picric acid:hydrocarbon ratio not in agreement with the expected equimolal ratio.

Anal. Calcd. for $C_{27}H_{17}O_7N_3$: C, 65.45; H, 3.46. Found: C, 67.05, 67.02; H, 3.63, 3.68.

The over-all yield of 9-methyl-3,4-benzpyrene from purified (1,2,3,11b-tetrahydro-7H-*meso*-benzanthrenyl-3)-acetic acid (V) was 38%. When the crude V, m.p. 150–200°, was carried through the reaction sequence described above without isolation of the acid VI or the ketone VII, the over-all yield was reduced to about 15% and pure 9-methyl-3,4-benzpyrene could only be obtained through the picrate.

8,9-Dimethyl-3,4-benzpyrene (IX).—A Grignard reagent was prepared in the usual manner from 0.24 g. (0.01 g. atom) of magnesium and 2.3 g. (0.016 mole) of methyl iodide in 20 ml. of absolute ether. The ketone VII, 0.63 g. (0.0022 mole), m.p. 135.5–137°, dissolved in 20 ml. of anhydrous benzene was added dropwise to the Grignard solution. After standing at room temperature for 2.5 hr., the reaction mixture was hydrolyzed with dilute hydrochloric acid. The organic layer was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent left **8-hydroxy-8,9-dimethyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene** as a viscous yellow oil.

The crude alcohol was dehydrated and dehydrogenated by heating with 0.1 g. of 10% palladium–charcoal at 270–340° for 0.5 hr. during which time about 65% of the theoretical amount of hydrogen was evolved. After cooling, the hard cake was dissolved in boiling benzene and the solution filtered to remove the catalyst. The crude hydrocarbon was chromatographed through an alumina column and concentration of the eluents yielded 0.39 g. of **8,9-dimethyl-3,4-benzpyrene (IX)** as yellow needles, m.p. 214.5–217° (vac.). The mother liquors yielded an additional 0.05 g. of hydrocarbon, m.p. 214.5–216° (vac.), making the total yield 0.44 g. (72% from VII). An analytical sample, m.p. 214.5–216° (vac.), was prepared by crystallization from ethyl acetate followed by sublimation at reduced pressure.

Anal. Calcd. for $C_{22}H_{16}$: C, 94.25; H, 5.75. Found: C, 93.89; H, 5.97.

A picrate of IX was prepared using a saturated solution of picric acid in benzene. Crystallization of the picrate from benzene yielded dark brown needles, m.p. 217.5–219°.

Anal. Calcd. for $C_{28}H_{19}O_7N_3$: C, 66.01; H, 3.76. Found: C, 65.90; H, 3.57.

Ultraviolet Absorption Spectra.—The ultraviolet absorption spectra of 9-methyl- and 8,9-dimethyl-3,4-benzpyrene in 95% ethanol were measured with a model DU Beckman recording spectrophotometer. Maxima and (log ϵ) values are: 9-methyl-3,4-benzpyrene (VIII), 259 mμ (4.62), 268 mμ (4.72), 287 mμ (4.68), 301 mμ (4.74), 369 mμ (4.40) and 390 mμ (4.47); 8,9-dimethyl-3,4-benzpyrene (IX), 259 mμ (4.64), 270 mμ (4.69), 291 mμ (4.64), 304 mμ (4.76), 372 mμ (4.40) and 392 mμ (4.45).

ALBUQUERQUE, NEW MEXICO

[CONTRIBUTION FROM ABBOTT LABORATORIES]

Muscle-relaxing Compounds Derived from 1,4-Dichloro-2-butene[1]

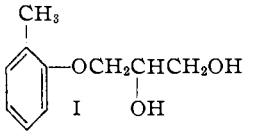
BY BRUCE W. HORROM AND HAROLD E. ZAUGG

RECEIVED OCTOBER 31, 1956

Several aryloxy and alkoxy butanediols were synthesized for testing as muscle-relaxants. These compounds were all derived from 1,4-dichloro-2-butene. The methods of their preparation and their physical constants are reported.

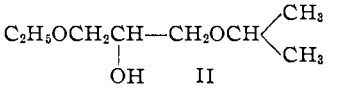
Many derivatives and analogs of the glycerol ethers have been made[2–5] and studied[6–9] for their muscle-relaxing properties.

In the aromatic series, mephenesin (I) remains one of the most useful compounds studied although



I

fairly short acting. In the aliphatic series, 3-ethoxy-1-isopropoxy-2-propanol (II) is less potent



II

(1) Presented before the Division of Medicinal Chemistry, 128th National American Chemical Society Meeting, Minneapolis, Minn., September 11–16, 1955.

(2) J. R. Geigy, A.-G., British Patent 555,191; *C. A.*, **39**, 1252[3] (1945).

(3) K. E. Marple, E. C. Shokal and T. W. Evans, U. S. Patent 2,380,185.

(4) H. L. Yale, E. J. Pribyl, W. Braker, F. H. Bergeim and W. A. Lott, THIS JOURNAL, **72**, 3710 (1950).

(5) B. J. Ludwig, W. A. West and W. E. Currie, *ibid.*, **74**, 1935 (1952).

(6) F. M. Berger, *J. Pharmacol. & Exper. Therap.*, **93**, 470 (1948).

(7) C. H. Hine, B. E. Christensen, F. J. Murphy and H. Davis, *ibid.*, **97**, 414 (1949).

(8) H. Davis, M. Neal, F. J. Murphy and C. H. Hine, *ibid.*, **98**, 6 (1950).

(9) J. S. Goodsell, J. E. P. Toman, G. H. Everett and R. K. Richards, *ibid.*, **110**, 251 (1954).

than mephenesin but more prolonged in its action.[8]

It has been suggested[7] that muscle relaxant activity in this series depends on a favorable oil-water partition coefficient. Riley[10] has also indicated that the short duration of action of mephenesin-like drugs may be due to the rapid metabolism of these compounds through the oxidation of the terminal primary hydroxyl group.[11] It was felt that the introduction of an alkoxymethyl group into the glycerol side chain of the compounds of mephenesin-type might slow their metabolic rates of destruction without unfavorably affecting their partition coefficients, thereby possibly producing drugs of prolonged duration of effect. Lott[12] has reported that the aryloxybutanediols of the type prepared by Yale,[4] *et al.*, are very insoluble in water. We have found that the introduction of a methoxyl group into the ω-position of the butane side chain results in compounds of greater water solubility. The solubilities of several compounds in Table I were determined in water at 25°. They are as follows: compound 5, 1.83%; compound 6, 5.25%; compound 11, 0.21%; and compound 12, 0.74%. It is interesting to note that compound 12 which had about the same solubility as mephenesin was the most active of these four compounds.

(10) R. F. Riley, THIS JOURNAL, **72**, 5712 (1950).

(11) The work of Riley has been confirmed recently by Ludwig, *et al.* [B. J. Ludwig, H. Luts and W. A. West, *ibid.*, **77**, 5751 (1955)].

(12) W. A. Lott, *Trans. N. Y. Acad. Sci.*, [2] **11**, 1 (1948).

TABLE I

1,4-DISUBSTITUTED-2-BUTENES AND RELATED BUTANES

No.	Compound	Yield, %	B.p. (uncor.) °C.	Mm.	$n^{25}D$	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	1-Chloro-4-phenoxy-2-butene	47.5	111–113	0.3	1.5440	$C_{10}H_{11}ClO$	65.75	65.78	6.07	6.12
2	1,4-Diphenoxy-2-butene	27			89–90[a,b]	$C_{16}H_{16}O_2$	79.97	79.99	6.71	7.08
3	1-Ethoxy-4-phenoxy-2-butene	83	99–102	0.8	1.5096	$C_{12}H_{16}O_2$	74.96	75.12	8.39	8.49
4	1-Methoxy-4-phenoxy-2-butene	92.5	106–108	.6	1.5178	$C_{11}H_{14}O_2$	74.12	74.02	7.91	8.04
5	2,3-Dihydroxy-1-ethoxy-4-phenoxy-butane	38	120–122	.11	66–68[a]	$C_{12}H_{18}O_4$	63.69	63.39	8.01	7.88
6	2,3-Dihydroxy-1-methoxy-4-phenoxy-butane	31			61–62[a,c]	$C_{11}H_{16}O_4$	62.24	62.49	7.59	7.31
7	1-Chloro-4-(*o*-toloxy)-2-butene	52	108–110	.5	1.5400	$C_{11}H_{13}ClO$	67.17	67.12	6.66	6.46
8	1,4-Di-(*o*-toloxy)-2-butene	28			97–98[a,c]	$C_{18}H_{20}O_2$	80.18	80.29	7.51	7.45
9	1-Ethoxy-4-(*o*-toloxy)-2-butene	85	102–104	.7	1.5096	$C_{13}H_{18}O_2$	75.69	75.80	8.79	8.84
10	1-Methoxy-4-(*o*-toloxy)-2-butene	94.5	112–113	.3	1.5170	$C_{12}H_{16}O_2$	74.96	75.19	8.39	8.29
11	2,3-Dihydroxy-1-ethoxy-4-(*o*-toloxy)-butane	33.8	131–132	.11	87–88[a]	$C_{13}H_{20}O_4$	64.97	65.18	8.38	8.30
12	2,3-Dihydroxy-1-methoxy-4-(*o*-toloxy)-butane	37.5			83–84[a,c]	$C_{12}H_{18}O_4$	63.69	63.93	8.01	8.04
13	2-Bromo-1,4-diethoxy-3-hydroxy-butane	77	91–93	.5	1.4644	$C_8H_{16}BrO_3$	39.84	39.82	7.11	7.11
14	1,4-Diethoxy-2,3-dihydroxybutane	79	94–95	.8	1.4415	$C_8H_{18}O_4$	53.91	53.99	10.18	10.31
15	1,4-Diethoxy-2,3-epoxybutane	83.5	93–94	17	1.4218	$C_8H_{16}O_3$	59.97	59.61	10.07	10.18
16	1,4-Diethoxy-2-hydroxybutane	80	93–96	20	1.4235	$C_8H_{18}O_3$	59.23	59.37	11.18	11.27
17	3-Hydroxy-1,2,4-triethoxybutane	77	69–70	0.12	1.4267	$C_{10}H_{22}O_4$	58.22	57.82	10.75	11.02

[a] M.p., °C. (uncor.). [b] Crystallized from ethanol. [c] Crystallized from Skelly B.

The general methods of preparation of the aromatic derivatives are illustrated as

$$ClCH_2CH{=}CHCH_2Cl + \mathit{A}ROH \xrightarrow[\text{acetone}]{K_2CO_3} \mathit{A}ROCH_2CH{=}CHCH_2Cl + \mathit{A}ROCH_2CH{=}CHCH_2O\mathit{A}R$$

III

$\mathit{A}R$ = phenyl, *o*-tolyl; R = ethyl, methyl

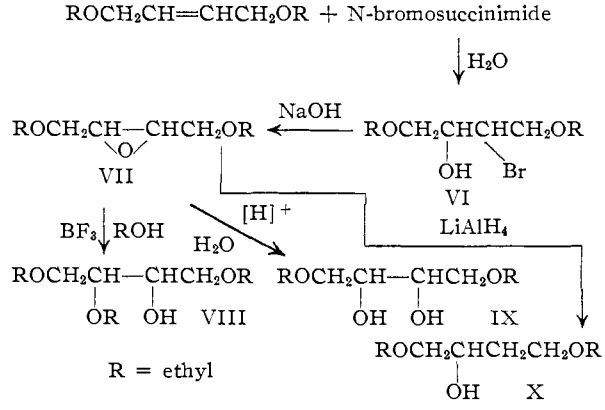
NaOR / ROH

$$\mathit{A}ROCH_2CH{=}CHCH_2OR \xrightarrow[H_2O\text{–acetone}]{KMnO_4} \mathit{A}ROCH_2CH(OH){-}CH(OH)CH_2OR$$

IV V

The intermediate 1-aryloxy-4-chloro-2-butenes (III) were prepared in fair yield by the iodide-catalyzed potassium carbonate procedure of Hurd and Perletz.[13] Much lower yields of the monosubstituted products were obtained when a sodium ethoxide–alcohol procedure was used. The alkyl ethers IV were synthesized in good yields by means of a sodium–alcohol procedure. Infrared data, although equivocal, support the 1,4-disubstituted structures as shown. The possibility of the formation of the corresponding 1,2-isomers by rearrangement during reaction is not ruled out.

Attempts to prepare the epoxide of the aromatic derivatives by means of peracetic acid failed. N-Bromosuccinimide did not yield the desired bromohydrin and *t*-butyl hypochlorite failed to give the chlorohydrin. The dihydroxy derivatives could not be prepared by means of either peroxytrifluoroacetic acid or performic acid. These aromatic butenes which appeared to be resistant to oxidation also decolorized bromine only slowly. The oxidation of these compounds to the desired glycols (V) was carried out successfully by means of potassium permanganate in aqueous acetone. A few completely aliphatic glycerol ethers were also prepared starting with 1,4-dichloro-2-butene as



Several of the compounds reported here have fair muscle relaxant activity. However, none in the aromatic or aliphatic series was found to possess either potency approaching that of mephenesin or duration of action approaching that of 3-ethoxy-1-isopropoxy-2-propanol.

(13) C. D. Hurd and P. Perletz, THIS JOURNAL, **68**, 38 (1946).

Acknowledgment.—We are indebted to Mr. E. F. Shelberg, Mr. Robert Berg and other members of the Abbott Microanalytical Department for the analyses reported here. We are also grateful to Mr. Grant Barlow of the Abbott Physical Chemistry Department for the solubility determinations.

Experimental

The 1,4-dichloro-2-butene used in these experiments was a commercial grade obtained from the Carbide and Carbon Chemicals Co.

The analytical data and other physical constants for the following compounds are listed in Table I.

1-Chloro-4-phenoxy-2-butene and 1,4-Diphenoxy-2-butene.—A mixture of 199.3 g. (2.12 moles) of phenol, 68 g. (0.49 mole) of potassium carbonate and 300 cc. of dry acetone under reflux was treated dropwise with stirring with a mixture of 375 g. (3 moles) of 1,4-dichlorobutene-2, 6 g. of powdered potassium iodide and 300 cc. of dry acetone. The reaction mixture was refluxed overnight and filtered from the inorganic salts which were washed well with acetone. The combined filtrate and washings were concentrated. Distillation of the residual red oil yielded 183.3 g. (47.5%) of a clear colorless oil, b.p. 108–122° (0.6 mm.). Redistillation gave b.p. 111–113° (0.3 mm.).

The hot liquid residue from the distillation flask was poured into a crystallization dish and the oil solidified upon cooling. There was obtained 133 g. (27%) of 1,4-diphenoxy-2-butene, m.p. 88–90°. Recrystallization from ethanol gave colorless needles, m.p. 89–90°.

The analogous toloxy derivatives (compounds 7 and 8, Table I) were obtained in the same manner.

1-Ethoxy-4-phenoxy-2-butene.—Sodium ethoxide was prepared from 3 g. (0.126 g. atom) of sodium metal and 75 cc. of 12A absolute alcohol. To this stirred and refluxing mixture was added dropwise over a period of 1 hr. 23 g. (0.126 mole) of 1-chloro-4-phenoxybutene-2. The mixture was refluxed for another 3.5 hr. The precipitated sodium chloride was removed by filtration. After washing the salt thoroughly with ether, the combined filtrate and washings were concentrated. The resulting oil was taken up in ether, washed to neutrality with water, dried over magnesium sulfate and after filtering and concentrating again, the residue was distilled. There was obtained 20 g. (83%) of a clear colorless oil, b.p. 99–102° (0.8 mm.). Compounds 4, 9 and 10 (Table I) were made by this procedure.

2,3-Dihydroxy-1-ethoxy-4-phenoxybutane.—A 5-liter flask equipped with a stirrer and thermometer and containing 20 g. (0.104 mole) of 1-ethoxy-4-phenoxy-2-butene in 1500 cc. of ethanol was cooled by means of a Dry Ice–acetone-bath; 24 g. (0.125 mole) of potassium permanganate dissolved in 800 cc. of water was added dropwise with stirring, keeping the temperature as near to −40° as possible. Two hours was required for the addition of the permanganate and the mixture was stirred for another 2 hr. at −40°. After refrigerating overnight, the solution was filtered from the manganese salts by means of a filter aid. The salts were washed well with acetone and the combined filtrate and washings were concentrated *in vacuo* to *ca.* 50 cc. Two phases resulted and the brown oil was taken up in ether, washed with dilute potassium hydroxide and water and dried over anhydrous magnesium sulfate. Filtration and removal of the ether followed by distillation of the residue gave a clear colorless oil, b.p. 120–122° (0.11 mm.), which solidified immediately yielding 9 g. (38%) of a solid, m.p. 66–68°.

The water phase from above was acidified and 3 g. of an acid was obtained which proved to be, by mixed melting point, phenoxyacetic acid. The odor of phenol also was present.

The dihydroxybutanes 6, 11 and 12 in Table I were prepared essentially as described above. However, the desired products were obtained by evaporation of the ether and recrystallization of the solid product instead of by distillation.

2-Bromo-1,4-diethoxy-3-hydroxybutane.—A mixture of 57.6 g. (0.2 mole) of 1,4-diethoxy-3-butene,[14] 80 g. (0.46 mole) of N-bromosuccinimide, 132 cc. of water and 0.6 cc. of glacial acetic acid was stirred at room temperature for 21 hr. according to the method of Raphael.[15] At the end of this time the oily layer had become heavier than the aqueous layer. It was taken up in ether and washed with sodium bicarbonate solution and water. After drying over anhydrous magnesium sulfate, filtering and removing the ether, 84 g. of crude product was obtained. Distillation gave 73.6 g. (77%), b.p. 91–92.5° (0.5 mm.).

1,4-Diethoxy-2,3-epoxybutane.—By the method of Evans,[16] *et al.*, 72 g. (0.30 mole) of the bromohydrin VI in 50 cc. of ether was cooled to −20° and treated with stirring over a 10–15 minute period with a solution of 7 g. of sodium hydroxide in 10 cc. of water. The mixture was allowed to stir overnight at room temperature. The next day, the ether layer was separated and the aqueous residue was extracted with several portions of ether. The combined extracts were dried over anhydrous magnesium sulfate, filtered and concentrated. The residual orange oil upon distillation gave 40.4 g. (83.5%), b.p. 93–94° (17 mm.).

1,4-Diethoxy-2,3-dihydroxybutane.—This glycol was prepared by treating 13 g. (0.081 mole) of the epoxide VII with 30 cc. of boiling water containing 0.45 g. (0.25 cc.) of concentrated sulfuric acid. The epoxide went into solution in a few minutes. The reaction mixture was cooled and neutralized with 1 g. of barium carbonate. After filtering through a filter aid, the solution was concentrated almost to dryness, extracted with ether, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was distilled to give 11.4 g. (79%), b.p. 94–95° (0.8 mm.).

1,4-Diethoxy-2-hydroxybutane.—In the manner of Trevoy and Brown,[17] 13 g. (0.081 mole) of the epoxide VII in ether was added dropwise with stirring to 3.8 g. (0.10 mole) of lithium aluminum hydride in ether. The rate of addition was regulated to maintain gentle reflux. The mixture was refluxed for 5 hr. after addition was complete and allowed to stand at room temperature overnight. Water was added dropwise until addition of more water caused no further refluxing of the ether. After filtering and washing the lithium salts with ether, the combined washings and filtrate were dried over anhydrous magnesium sulfate. The ether solution was concentrated after filtration and the residue yielded, on distillation, 10.5 g. (80%) of an oil, b.p. 93–96° (20 mm.).

3-Hydroxy-1,2,4-triethoxybutane.—To a refluxing solution of 0.2 cc. of boron trifluoride–etherate in 30 cc. of absolute alcohol was added dropwise with stirring 18.4 g. of the epoxide VII. The reaction mixture was stirred and refluxed for several hours longer and allowed to stand overnight. After the addition of 0.5 g. of calcium hydroxide, stirring was continued for several hours at room temperature. The mixture was filtered and the alcohol removed by distillation *in vacuo*. The residual colorless oil was distilled to give 18.2 g. (77%), b.p. 69–70° (0.12 mm.).

NORTH CHICAGO, ILLINOIS

(14) G. F. Deebel, U. S. Patent 2,555,270.

(15) R. A. Raphael, *J. Chem. Soc.*, 404 (1952).

(16) T. W. Evans, K. E. Marple and E. C. Shokal, U. S. Patent 2,314,039.

(17) Trevoy and Brown, THIS JOURNAL, **71**, 1675 (1949).