Catechol Monoglyceryl Ether Carbamates

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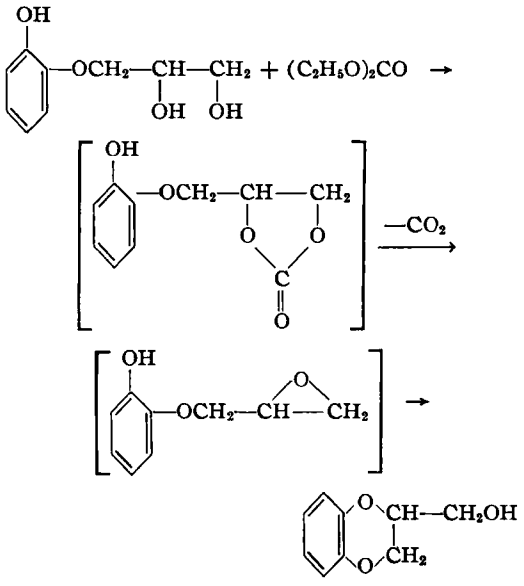
A series of carbamates and N-methylcarbamates derived from 3-(*o*-hydroxyphenoxy)-1,2-propanediol was prepared and screened for muscle relaxant activity. An ester interchange between the above diol and diethyl carbonate failed to give 4-(*o*-hydroxyphenoxymethyl)-1,3-dioxolone-2; 2-hydroxymethyl-1,4-benzodioxane was obtained instead. Prior benzylation of the phenolic hydroxyl resulted in the normal formation of the dioxolone. None of the compounds possessed muscle relaxant activity.

THE SUCCESS of 3-(*o*-methoxyphenoxy)-2-hydroxy-1-propyl carbamate, methocarbamol[1] as a muscle relaxant prompted evaluation of similar activity in carbamates derived from the monoglycerol ether of catechol, 3-(*o*-hydroxyphenoxy)-1,2-propanediol (1).

DISCUSSION

The monocarbamates were prepared by the reaction of ammonia and methylamine with 4-(*p*-benzyloxyphenoxymethyl)-1,3-dioxolone-2, followed by debenzylation with hydrogen over palladium-on-charcoal. The blocking of the phenolic hydroxyl group was required when it was discovered that 3-(*o*-hydroxyphenoxy)-1,2-propanediol would not form the corresponding cyclic carbonate, 4-(*o*-hydroxyphenoxymethyl)-1,3-dioxolone-2, upon ester interchange with diethyl carbonate. Instead 2-hydroxymethyl-1,3-benzodioxane was formed. It may be that the initially formed dioxolone decomposed under the conditions of the experiment to give the 1,2-epoxide which then cyclized to the dioxane by reaction with the phenolic hydroxyl



The activation of pyrolysis of cyclic carbonates by hydroxyl groups has been reported by D. B. Pattison (2). For example, he found that a mixture of 2,2-diethylpropanediol and its cyclic carbonate could be distilled at 220° at slightly reduced pressure, whereas the cyclic carbonate of trimethylolpropane decomposed rapidly at 180–200° to give 3-ethyl-3-oxetane methanol. It may well be that a phenolic group may exert a still more powerful influence on the elimination of CO_2 since the internal temperature during the experiment did not exceed 140°.

3-(*o*-Benzyloxyphenoxy)-1,2-propanediol (Table I, No. 1) was prepared by the reaction of 3-(*o*-hydroxyphenoxy)-1,2-propanediol with benzyl chloride in the presence of aqueous sodium hydroxide.

Compound 1 was heated with an excess of diethyl carbonate in the presence of sodium methylate to form 4-(*o*-benzyloxyphenoxymethyl)-1,3-dioxolone-2 (Table I, No. 2).

Compound 2 reacted readily with ammonia and methylamine in isopropyl alcohol solution to give in each case a mixture of two isomeric monocarbamates. These were separated by fractional crystallization into the primary and secondary monocarbamates, Table I, Nos. 3–6. The higher melting member of the pair was tentatively assigned the secondary carbamate structure (3).

Each of these monocarbamates was then debenzylated by hydrogenolysis over palladium-on-charcoal to the corresponding 3-(*o*-hydroxyphenoxy)-1(2)-2(1)-propyl carbamates (N-methylcarbamates) Table I, Nos. 7–10

3-(*o*-N-methylcarbamoxyphenoxy)-1,2-bis-N-methylcarbamoxypropane, Table I, No. 11, was prepared by the reaction of 3-(*o*-hydroxyphenoxy)-1,2-propanediol with excess methyl isocyanate.

The reaction of Compound 1 with methyl isocyanate yielded 3-(*o*-benzoyloxyphenoxy)-1,2-bis-N-methylcarbamoxypropane, Table I, No. 12. Debenzylation of Compound 12 gave 3-(*o*-hydroxyphenoxy)-1,2-bis-N-methylcarbamoxypropane, Table I, No. 13.

EXPERIMENTAL

Reaction of 3-(*o*-Hydroxyphenoxy)-1,2-propanediol with Diethyl Carbonate.—A mixture of 18.4 Gm. (0.1 mole) of 3-(*o*-hydroxyphenoxy)-1,2-propanediol, 35.4 Gm. (0.3 mole) of diethyl carbonate, and 0.5 Gm. of sodium methylate was heated until the distillation of ethyl alcohol ceased. A 1-Gm. quantity of ammonium chloride was added to destroy the sodium methylate. The excess diethyl carbonate was removed at reduced pressure and a maximum internal temperature of 140°. The resi-

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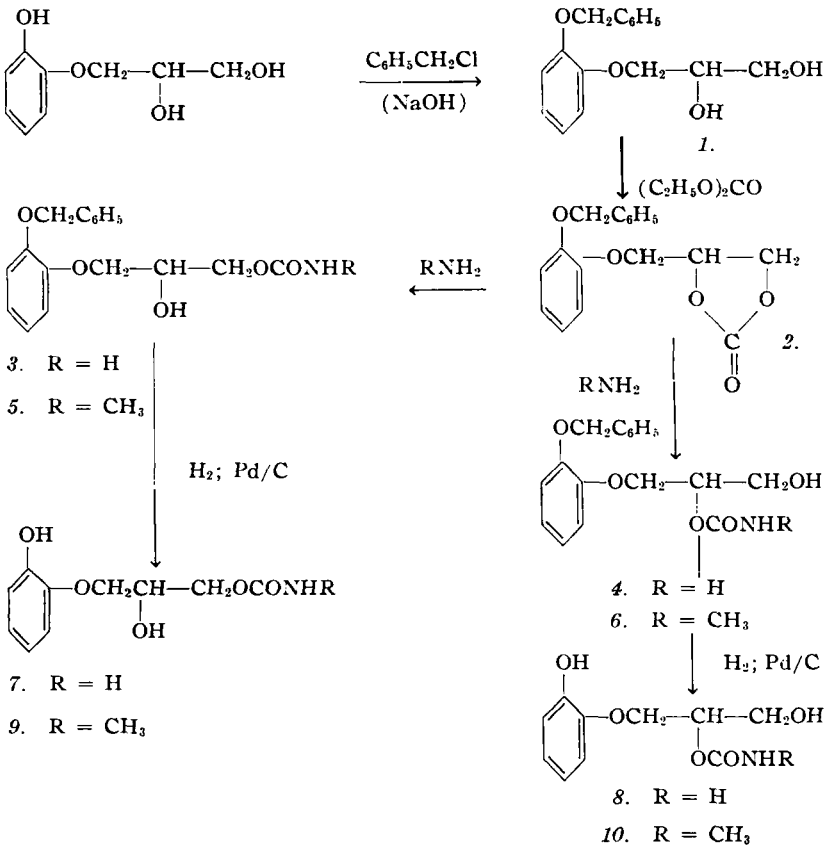
[1] Marketed as Robaxin by A. H. Robins Co., Inc., Richmond, Va.



due was extracted with boiling cyclohexane to give on cooling 7.9 Gm. of a solid, m.p. 83–86°. Recrystallized from ethyl acetate, it melted at 89–90°. A large depression in melting point was found on admixing with starting material (m.p. 90°). A test for a phenolic group with $FeCl_3$ was negative, and the infrared absorption spectrum showed no maximum for a carbonyl group. The IR absorption spectrum, however, was found to be identical with that of 2-hydroxymethyl-1,4-benzodioxane, which was prepared according to Grün (4) from epichlorohydrin and catechol, m.p. 89–90°. There was no depression in melting point on mixing the two compounds.

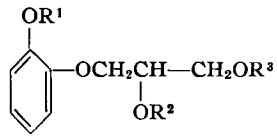
3 - (*o* - Benzyloxyphenoxy) - 1,2 - propanediol.—A mixture of 92.1 Gm. (0.5 mole) of 3-(*o*-hydroxyphenoxy)-1,2-propanediol, 62.5 Gm. (0.5 mole) of benzyl chloride and a solution of 24 Gm. (0.6 mole) of sodium hydroxide in 500 ml. water was heated to reflux with stirring for 2 hours. The mixture was cooled and the product extracted with ether. The ether was removed and the residue vacuum distilled to yield 82.1 Gm. (59.8%) of 3-(*o*-benzyloxyphenoxy)-1,2-propanediol-1, b.p. 200–218° at 0.4 mm. The product solidified on standing; the melting point was 81.0 to 82.5° after recrystallization from carbon tetrachloride. The crude distilled material was found to be suitable for subsequent reactions.

4 - (*o* - Benzyloxyphenoxymethyl) - 1,3 - dioxolone-2.—A mixture of 27.4 Gm. (0.1 mole) of 3-(*o*-benzyloxyphenoxy)-1,2-propanediol, 35.4 Gm. (0.3 mole) of diethyl carbonate, and 0.3 Gm. of sodium methylate was heated until ethyl alcohol distillation ceased (maximum internal temperature, 135°). A 0.5-Gm. quantity of ammonium chloride was added to destroy the sodium methylate, and excess diethyl carbonate was removed by vacuum distillation. The residue was dissolved in 400 ml. of hot isopropyl alcohol, treated with 0.5 Gm. of Darco G-60, filtered, and allowed to crystallize to yield 24 Gm. (80%) of 4 - (*o* - benzyloxyphenoxymethyl) - 1,3 - dioxolone-2, m.p. 74–75°.

3 - (*o* - Benzyloxyphenoxy) - 1(2) - hydroxy - 2(1)-propyl Carbamates and N-Methylcarbamates.—The general method for the preparation of these hydroxypropyl carbamates was as follows: ammonia or methylamine (1.2 moles) dissolved in isopropyl (or aqueous isopropyl) alcohol was reacted with compound 2, (1 mole). After standing at room temperature for 4–24 hours, the volatile material was distilled at reduced pressure, and the residue recrystallized from ethyl acetate or isopropyl alcohol to give the higher melting 1-hydroxy-2-carbamate (N-methylcarbamate). The residue from the mother liquor of this crystallization was then recrystallized from petroleum ether-benzene to give the lower melting isomer, the 2-hydroxy 1-carbamate (N-methylcarbamate). The yields of both isomers are based on the amount of Compound 2.

3 - (*o* - Hydroxyphenoxy) - 1(2) - hydroxy - 2(1)-propyl Carbamates and N-Methylcarbamates.—The general method for the removal of the benzyl group from the above benzyloxy carbamates was to shake an isopropyl alcohol solution of the benzyl ether with hydrogen at 2–5 p.s i. over 15% palladium-on-charcoal at 25–50° (the reaction mixture was heated if the hydrogen absorption was sluggish

TABLE I.—COMPOUNDS PREPARED



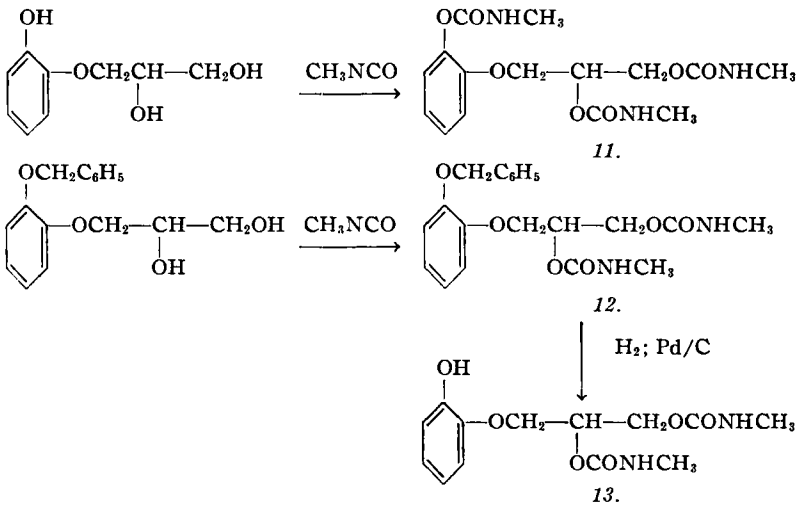
No.	R¹	R²	R³	M.p., °C.	Yield, %	Formula	Anal. Calcd. % C	Calcd. % H	Found % C	Found % H
1	$CH_2C_6H_5$	H	H	81–82.5	59.8	$C_{16}H_{18}O_4$	70.01	6.60	70.28	6.61
2	$CH_2C_6H_5$	—CO—		74–75	80.0	$C_{17}H_{16}O_5$	67.99	5.37	67.82	5.57
3	$CH_2C_6H_5$	H	$CONH_2$	73.6–74.8	24.7	$C_{17}H_{19}O_5N$	4.41% N		4.18% N	
4	$CH_2C_6H_5$	$CONH_2$	H	86.6–87.6	48.6	$C_{17}H_{19}O_5N$	4.41% N		4.21% N	
5	$CH_2C_6H_5$	H	$CONHCH_3$	53–55	58.2	$C_{18}H_{21}O_5N$	4.23% N		4.16 N	
6	$CH_2C_6H_5$	$CONHCH_3$	H	66.5–68	16.7	$C_{18}H_{21}O_5N$	4.23% N		4.12% N	
7	H	H	$CONH_2$	116–118	72.0	$C_{10}H_{13}O_5N$	6.17% N		6.02% N	
8	H	$CONH_2$	H	125–126	59.2	$C_{10}H_{13}O_5N$	6.17% N		6.06% N	
9[a]	H	H	$CONHCH_3$	76–78	45.7	$C_{11}H_{15}O_5N$	5.81% N		5.68% N	
10[a]	H	$CONHCH_3$	H	78–79.5	77.0	$C_{11}H_{15}O_5N$	5.81% N		5.71% N	
11	$CONHCH_3$	$CONHCH_3$	$CONHCH_3$	122–124	61.5	$C_{15}H_{21}O_7N_3$	11.85% N		11.34% N	
12	$CH_2C_6H_5$	$CONHCH_3$	$CONHCH_3$	122–124	54.7	$C_{20}H_{24}O_6N_2$	7.21% N		7.26% N	
13	H	$CONHCH_3$	$CONHCH_3$	55–57	54.3	$C_{13}H_{18}O_6N_2$	9.39% N		9.12% N	

[a] Mixed m.p. 73–76°.

or did not occur at room temperature). The reaction mixture was filtered from the catalyst, evaporated to dryness, and recrystallized from petroleum ether–benzene.

3-(*o*-N-Methylcarbamoxyphenoxy)-1,2-bis-N-methylcarbamoxypropane.—A benzene solution of 36.8 Gm. (0.2 mole) of 3-(*o*-hydroxyphenoxy)-1,2-propanediol was stirred with a large excess of methyl isocyanate and a few drops of pyridine as catalyst until the product crystallizing from the solution was no longer oily. Filtration yielded 43.7 Gm. (61.5%) of 3-(*o*-N-methylcarbamoxyphenoxy)-1,2-bis-N-methylcarbamoxypropane, Table I, No. 11; m.p. 122–124°.

3-(*o*-Benzyloxyphenoxy) and 3(*o*-Hydroxyphenoxy)-1,2-bis-N-Methylcarbamoxypropane.—A benzene solution of 19.2 Gm. (0.07 mole) of Compound 1 was reacted with an excess of methyl isocyanate and a few drops of pyridine. The product which precipitated was filtered to give 14.9 Gm. (54.7%) of 3-(*o*-benzyloxyphenoxy)-1,2-bis-N-methylcarbamoxypropane, Table I, No. 12, m.p. 122–124°. Compound 12, 11.6 Gm., was then debenzylated to 4.8 Gm. (54.3%) of 3-(*o*-hydroxyphenoxy) 1,2-bis-



N-methylcarbamoxypropane, Table I, No. 13, m.p. 55–57°, using the previously given procedure.

BIOLOGICAL RESULTS

All of the above carbamates except Compound 13, for which no suitable vehicle could be found, were screened for muscle relaxant activity in mice. A substance was said to possess muscle relaxant activity if a given dose caused the hind portion of the test animal to go limp while it was still able to walk on its front legs, dragging the back ones behind. All known muscle relaxants gave this test. Using this criterion, none of the above compounds showed significant muscle relaxant activity up to 1000 mg./Kg. However, the ability to delay the onset of pentylenetetrazol induced convulsions appeared to be general, particularly in Compounds 9 and 10.

No deaths to mice resulted from oral intubation of doses up to 1 Gm. per kilogram. Ataxia, paralysis, convulsions, and decreased respiration were notably absent in all tests at these levels.

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Toxicity of Plastics Used in Medical Practice I

Investigation of Tissue Response in Animals by Certain Unit Packaged Polyvinyl Chloride Administration Devices

By W. H. LAWRENCE†, J. L. MITCHELL‡, W. L. GUESS, and J. AUTIAN

In the past workers in our laboratory and other investigators have noted that polyvinyl chloride tubings used in medical practice, as administration or collection devices, will release one or more constituents to several types of solvent systems used in pharmacy. Since a great many formulations may be employed in manufacturing these plastic tubings, it was thought that a toxicity study might reveal if one or more of the currently used plastic administration devices might contain an ingredient which could produce a tissue response when implanted in animals. The results of the study revealed that under the experimental conditions used in this study a number of the tubings will produce tissue response while others will not.

For the past number of years, workers in our laboratory have attempted to focus attention on certain problems which might develop in the improper use of plastics, while at the same time encouraging research to develop products which would give the advantages of plastics without introducing potential hazards (1–5). Several approaches in research to the plastic problem have since been undertaken by the laboratory from an academic viewpoint and as a public health service. The work reported in this paper is the first of a series devoted to the exploration of the acute and toxic properties of plastics and the various ingredients which might be incorporated within the polymer to achieve a desired plastic which may be used in medical practice. Specifically, this paper will be devoted to ascertaining if certain plastic tubings (primarily of the polyvinyl chloride type) which are parts of administration devices might contain an ingredient or ingredients which could be considered toxic if released into animal tissue.

EXPERIMENTAL

Selection of Samples for Investigation.—Various types of administration devices having a polyvinyl chloride tubing as a component were obtained in their original package. A number of these packages indicated that the contents were sterile and nonpyrogenic. Each sample was assigned a code number with the manufacturer's name designated by a specific letter. Forty-eight different samples of administration devices from 17 manufacturers or distributors were employed in the investigation (see Table I). Several polyethylene tubings and one unidentified tubing used in a hospital were also included in the total number of samples.

Implantation Studies.[1]—In all the studies reported here only the tubings were evaluated, the other portions of the administration devices being stored for

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[1] This technique was recommended to our laboratory by Dr. J. H. Brewer and Dr. H. H. Bryant, Hynson, Westcott and Dunning Laboratory, Baltimore, Md.