

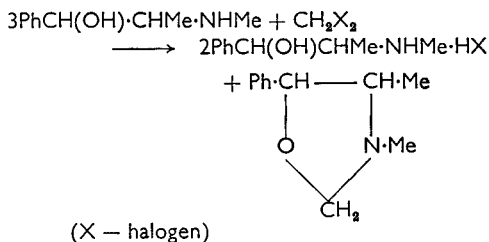
Reaction of ephedrine with chloroform

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IN an official test for ephedrine (British Pharmacopoeia, 1958; British Pharmaceutical Codex, 1963) a solution of the alkaloid in chloroform is allowed to evaporate spontaneously to give a crystalline solid, identical in properties with ephedrine hydrochloride.

It has now been shown that when (–)-ephedrine is refluxed with chloroform B.P. the resulting ephedrine hydrochloride is contaminated with bromide ion. This arises from the impurity, bromochloromethane, which together with dichloromethane is present in chloroform B.P. (Caws & Foster, 1957). When (–)-ephedrine is refluxed with pure bromochloromethane a mixture of the hydrobromide and hydrochloride salts of the alkaloid is formed in equimolecular proportions. (–)-Ephedrine apparently reacts more readily with chloroform B.P. than with purified chloroform in which bromochloromethane is absent.

In addition to the alkaloidal salts a colourless oil is obtained whose infra-red spectrum is identical with 3,4-dimethyl-5-phenyloxazolidine. This is formed from the dihalomethane in accordance with the equation:



The formation of 3,4-dimethyl-5-phenyloxazolidine is in line with the reported formation of an oxazolidone from ephedrine and carbon tetrachloride (Hyne & Calosing, 1963; Pesez & Bartos, 1963).

EXPERIMENTAL

Chloroform B.P. was purified by the method of Caws & Foster (1957). This yielded chloroform (b.p. 60·5–61·0° n_D^{20} 1·4455) free from bromochloromethane and dichloromethane. (–)-Ephedrine, anhydrous: b.p. 132°/5 mm was obtained by vacuum distillation of (–)-ephedrine B.P. 1958. This was used immediately. Infra-red spectra were recorded in potassium bromide discs.

Comparison of reaction rates. The reaction of ephedrine with chloroform was followed by measuring the amount of halide ion liberated after

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definite time intervals at 60°. Proportions of base to chloroform of 0.01 to 0.03 moles gave measurable quantities of halide ion using the technique of Williams (1959). The results (Fig. 1) indicate (a) that both (—)-ephedrine B.P. (1958, hemihydrate) and (—)-ephedrine, anhydrous, are much more reactive towards chloroform B.P. than to purified chloroform and (b) that (—)-ephedrine B.P. is more reactive than (—)-ephedrine, anhydrous, towards both samples of chloroform.

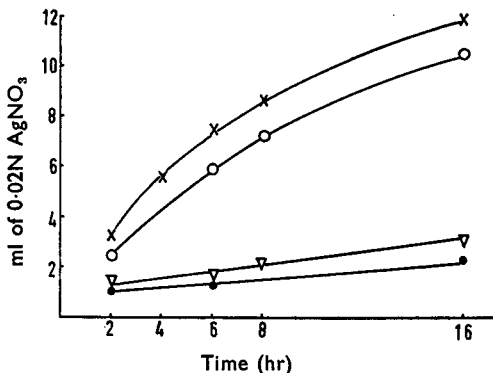


FIG. 1. Reaction between ephedrine, 0.01 moles, and chloroform, 0.03 moles. Temperature 60°. ×, Ephedrine B.P. and chloroform B.P. ○, Ephedrine, anhydrous and chloroform B.P. ∇, Ephedrine B.P. and purified chloroform. ●, Ephedrine, anhydrous and purified chloroform.

Investigation of reaction products. The alkaloid was refluxed (48 hr) with excess chloroform (B.P. or purified). The precipitate was filtered off and the filtrate refluxed further up to 48 hr when additional precipitate was formed. Concentration of the filtrate under vacuum gave further small amounts of solid and finally, unchanged ephedrine. The bulked crystalline product was washed with solvent and dried in a vacuum.

The results from various experiments are as follows:

(a) Ephedrine B.P. 1958 (17.4 g, 0.1 mole) in chloroform B.P. (1.5 moles) gave a product (2.3 g) m.p. 213°. Found: Cl, 14.5; Br, 8.8%.

(b) (—)-Ephedrine, anhydrous (16.5 g, 0.1 mole) in chloroform B.P. (1.5 mole) gave a product (1.6 g) m.p. 215°. Found: Cl, 10.4; Br, 14.7%.

(c) Ephedrine B.P. 1958 (8.7 g, 0.05 mole) in purified chloroform (0.5 mole) gave a product (0.47 g) m.p. 219°. Found: Cl, 17.8. Calc. for $C_{10}H_{15}NO.HCl$; Cl, 17.6%.

(d) (—)-Ephedrine, anhydrous (16.5 g, 0.1 mole) in purified chloroform (0.5 mole) gave a product (0.17 g) m.p. 217°. Found: Cl, 17.9. Calc. for $C_{10}H_{15}NO.HCl$; Cl, 17.6%.

In (a) and (b) the product had an infra-red spectrum identical with the ephedrinium ion. The product in (c) and (d) gave no depression on admixture with authentic ephedrine hydrochloride.

(e) Ephedrine B.P. 1958 (0.5 g) was dissolved in redistilled bromochloromethane (10 ml) and the solution allowed to stand at room temperature for several hr. The solid mass was filtered off and washed with chloroform to give a white crystalline solid (0.34 g) m.p. 212°. Found: C, 53.6; H, 6.8; Br, 18.0; Cl, 8.0; N, 6.3. Calc. for an equimolecular mixture of $C_{10}H_{15}NO.HCl$ and $C_{10}H_{15}NO.HBr$: C, 53.6; H, 7.2; Br, 17.9; Cl, 7.9; N, 6.3%.

(f) (—)-Ephedrine, anhydrous (16.5 g, 0.1 mole) in dry benzene (75 ml) was refluxed (48 hr) with redistilled bromochloromethane (65 g, 0.5 mole). After removal of the crystalline solid the filtrate was further refluxed (12 hr) when more solid separated. Total yield: 13.6 g, m.p. 213°, producing no depression on admixture in equal proportions with authentic ephedrine hydrochloride and hydrobromide. The infra-red spectrum was identical with that of ephedrinium ion. Found: Br, 17.1; Cl, 8.4; N, 6.2. Calc. for an equimolecular mixture of $C_{10}H_{15}NO.HCl$ and $C_{10}H_{15}NO.HBr$: Br, 17.9; Cl, 7.9; N, 6.3%. After removal of all solids the filtrate was concentrated to yield a colourless oil (A) (5.48 g) b.p. 122°/8 mm, n_D^{20} 1.5248, $[\alpha]_D^{20}$ -5.0 (EtOH).

(g) (—)-Ephedrine, anhydrous (16.5 g, 0.1 mole) in dry benzene (75 ml) was refluxed (48 hr) with redistilled dibromomethane (87 g, 0.5 mole). After removal of the precipitate the filtrate was further refluxed (12 hr) when the solid formed was again filtered off. Total yield: 14.63 g, m.p. 211°, giving no depression on admixture with ephedrine hydrobromide. The infra-red spectrum was identical with that of ephedrine hydrobromide. Found: Br, 32.5. Calc. for $C_{10}H_{15}NO.HBr$: Br, 32.5%. Concentration of the filtrate gave a colourless oil (B) (4.89 g) b.p. 118°/6 mm, n_D^{20} 1.5242, $[\alpha]_D^{20}$ -5.2 (EtOH).

(—)-3,4-Dimethyl-5-phenyloxazolidine was prepared from (—)-ephedrine and formaldehyde (Bergmann, Zimkin & Pinchas, 1952). This was a colourless oil b.p. 125°/12 mm, n_D^{20} 1.5242, $[\alpha]_D^{20}$ -5.6 (EtOH). Found: C, 74.0; H, 8.5; N, 8.0. Calc. for $C_{11}H_{15}NO$: C, 74.6; H, 8.5; N, 7.9%.

The infra-red spectrum (liquid) of this compound was identical with (A) and (B) above.

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