[CONTRIBUTION FROM THE SCHOOL OF PHARMACY, UNIVERSITY OF GEORGIA]

Some Hemiacetals of Chloral with Cyclic Alcohols

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Introduction

Some interest has been shown in the hemiacetals of chloral, $CCl_3CHOH(OR)$, as neurophilic agents.[3] This paper describes the synthesis of some hemiacetals of chloral with cyclic alcohols, and reports preliminary pharmacological data on one of them.

Experimental

The chloral used in this work was obtained by mixing U. S. P. grade chloral hydrate with 1.8 times its weight of concentrated sulfuric acid, allowing the chloral to separate, and then distilling it off in an all-glass apparatus. The cyclohexanol and *p*-methylcyclohexanol, obtained from the Eastman Kodak Company, the 1-ethynylcyclohexanol from Farchan Laboratories, and the 3,3,5-trimethylcyclohexanol from the Carbon and Carbide Chemicals Corporation, were dried over anhydrous sodium sulfate, and used without further purification.

One-tenth mole each of chloral and the cyclic alcohol in separate flasks were cooled to 2°. The alcohol was added in ten equal portions at ten-minute intervals to the chloral, placing both flasks in the refrigerator after each addition. The mixture was kept at 2° until it solidified, which required not more than three days, stored for several days in an evacuated desiccator containing calcium chloride and then recrystallized from petroleum ether, b. p. 75–85°.

The high solubility of these hemiacetals (Table I) in a wide variety of solvents makes difficult their isolation and purification. Of the many solvents and combinations of solvents tried, only ligroin was suitable, and the fraction boiling between 75–85° gave the best results.

Several cyclic alcohols, *o*-methylcyclohexanol, *m*-methylcyclohexanol and *p-t*-butylcyclohexanol, gave hemiacetals with chloral which did not solidify under the experimental conditions. Efforts to purify them by careful distillation at pressures ranging from 2 to 20 mm. and at atmospheric pressure, with the use of glass wool,[4] resulted in their almost complete dissociation into chloral and the alcohol.

TABLE I

HEMIACETALS OF CHLORAL WITH CYCLIC ALCOHOLS $CCl_3CHOH(OR)$

R	Formula	Yield, %	M. p., °C.	C analyses, % Calcd.	C analyses, % Found	H analyses, % Calcd.	H analyses, % Found
Cyclohexyl	$C_8H_{13}O_2Cl_3$	82	64	38.88	39.01	5.25	5.45
p-Methylcyclohexyl	$C_9H_{15}O_2Cl_3$	30	60	41.30	41.24	5.73	5.74
1-Ethynylcyclohexyl	$C_{10}H_{14}O_2Cl_3$	41	55	44.19	43.71	4.78	4.70
3,3,5-Trimethylcyclohexyl	$C_{11}H_{19}O_2Cl_3$[a]	33	73	45.61	46.05	6.57	7.17

[a] This compound was prepared also from a sample of 3,3,5-trimethylcyclohexanol which is distributed under the name "Cyclonol" as a synthetic substitute for menthol by W. J. Bush and Co., Inc.

Pharmacological.—1-Cyclohexoxy-2,2,2-trichloroethanol in a dosage of 800 mg./kg. narcotized all of five rats injected for an average latent period of fifty minutes, and in a dosage of 1500 mg./kg. gave 100% mortality in a like number of rats.

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Summary

Four new hemiacetals of chloral with cyclic alcohols have been synthesized and described. The relative narcotic activity and toxicity in rats of one of these compounds have been ascertained.

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(4) Morton, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1938, p. 104.