Anal.—Calcd. for $C_{14}H_{15}NO$: C, 78.8; H, 7.1; N, 6.6. Found: C, 78.9; H, 7.4; N, 6.3.

2-(p-Chlorophenyl)-3-methyloxazolidine (Vb)—As described for V*a*, this compound was prepared from IV*b* in a yield of 80%[8]; b.p. 92–94° (0.1 mm.), n_D^{20} 1.5394.

Anal.—Calcd. for $C_{10}H_{12}ClNO$: C, 60.8; H, 6.1; Cl, 17.9; N, 7.1. Found: C, 60.9; H, 6.3; Cl, 18.0; N, 6.9.

4-(Butyl-2-hydroxyethyl)amino-1-methylpiperidine (IIIb)—Compound II*b* (10 g.), 1 g. of platinum oxide and 80 ml. of methanol absorbed one molar equivalent of hydrogen during 6 hr. giving 9.6 g. of III*b*, b.p. 86° (0.05 mm.), $\nu_{max.}^{film}$ 3,250 cm.$^{-1}$.

Anal.—Calcd. for $C_{12}H_{26}N_2O$: C, 67.2; H, 12.2; N, 13.1. Found: C, 67.0; H, 12.4; N, 13.0.

Similarly prepared (quantitative yield) were III*a* (*Anal.*—Calcd. for $C_{10}H_{22}N_2O_2$: C, 59.4; H, 11.0; N, 13.9. Found: C, 59.3; H, 10.7; N, 13.9) and III*c*, b.p. 43° (0.15 mm.) (*Anal.*—Calcd. for $C_9H_{20}N_2O$: C, 62.7; H, 11.7; N, 16.3. Found: C, 62.6; H, 11.7; N, 15.8) from II*a* and II*c*, respectively.

2-[Methyl(2-naphthylmethyl)]aminoethanol (VIa)—Hydrogenation of 9 g. of V*a* in methanol (1 g. of platinum oxide) required 1.5 hr. and gave a 90% yield of VI*a* after short-pass distillation at 150° (0.1 mm.); $\nu_{max.}^{film}$ 3,250 cm.$^{-1}$.

[8] Also isolated in 10% yield was the 2-methylaminoethanol salt of *p*-chlorobenzoic acid, m.p. 95–97° alone or in mixture with authentic material. This must have resulted from a Cannizzaro reaction on IV*b*.

Anal.—Calcd. for $C_{14}H_{17}NO$: C, 78.1; H, 8.0; N, 6.5. Found: C, 78.2; H, 8.2; N, 6.7.

The hydrochloride of VI*a* (from acetone) melted at 114–115°.

Anal.—Calcd. for $C_{14}H_{18}ClNO$: C, 66.8; H, 7.2; Cl, 14.1; N, 5.6. Found: C, 66.6; H, 7.1; Cl, 14.2; N, 5.5.

Similarly V*b* gave VI*b*; hydrochloride salt, m.p. 126–127° (from methanol); $\nu_{max.}^{CHCl_3}$ 3,400, cm.$^{-1}$ yield 99%.

Anal.—Calcd. for $C_{10}H_{15}Cl_2NO$: C, 50.9; H, 6.4; Cl, 30.0; N, 5.9. Found: C, 50.8; H, 6.4; Cl, 29.7; N, 5.8.

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New Compounds: Preparation of Some Esters of Trihalogenated Alcohols

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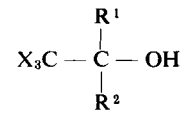
Abstract □ The syntheses of a number of esters of trihalogenated monohydroxy alcohols are described. The results of preliminary pharmacological tests are reported.

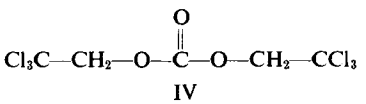
Keyphrases □ Trihalogenated monohydroxy alcohol esters—synthesis □ Analgesic activity—trihalogenated monohydroxy alcohol esters

The useful depressant properties of trihalogenated monohydroxy alcohols such as 2,2,2-trichloroethanol (I), 2,2,2-tribromoethanol (II), and 1,1,1-tribromo-2-methyl-2-propanol (III) are well-known (1). A number of esters of the alcohols above also have been evaluated for hypnotic activity (1). Recently, Swintosky *et al.* (2)



I, X = Cl, $R^1 = R^2 = H$
II, X = Br, $R^1 = R^2 = H$
III, X = Br, $R^1 = R^2 = CH_3$

reported on the sedative properties of bistrichloroethyl carbonate (IV). The presence of the 3,4,5-trimethoxybenzoyl and 3,4,5-trimethoxycinnamoyl group in the rauwolfia alkaloids (3) and other artifacts possessing CNS activities prompted the preparation of 3,4,5-trimethoxybenzoates and 3,4,5-trimethoxycinnamates of some of the same trihalogenated monohydroxy alcohols.



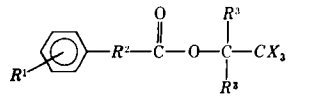
IV

The esterifications of alcohols substituted in the β-position by halogens are difficult because of their acidic nature arising from the inductive effect of the halogens. Such alcohols as 2,2,2-trichloroethanol and 2,2,2-tribromoethanol are not easily esterified by an acid. With an acid halide, esterification has been accomplished by heating the alcohol and acyl halide at temperatures up to 130° without a solvent medium (4–7). Hill reported (8, 9) that acidic alcohols were easily esterified with acyl halides under mild conditions using catalytic amounts of aluminum chloride or aluminum bromide. The results of the preparations of esters of representative acid chlorides utilizing the procedure of Hill (8, 9) are summarized in Table I.

Preliminary pharmacological studies[1] in mice were carried out with Compounds 3, 4, 5, 6, and 7 of Table I.

[1] The authors are grateful to Dr. H. Leo Dickison, Bristol Laboratories, Syracuse, N. Y. for the pharmacological data.

Table I—Esters of Trihalogenated Monohydroxy Alcohols



No.	R^1	R^2	R^3	X	M.p., °C. Recrystn. Solvent[a]	% Yield	Mol. Formula	Anal. Calcd.	Anal. Found
1	3,4,5-OCH_3	—	H	Br	103–104, M	80	$C_{12}H_{13}Br_3O_5$	C, 30.25 H, 2.74	C, 30.36 H, 2.93
2	3,4,5-OCH_3	—	CH_3	Br	130–131, A	—	$C_{14}H_{17}Br_3O_5$	C, 33.29 H, 3.39 Br, 47.48	C, 33.39 H, 3.42 Br, 47.38
3	3,4,5-OCH_3	—	H	F	64–65, A	70	$C_{12}H_{13}F_3O_5$	C, 48.90 H, 4.45 F, 19.37	C, 49.56 H, 4.64 F, 19.40
4	H	—CH=CH—	H	Br	52–53, P	78	$C_{11}H_9Br_3O_2$	C, 31.99 H, 2.197 Br, 58.07	C, 32.06 H, 2.28 Br, 57.94
5	H	—CH=CH—	H	F	82/0.7 mm.[b]	80	$C_{11}H_9F_3O_2$	C, 57.42 H, 3.90 F, 24.7	C, 57.14 H, 4.20 F, 24.9
6	3,4,5-OCH_3	—CH=CH—	H	Br	137–138, E	31	$C_{14}H_{15}Br_3O_5$	C, 33.42 H, 3.00 Br, 47.60	C, 33.26 H, 3.03 Br, 47.60
7	3-OCH_3	—	H	Br	52–53, M	82	$C_{10}H_9Br_3O_3$	C, 28.80 H, 2.17 Br, 57.51	C, 28.78 H, 2.22 Br, 56.98

[a] A = acetone; E = ethanol; P = petroleum ether (30–45°); M = methanol. [b] Boiling point.

Compounds 4 and 5 demonstrated mild analgesic activity at 150 mg./kg., whereas Compounds 3, 6, and 7 were inactive in CNS and analgesic studies.

EXPERIMENTAL[2]

The trihalogenated alcohols and most of the acid chlorides were obtained from commercial sources. 3,4,5-Trimethoxycinnamoyl chloride was prepared according to the procedure described in the literature (10).

Esters of Trihalogenated Monohydroxy Alcohols (Table I)—The esterifications of the trihalogenated alcohols were effected according to the procedure described by Hill (8, 9). To a mixture of 0.02 mole of halogenated alcohol and 0.02 mole of acid chloride in 10 ml. of carbon tetrachloride was added in small portions 0.529 g. (0.004 mole) of finely powdered aluminum chloride. The reaction mixture was allowed to stand for 10 min. at room temperature and thereafter refluxed for 3 hr. The solvent was removed under reduced pressure and the residue treated with excess ice-cold dilute hydrochloric acid. The precipitated solid was removed by filtration and washed successively with a saturated solution of sodium bicarbonate and water. The air-dried solid was recrystallized from a suitable solvent.

In the case of Compound 5 of Table I, the reaction mixture was poured into cold dilute hydrochloric acid and extracted with ether. The ether extract was dried, evaporated, and the residue distilled under reduced pressure to give the desired product.

[2] All melting points were taken on a Fisher-Johns apparatus and are not corrected.

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