six and thirteen injections. Yet the average which must be taken is good, and the majority of the findings are close to the average. The method we present is simpler than that presented by others, in that the tincture may be used directly. The alcohol is not an interfering agent, since it kills, not by action on the heart but by action on the respiratory center, and several times the volume contained in the tincture is required to kill. Pentobarbital, as we have used it, is as good an anesthetic for cats, as for dogs.

In terms of the International Standard, the U. S. P. Reference Powder is 80/62 = 129% or 29 per cent stronger.

The experiments recorded in this paper and that by Blickensdorfer and McGuigan show:

1. That by the use of both dogs and cats, the U. S. P. Reference Powder is 20 per cent stronger than it is labeled. Instead of the factor 0.745, the factor 0.62 is more nearly correct.

2. When a tincture is prepared using 0.62 Gm. of the reference powder in 10 cc. alcohol, or 6.2 Gm. in 100 cc., the dose for dogs is 1.2 cc. per Kg. body weight. The dose for cats is 1.0 cc. per Kg.

3. The results are in harmony with the Hatcher dose for the cat, and agree closely with the results reported by other investigators using the frog method.

We wish to thank the Board of Trustees of the United States Pharmacopœial Convention for furnishing the Digitalis Reference Powder and the International Powder. We express our thanks to Professor E. Fullerton Cook for his courtesy and coöperation.

The Action of Ephedrine on Halogenated Organic Compounds*

By Frank A. Steldt and K. K. Chen

The fact that ephedrine base reacts with chloroform to give ephedrine hydrochloride was first pointed out by Peterson in 1927 (1). To date no other organic compounds have been reported to have a similar reaction with ephedrine, although *a priori* it would seem possible. In order to test the validity of this idea, the present investigation was undertaken.

EXPERIMENTAL

A total of thirty-one halogenated organic compounds was examined. As shown in Tables I and II, twenty-three of the compounds reacted with ephedrine base to give the corresponding halide salt, and one, *o*-chlorobenzaldehyde, gave an addition product. The formation of the last substance is not surprising for ephedrine has been known to react with certain aldehydes, forming addition products in the proportion of one molecule of ephedrine to one molecule of aldehyde with the elimination of one

Table I.—Reaction with Ephedrine Base

Number	Name of Compound	Reaction with Ephedrine Base
1	Allyl bromide	+
2	Allyl iodide	+
3	Allyl chloride	+
4	*i*-Amyl bromide	+
5	*i*-Amyl chloride	+
6	Benzotrichloride	+
7	Benzyl chloride	+
8	Bromal	+
9	Bromoform	+
10	Carbon tetrachloride	+
11	Chloral	+
12	*o*-Chlorobenzaldehyde	+
13	β-β′-Dichlorethyl ether	+
14	Ethyl chloride	+
15	Ethylene chlorhydrin	+
16	Ethylene bromohydrin	+
17	Ethylene dichloride	+
18	Glycerol α-monochlorohydrin	+
19	*n*-Propyl chloride	+
20	Propylene dichloride	+
21	Tribromoethanol (avertin)	+
22	Tribromoethylene	+
23	Trichloroethylene	+
24	*i*-Amyl iodide	+
25	Bromobenzene	−
26	Chlorobenzene	−
27	*o*-Chlorophenol	−
28	Iodobenzene	−
29	*tert*-Butyl chloride	−
30	*o*-Chlorophenetole	−
31	Trichlorobenzene	−

* From the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana.

Table II.—Compounds Formed with Ephedrine Base

Number	Name of Compound	Time of Reaction	M. P. of Compound Formed, ° C. (Corr.)	New Compound Formed	Remarks
10	Carbon tetrachloride	5 minutes	219	Ephedrine hydrochloride	Yellow color on standing
23	Trichloroethylene	Over night	219	Ephedrine hydrochloride	
5	*i*-Amyl chloride	5 days	218.5–219	Ephedrine hydrochloride	
13	β-β'-Dichlorethyl ether	3 hours	213 –215	Ephedrine hydrochloride	
3	Allyl chloride	15 minutes	219	Ephedrine hydrochloride	
11	Chloral	3 hours	217 –218.5	Ephedrine hydrochloride	Heat evolved
19	*n*-Propyl chloride	2 days	218 –219	Ephedrine hydrochloride	
17	Ethylene dichloride	2 days	219 –220	Ephedrine hydrochloride	
20	Propylene dichloride	2 days	219 –220	Ephedrine hydrochloride	
6	Benzotrichloride	2 hours	219 –220	Ephedrine hydrochloride	
7	Benzyl chloride	5 minutes	216 –217	Ephedrine hydrochloride	
14	Ethyl chloride	Over night	216 –217	Ephedrine hydrochloride	Sealed tube; amine odor noted on opening
12	*o*-Chlorobenzaldehyde	15 minutes	123	Addition product	
1	Allyl bromide	5 minutes	204 –205	Ephedrine hydrobromide	Much heat evolved
2	Allyl iodide	15 minutes	164 –165	Ephedrine hydroiodide	Much heat; ppt. brown, tarry
9	Bromoform	3 days	205 –206	Ephedrine hydrobromide	
22	Tribromoethylene	4 hours	206 –207	Ephedrine hydrobromide	Much heat; gas evolved
24	*i*-Amyl iodide	2 days	155 –159	Ephedrine hydroiodide	
8	Bromal	Immediate reaction	208.5	Ephedrine hydrobromide	Much heat; gas evolved; dark brown tarry ppt. in several days
21	Tribromoethanol	4 hours	206 –207	Ephedrine hydrobromide	
15	Ethylene chlorohydrin	2 days	212 –214	Ephedrine hydrochloride	Easily forms saturated soln. with ephedrine hydrochloride
16	Ethylene bromohydrin	2 days	206 –207	Ephedrine hydrobromide	
18	Glycerol α-monochlorohydrin	2 days	217 –218	Ephedrine hydrochloride	
4	*i*-Amyl bromide	4 hours	206 –207.5	Ephedrine hydrobromide	

molecule of water (2). Of special interest are the reactions of ephedrine base with chloral, carbon tetrachloride or avertin (tribromoethanol). It thus becomes obvious that ephedrine on the one hand and chloral, carbon tetrachloride and avertin on the other are incompatible in prescription writing.

The reagents used were the purest obtainable on the market. When impurities due to preparation or spontaneous decomposition were suspected, they were distilled under reduced pressure. The ephedrine base employed was the anhydrous, natural laevo-rotatory form. Each experiment was conducted as follows: Approximately 0.2 Gm. ephedrine base was placed in a test-tube and 5 cc. of the halogenated compound added. The tube was then shaken until the ephedrine went into solution, stoppered loosely and allowed to stand at room temperature for several days. Sometimes frequent shaking facilitated precipitation. The time of reaction varied greatly; in some cases precipitation was complete in five minutes and in others several days were necessary. A positive reaction usually ended in a crystalline white precipitate, although with the bromo and iodo derivatives brown gummy precipitates resulted in a few instances. Heat was evolved in several cases, accompanied by ebullition and effervescence. Upon completion of the reaction, the precipitate was filtered off and washed with ether; then recrystallized from alcohol. The melting point was deter-

mined, and for the sake of identification, a mixed melting-point determination with the respective known ephedrine halides was made.

The compound formed by the reaction of ephedrine base with *o*-chlorobenzaldehyde crystallized in colorless prisms melting at 123° C. (corrected) and had a specific rotation of $[\alpha]_D^{27} = -74.5°$ in alcohol. The substance was insoluble in water and soluble in all common organic solvents, such as ether, acetone, chloroform, ethyl acetate, benzene and alcohol. The reaction took place with great facility, 15 minutes being sufficient for its completion. That it is an addition product of ephedrine and *o*-chlorobenzaldehyde, having the empirical formula $C_{17}H_{18}ONCl$, with the loss of one molecule of water, was proved by combustion analyses as follows:

For $C_{17}H_{18}ONCl$:

Calculated	C = 70.93;	H = 6.31;	N = 4.87; Cl = 12.33.
Found	C = 70.94;	H = 6.25;	N = 4.71; Cl = 12.12.
	C = 70.92;	H = 6.23;	N = 4.69; Cl = 11.88.

In consideration of the results, it becomes apparent that ephedrine readily extracts the halogens from the alkyl, allyl and substituted alkyl halides to form the corresponding halogen salt. To the last class belong the halohydrins, benzyl chloride, benzotrichloride, chloral, bromal and avertin. It fails to react with less reactive substances such as *tert*-butyl chloride. It also fails to react with the halogen atom attached to the benzene ring, although it easily attacks the same when located on the side chain of aromatic compounds. The addition compound with *o*-chlorobenzaldehyde follows a different pattern of reaction since the position of the chlorine atom is obviously not altered.

The exact mechanism of the reaction between ephedrine base and halogenated organic compounds is not yet known, although suggestive explanations may be found in the works of organic chemistry. According to Whitmore (3), (4), amines can react with allyl and alkyl halides to remove halogen acid—this property of amines being due to their basic nature. Similarly, halohydrins (5) hydrolyze rapidly in the presence of weak bases. Since our tests were not made under strictly anhydrous conditions, there was the possibility that the moisture present in the reagents and the atmosphere may have been sufficient for hydrolysis. The insolubility of the ephedrine salts in the reagents used perhaps also favors the displacement of the equilibrium toward their stability after they are formed. Further investigations will be necessary in order to determine the true mechanism of this reaction.

CONCLUSION

1. Of thirty-one halogenated organic compounds studied, anhydrous ephedrine base reacts with alkyl, allyl and substituted alkyl halides to form the corresponding ephedrine halide salt.

2. Carbon tetrachloride, chloral and avertin (tribromoethanol) are therefore incompatible with ephedrine base in prescription compounding.

3. Anhydrous ephedrine base does not react with the halogen atom that is attached to the benzene ring.

4. Anhydrous ephedrine base combines with *o*-chlorobenzaldehyde to form an addition product, $C_{17}H_{18}ONCl$, by the elimination of one molecule of water.

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(5) Whitmore, F. C., *Ibid.*, page 376.

The Preparation of Alkaline Bismuth Saccharates*

By G. O. Doak, Ph.D.

Bismuth in the form of the hydroxide or a soluble salt will dissolve in alkaline solutions of polyhydroxy acids or other polyhydroxy compounds to form solutions which vary in stability with the nature of the hydroxy compound used. In many cases the resulting bismuth complex can be precipitated from solution by the addition of alcohol. The literature contains innumerable examples of this reaction and a number of different structures have been advanced for the resulting bismuth complexes. Warren (1) has discussed the extreme variation in the different bismuth tartrates appearing on the market. Corfield and Adams (2) state that the composition of the bismuth tartrates varies with the method used for preparation. Other authors have recorded similar results with other polyhydroxy acids. Rosenheim (3) has studied these compounds and has assigned structures in

* From the Research Laboratories of George A. Breon and Co., C. W. Sondern, Ph.D., Director.