeutic agent. No doubt its physical properties had much to do with this neglect because it is a bad tasting, hygroscopic liquid that often produces gastric irritation.

Recognizing that chloral hydrate and trichloroethanol are useful drugs, the authors felt it would be desirable to convert one of them to a more acceptable chemical form that would, after oral ingestion, be reconverted to the parent drug. Ideally this form should be a solid that can be conveniently formulated as tablets, capsules, or liquid forms, and it was thought that the carbonate derivative of trichloroethanol bis-(2,2,2-trichloroethyl) carbonate (or trichloroethyl carbonate[1]) might meet these criteria. This compound was reported in recent communications (8, 9).

EXPERIMENTAL

Chemistry—*Synthesis*—To a solution of 20 ml. of phosgene in 100 ml. of toluene was slowly added with stirring and cooling a mixture of 74.7 Gm. (0.5 mole) of trichloroethanol and 39.6 Gm. (0.5 mole) of pyridine. The mixture was stirred for 3 hr. at room temperature and the excess phosgene was removed *in vacuo*. Pyridine hydrochloride was filtered off and the filtrate was washed with 10% sodium hydroxide, dried, and concentrated. Dilution with hexane gave 58.4 Gm. of product, m.p. 86–87°.

Anal.—Calcd. for $C_5H_4Cl_6O_3$: C, 18.49; H, 1.24; Cl, 65.49. Found: C, 18.59; H, 1.28; Cl, 65.30.

Pharmacology—Initial testing of the trichloroethyl carbonate was aimed primarily at comparing its (*a*) acute oral toxicity and (*b*) CNS depressant activity with the parent drug trichloroethanol. For the latter, the effects of the two drugs on spontaneous motor activity in mice was measured, since it is well known that agents causing CNS depression in rodents will cause a concomitant decrease in spontaneous motor activity (10).

Acute Oral Toxicity in Mice—Male Carworth Farms mice (18–23 Gm.) were randomly divided into groups of 10 and dosed orally with suspensions of drug in 1% tragacanth. Suspensions were prepared with the aid of a Thomas glass-Teflon tissue grinder. Grinding was just sufficient (1–3 min.) to ensure a uniform suspension. Concentrations of drug were calculated so that each animal received a dose-volume of 10 ml./Kg. and a control group of 10 mice received 10 ml./Kg. of vehicle. After dosing, the animals were housed 10 per cage. They were observed for several hours immediately after dosing and then checked daily until no deaths occurred for 2 successive days following the fifth day post-drug. All deaths occurred within 48 hr. after dosing. The LD_{50}'s and 95% confidence limits were calculated by the logit χ^2 method of Berkson (11).

CNS Depressant Activity—Spontaneous Motor Activity (SMA) in Mice—Male Carworth Farms mice (15–25 Gm.) were randomly divided into groups of 10 and dosed with suspensions of drug in 1% tragacanth. Suspensions were prepared with the aid of a Thomas glass-Teflon tissue grinder as before and concentrations were calculated so that each animal received a dose volume of 10 ml./Kg. A control group received 10 ml./Kg. of vehicle. A 30-min. optimal pretreatment time for the drugs was determined in exploratory trials. Spontaneous motor activity was measured by means of an actophotometer. Exactly 30 min. after being dosed, an animal was placed into the activity chamber and its SMA, measured by the number of times the animal interrupted the light beams in the chamber, was determined for a 10-min. period. All counts were made on individual animals, and the reduction in SMA for each group was calculated by means of the following equation:

$$\% \text{ reduction in SMA} = \frac{\left(\begin{matrix}\text{mean count of}\\ \text{control group}\end{matrix}\right) - \left(\begin{matrix}\text{mean count of}\\ \text{treated group}\end{matrix}\right)}{\text{mean count of control group}} \times 100$$

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[1] Chlorethate.

Table I—Acute Oral Toxicities of Trichloroethyl Carbonate and Trichloroethanol in Mice (Male CF_1)

Dose, mg./Kg.	% Mortality	LD_{50} and 95% Fiellet Limits
	Trichloroethyl Carbonate	
800	0	
900	30	
1000	30	
1100	80	1003(939–1089)mg./Kg.[a]
1200	100	
	Trichloroethanol	
400	0	
600	10	
800	40	930(769–1264)mg./Kg.
1000	50	
1600	100	

[a] Not statistically significantly different from trichloroethanol.

Table II—Depression of Spontaneous Motor Activity (SMA) by Trichloroethyl Carbonate or Trichloroethanol Orally in Mice

Dose, mg./Kg.	% Reduction in SMA	ED_{50} and 95% Confidence Limits
	Trichloroethyl Carbonate	
150	14	288(175–483)mg./Kg.[a]
250	38	
350	61	
450	63	
	Trichloroethanol	
200	13	212(130–290)mg./Kg.
300	77	
400	84	
500	83	

[a] Not statistically significantly different from trichloroethanol.

The ED_{50}'s and 95% confidence limits were calculated by the method described by Tedeschi *et al.* (12).

RESULTS AND DISCUSSION

Synthesis and Properties of Trichloroethyl Carbonate—No particular difficulties were encountered in the synthesis of this new compound, though cognizance must be taken of its latent capability for undergoing hydrolytic cleavage. By the laboratory method employed, yield of compound was 72%.

Conversion of trichloroethanol to its carbonate results in a profound change in physical-chemical properties. Whereas trichloroethanol is a dense, hygroscopic liquid of ethereal odor, the carbonate is an odorless, friable, white, crystalline, solid, m.p. 86–87°. Trichloroethanol has a disagreeable taste, but the carbonate is virtually tasteless. Trichloroethanol is soluble in water to about 1 in 12, but the carbonate dissolves in water only to about 4 mcg./ml. Trichloroethyl carbonate is essentially a lipophilic compound showing the following approximate solubilities at room temperature in several solvents: ethanol (2.6%), methanol (4.9%), ethyl ether (43%), chloroform (49%), carbon tetrachloride (37%).

Trichloroethanol has not lent itself to convenient use in therapeutics, but trichloroethyl carbonate possesses pharmaceutical characteristics that permit it to be encapsulated or tableted. In conjunction with appropriate suspending agents, it can be dispersed in water for convenient oral administration.

Acute Oral Toxicity in Mice—The oral LD_{50}'s of the carbonate and the alcohol are 1003 and 930 mg./Kg., respectively (Table I). This indicates the two compounds are equitoxic in mice.

CNS Depressant Activity—Spontaneous Motor Activity in Mice—The oral ED_{50}'s of the carbonate and the alcohol are 288 and 212 mg./Kg., respectively. This indicates the two compounds are equipotent in depressing spontaneous motor activity in mice.

These studies show that, mg. for mg., trichloroethyl carbonate and trichloroethanol are approximately equipotent in depressing spontaneous motor activity and also about equitoxic orally in mice. Studies with other carbonate derivatives, which will be reported in subsequent papers, show that the carbonate linkage is quite labile and subject to enzymatic cleavage by enzymes present in dilute human plasma. The authors infer from these observations that the pharmacological activities manifested after oral administration of trichloroethyl carbonate are the result of *in vivo* regeneration of the parent drug, trichloroethanol. Hydrolytic cleavage of trichloroethyl carbonate yields two molecules of trichloroethanol and a molecule of carbon dioxide for each molecule of parent drug:

$$CCl_3CH_2OC(=O)OCH_2CCl_3 + H_2O \rightarrow 2\ CCl_3CH_2OH + CO_2$$

Subsequent pharmacological studies have been aimed at qualitative as well as quantitative comparisons between trichloroethyl carbonate, trichloroethanol, and chloral hydrate. The results of these studies and of pharmaceutical studies will be reported in future publications. Pharmacology, safety, and utility of this compound in humans have been reported elsewhere (13).

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