[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

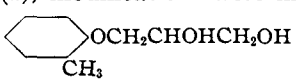
# Muscle-relaxing Compounds Similar to 3-(*o*-Toloxy)-1,2-propanediol.[1] I. Aromatic Ethers of Polyhydroxy Alcohols and Related Compounds[2,3]

BY HARRY L. YALE, EDWARD J. PRIBYL, WILLIAM BRAKER, FRANK H. BERGEIM AND W. A. LOTT

Following the preliminary reports[4] of the efficacy of substituted aromatic ethers of glycerol in producing skeletal muscle relaxation, a large number of related compounds were prepared in these laboratories to determine the correlation between chemical structure and muscle-relaxing activity.

This paper will describe only the synthesis of these compounds since their pharmacological evaluation has been discussed elsewhere.[5]

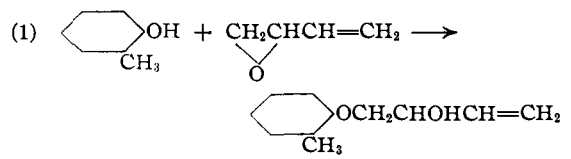
In preparing compounds structurally related to Tolserol (I), modifications were made both in



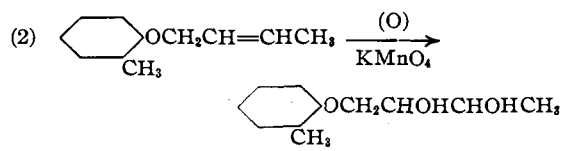
(I)

the aromatic nucleus and in the glycerol moiety. In the aromatic nucleus, these changes involved (a) the preparation of structural isomers by the variation of the position of the $CH_3$· group; (b) the replacement of the $CH_3$· group in the isomeric compounds by other alkyl· groups, $C_6H_5$·, Cl·, $C_2H_5OCONH$·, $C_6H_{11}$·, $HOCH_2$· or $CH_3O$· groups; and (c) the preparation of polysubstituted analogs. In the glycerol portion of the molecule, the changes involved (a) the preparation of the β-methyl- and β-ethylglycerol ethers; (b) the replacement of the terminal $HOCH_2$· group by H·, $CH_3$·, $CH_2$:CH·, and $CH_3CHOH$·; and (c) the etherification of one or both of the HO· groups. In addition, modifications were achieved by the replacement of the ether oxygen atom by a sulfur atom or the $SO_2$:, NH:, $CH_3CON$:, and $C_2H_5$-OCON: groups.

The aromatic ethers of the polyhydroxy alcohols were, in general, prepared by the reaction of a phenol and a halohydrin, employing aqueous sodium hydroxide, sodium ethoxide in ethanol or sodium hydroxide in dioxane as the HX acceptor. The corresponding aromatic thio ethers were similarly prepared. In addition, a number of ethers were prepared by the potassium hydroxide catalyzed reaction of a phenol with an epoxide.[6]



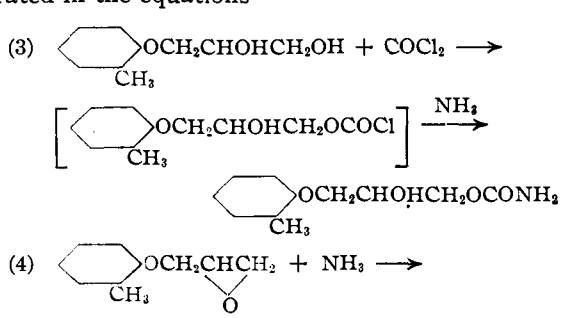
By the oxidation of crotyl *o*-tolyl ether with potassium permanganate in aqueous acetone, there was obtained 1-(*o*-toloxy)-2,3-butanediol. Potassium permanganate was found to be superior to



performic acid[7] since it gave a crystalline product while performic acid gave a non-crystalline viscous oil.

The ethers which were obtained as solids could be purified by repeated crystallization. The liquid ethers were more troublesome and in some instances even repeated careful fractionation did not yield pure products. Apparently, the unknown impurities distilled in the same range as the product. An additional difficulty with these compounds was their hygroscopicity.

To study further the relationship of chemical structure to muscle-relaxing activity, other types of compounds were prepared. These included a group of carbamates, whose preparation is illustrated in the equations[8]



(1) 3-(*o*-Toloxy)-1,2-propanediol is marketed by E. R. Squibb & Sons under the registered name of Tolserol. The trade name will be employed in this paper. The same drug is distributed in England under the name Myanesin.

(2) Presented before the Division of Medicinal Chemistry, 116th Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 18–23, 1949.

(3) For the second paper of this series, see THIS JOURNAL, **72**, 3716 (1950).

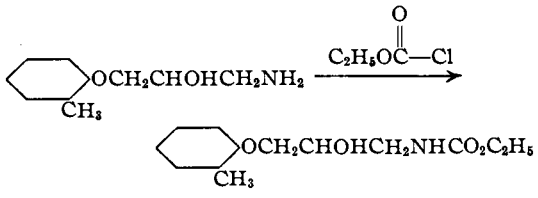
(4) Bradley and Berger, *Brit. J. Pharmacol.*, **1**, 265 (1946); Berger and Bradley, *Lancet*, **252**, 97 (1947); Mallinson, *ibid.*, **252**, 98 (1947); Bradley and Berger, *Nature*, **159**, 813 (1947); Berger, *J. Pharmacol. Exptl. Therap.*, **93**, 470 (1948).

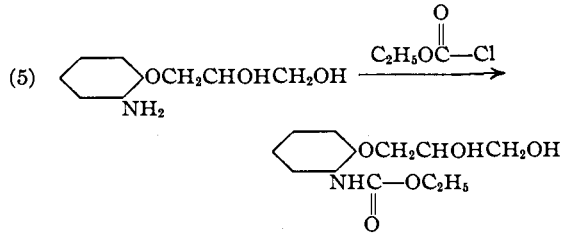
(5) Lott, *Trans. N. Y. Acad. Sci.*, [2] **11**, 1 (1948).

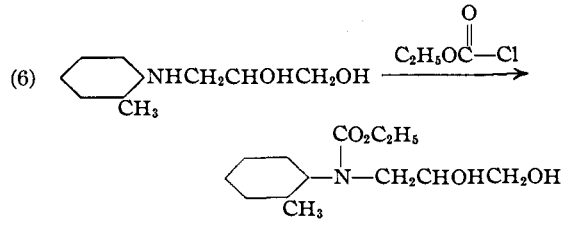
(6) Sexton and Britton, THIS JOURNAL, **70**, 3606 (1948), have shown that the reaction of phenols with propylene oxide in the presence of an alkaline catalyst gives a secondary alcohol.

(7) Swern, Billen and Scanlan, *ibid.*, **68**, 1504 (1946).

(8) In the reaction of Tolserol with phosgene (Equation 3), the structure of the final product has been represented as if only the primary HO- group were involved. It is well established that primary HO- groups react more rapidly with acid chlorides than do secondary HO- groups (*cf.* Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y. 1940, p. 210). The product obtained in this instance in 76% yield, had a sharp melting point and appeared to be homogeneous. In view of the high yield and sharp melting point, it is felt that further structural proof is not necessary. In equation 4 it has been assumed that the reaction of epoxides with aqueous ammonia gives almost exclusively the secondary alcohols, since secondary alcohols are usually obtained with alkaline reagents.



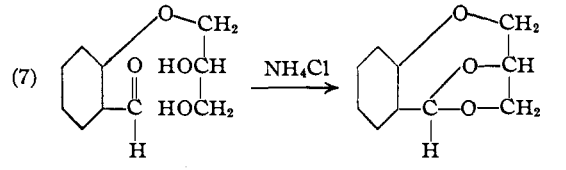




A group of miscellaneous compounds was also prepared by the reactions here given.

*o*-Toloxyacetone and ethylmagnesium bromide gave 2-methyl-1-(*o*-toloxy)-2-butanol. *o*-Tolylsulfinic acid and *o*-cresol, upon reaction with methyl vinyl ketone,[9] gave the corresponding β-substituted ketones. Several sulfones were prepared by the oxidation of an aryl glyceryl sulfide with hydrogen peroxide in glacial acetic acid. *o*-Toluidine and epichlorohydrin[10] gave N-(γ-chloro-β-hydroxypropyl)-*o*-toluidine, which was converted to 3-(*o*-toluino)-1,2-propanediol, the *nitrogen* analog of Tolserol.

When an attempt was made to convert 3-(*o*-formylphenoxy)-1,2-propanediol to its diethyl acetal, an interesting intramolecular acetal formation occurred to give, instead, 3,6-epoxy-1,5-benzodioxocin.

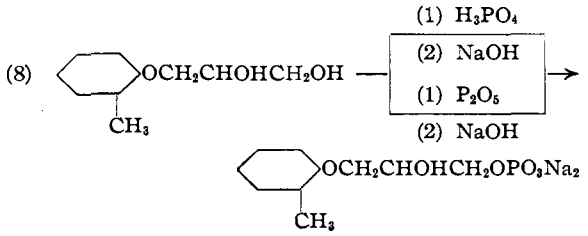


In order to increase solubility in water, Tolserol was first converted to the phosphoric acid ester by reaction with either phosphoric acid or phosphorus pentoxide and then to the disodium salt.[11]

(9) The procedures employed, but not the products, are described in U. S. Patent 2,010,828.

(10) Cohn and Friedlander, *Ber.*, **37**, 3034 (1904), have reported the preparation of N-(γ-chloro-β-hydroxypropyl)-*p*-toluidine by the reaction of *p*-toluidine and epichlorohydrin.

(11) We are not prepared to state that the product was homogeneous, and it may well have consisted of a mixture of two compounds, esterified through either the primary or secondary HO- groups.



A related attempt to increase the water solubility of *o*-toloxyethanol was unsuccessful. Although the intermediate diphenoxy-(*o*-toloxyethoxy)-phosphite was obtained, hydrogenolysis of this compound gave a product which could not be converted to a pure sodium salt.

**Acknowledgment.**—The microanalyses were carried out by Mr. J. F. Alicino of this Institute.

## Experimental Part

All temperatures reported are uncorrected.

The procedures which have been utilized most generally are outlined below. Those compounds which required special methods of preparation are described individually.

**Procedure 1.**—Equimolar amounts of the phenol, halohydrin and sodium hydroxide (in 20% aqueous solution) were heated and stirred on a steam-bath for two hours, the reaction mixture was cooled, and extracted with ether. The ether extracts were washed with 5–10% sodium hydroxide solution, saturated sodium chloride solution, dried, concentrated, and distilled *in vacuo*. The distilled products which solidified were recrystallized.

**Procedure 2.**—Equimolar amounts of the phenol, halohydrin and sodium ethoxide (in about 4% solution in absolute ethanol) were stirred and refluxed eight hours, the ethanol was distilled, and the residue treated with water and extracted with ether. The ether extracts were treated as in Procedure 1.

**Procedure 3.**—Equimolar amounts of the phenol and sodium hydroxide in dioxane (ratio of sodium hydroxide to dioxane, 1:4) were heated and stirred on the steam-bath to effect solution, then treated dropwise with an equimolar amount of halohydrin. The mixture was heated and stirred an additional hour, cooled, diluted with ether and filtered. The filtrate was concentrated, first under atmospheric pressure, then under reduced pressure, the residual oil was taken up in ether and the ether solution treated as in Procedure 1.

**Procedure 4.**—A 1% aqueous solution containing 2.0 moles of potassium permanganate was added with stirring during two hours to an acetone solution of 1.0 mole of the unsaturated compound (concentration about 1.5%), the temperature being maintained at 5–10°. The mixture was kept eighteen hours at room temperature and filtered. The filtrate was concentrated, first under atmospheric pressure and then under reduced pressure. The residue was dissolved in ether, the ether solution was washed with saturated sodium chloride solution, dried and concentrated. The residual solid was recrystallized.

**Procedure 5.**—A suspension of 1.0 mole of amine in ether (ratio 1:10) was treated at 5° with 1.0 mole of alkyl chlorocarbonate and 1.0 mole of sodium hydroxide (about 20% aqueous solution). The chlorocarbonate and sodium hydroxide solution were added in increments during thirty minutes with vigorous stirring. After an additional thirty minutes stirring, the ether layer was separated, dried, concentrated and the residual solid recrystallized.

**Procedure 6.**—To equimolar amounts of phenol and epoxy compound was added 0.5 g. of potassium hydroxide in 5 ml. of water and the mixture allowed to stand for one week at room temperature. Ether was added and the ethereal solution treated as in Procedure 1.

**2-Methyl-1-(*o*-toloxy)-2-butanol (XXIX).**—The Grignard reagent prepared from 7.2 g. (0.3 mole) of mag-

TABLE I

ETHERS OF POLYHYDROXY COMPOUNDS AND RELATED COMPOUNDS

| Compd. | Compound | Method of prepn. | Ref. | Yield, %[a] | B. p. (uncor.) °C. | Mm. | M. p., °C. (uncor.) | Empirica formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | 3-(*p*-Benzylaminophenoxy)-1,2-propanediol | 1 | | 20.0 | | | 102.5–103.0[ad] | $C_{16}H_{19}NO_3$ | 70.31 | 70.63 | 7.00 | 7.04 |
| II | 3-(2-Biphenyloxy)-1,2-propanediol | 1 | | 20.0 | | | 80–81[ae] | $C_{15}H_{16}O_3$ | 73.74 | 74.07 | 6.60 | 6.62 |
| III | 3-(2,4-Di-*s*-butylphenoxy)-1,2-propanediol | 2 | | 65.0 | 175–177 | 2 | 94–96[ab] | $C_{17}H_{28}O_3$ | 72.81 | 72.23 | 10.06 | 10.00 |
| IV | 3-(*p*-*t*-Butylphenoxy)-1,2-propanediol | 1 | | 45.0 | | | 83–84[ab] | $C_{13}H_{20}O_3$ | 69.61 | 69.56 | 8.98 | 8.78 |
| V | 3-(*o*-Carbamylphenoxy)-1,2-propanediol | 1 | | 40.0 | | | 95–96 | $C_{10}H_{14}N_2O_4$ | 53.08 | 52.92[av] | 6.24 | 6.52 |
| VI | 3-(*m*-Chlorophenoxy)-1,2-propanediol | 1 | | 53.0 | | | 68–69 | $C_9H_{11}ClO_3$ | 53.34 | 53.66[ax] | 5.47 | 5.60 |
| VII | 3-(4-Chloro-3-methylphenoxy)-1,2-propanediol | 1 | c | 42.0 | | | 93–94[ac] | $C_{10}H_{13}ClO_3$ | 55.42 | 55.39 | 6.04 | 6.00 |
| VIII | 3-(Cinnamyloxy)-1,2-propanediol | | b | 9.0 | 184–189 | 3 | | $C_{12}H_{16}O_3$ | 69.20 | 68.65 | 7.44 | 7.74 |
| IX | 3-(*o*-Cyclohexylphenoxy)-1,2-propanediol | 1 | | 40.0 | 182–185 | 1 | | $C_{15}H_{22}O_3$ | 71.96 | 72.05 | 8.86 | 8.74 |
| X | Cyclohexanecarboxylic acid, O[1] ester with glycerol | | d | 12.0 | | | 27–29[af] | $C_{10}H_{18}O_4$ | 59.38 | 59.38 | 8.97 | 8.92 |
| XI | *o*-(2,3-Dihydroxypropoxy)-carbanilic acid, ethyl ester | 5 | | 50.0 | | | 85–86[af] | $C_{12}H_{17}NO_5$ | 56.45 | 56.56 | 6.71 | 6.92 |
| XII | *p*-(2,3-Dihydroxypropoxy)-carbanilic acid, ethyl ester | 5 | | 50.0 | | | 98[ad] | $C_{12}H_{17}NO_5$ | 56.45 | 56.33 | 6.71 | 6.45 |
| XIII | N-(2,3-Dihydroxy-1-propyl)-*o*-methylcarbanilic acid ethyl ester | | b | 15.0 | 215 | 10 | | $C_{13}H_{19}NO_4$ | 61.64 | 61.33 | 7.56 | 7.88 |
| XIV | *o*-(2,3-Dihydroxypropoxy)-acetanilide | 1 | | 50.0 | | | 139–140[ak] | $C_{11}H_{15}NO_4$ | | | [am] | |
| XV | 3-(2,6-Dimethyl-4-pyrimidyloxy)-1,2-propanediol | 1 | | 32.0 | | | 120–121[ai] | $C_9H_{14}N_2O_3$ | | | [an] | |
| XVI | 1,2-Dimethoxy-3-(*o*-toloxy)-propane | | b | 57.0 | 150–151 | 17 | | $C_{12}H_{18}O_3$ | 68.54 | 68.60 | 8.62 | 8.74 |
| XVII | 3-[*o*-(2-Ethylisopropyl)-phenoxy]-1,2-propanediol | 1 | | 40.0 | 162–166 | 1 | | $C_{14}H_{22}O_3$ | 70.55 | 69.96 | 9.30 | 8.92 |
| XVIII | 3-(*p*-Ethoxyphenoxy)-1,2-propanediol | 1 | c | 23.0 | | | 80–81[ac] | $C_{11}H_{16}O_4$ | 62.24 | 62.20 | 7.59 | 7.62 |
| XIX | 3-(2-Ethyl-3-methylhexyloxy)-1,2-propanediol | 2 | | 5.0 | 152–154 | 8 | | $C_{12}H_{26}O_3$ | 66.01 | 65.70 | 12.00 | 11.81 |
| XX | 2-Ethyl-3-(*o*-toloxy)-1,2-propanediol | 2 | | 67.0 | 144–145 | 1 | | $C_{12}H_{18}O_3$ | 68.54 | 67.96 | 8.63 | 8.46 |
| XXI | $\alpha$-Ethylcinnamic acid, O[1] ester with glycerol | | b | 30.0 | 222–224 | 5 | | $C_{14}H_{18}O_4$ | 67.18 | 67.69 | 7.24 | 6.98 |
| XXII | 3-(*o*-Hydroxymethylphenoxy)-1,2-propanediol | | be | 90.0 | | | 98–99[af] | $C_{10}H_{14}O_4$ | 60.59 | 60.34 | 7.11 | 6.82 |
| XXIII | 1-(2-Hydroxyethoxy)-3-(*o*-toloxy)-2-propanol | 3 | | 81.4 | 187–188 | 3 | | $C_{12}H_{18}O_4$ | 63.69 | 63.20 | 8.01 | 8.02 |
| XXIV | 2-Hydroxy-3-(*o*-toloxypropyl)-trimethylammonium iodide | | b | 80.0 | | | 133[ak] | $C_{13}H_{22}INO_2$ | | | [at] | |
| XXV | 2-Hydroxy-3-(*o*-toloxy)-propylcarbamic acid, ethyl ester | 5 | | 50.0 | 179–180 | 0.5 | | $C_{13}H_{19}NO_4$ | 61.64 | 60.93 | 7.56 | 7.32 |
| XXVI | 2-Hydroxy-3-(*o*-toloxy)-propylcarbamic acid, allyl ester | 5 | | 80.0 | 218 | 4 | | $C_{14}H_{19}NO_4$ | 63.38 | 63.04 | 7.22 | 7.29 |
| XXVII | 2-Hydroxy-3-(*o*-toloxy)-propylcarbamic acid, 1-butanol ester | 5 | | 72.0 | 210–212 | 2 | | $C_{15}H_{23}NO_4$ | 64.03 | 63.71 | 8.24 | 7.94 |
| XXVIII | 2-Hydroxy-3-(*o*-toloxy)-propylcarbamic acid, 2-pentanol ester | 5 | | 13.0 | 199–202 | 1 | | $C_{16}H_{25}NO_4$ | 65.06 | 64.90 | 8.54 | 8.08 |

TABLE I (*Continued*)

| Compd. | Compound | Method of prepn. | Ref. | Yield, %[a] | B. p. (uncor.) °C. | Mm. | M. p., °C. (uncor.) | Empirical formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XXIX | 2-Methyl-1-(*o*-toloxy)-2-butanol | | [b] | 58.0 | 133–135 | 10 | | $C_{12}H_{18}O_2$ | 74.18 | 73.91 | 9.34 | 9.32 |
| XXX | 3-[*o*-(1-Methylisobutyl)phenoxy]-1,2-propanediol | 1 | | 55.0 | 173–176 | 2 | | $C_{14}H_{22}O_3$ | 70.55 | 69.91 | 9.30 | 9.18 |
| XXXI | 3-(*o*-Methoxyphenoxy)-1,2-propanediol | 2 | [c] | 40.0 | | | 78.5–79.5[ae] | $C_{10}H_{14}O_4$ | 60.59 | 61.13 | 7.11 | 7.24 |
| XXXII | 3-(*m*-Methoxyphenoxy)-1,2-propanediol | 1 | [c] | 38.0 | | | 73.0–73.5[ae] | $C_{10}H_{14}O_4$ | 60.59 | 60.91 | 7.11 | 7.32 |
| XXXIII | 3-(*p*-Methoxyphenoxy)-1,2-propanediol | 1 | [c] | 30.0 | | | 80.5–81.5[ab] | $C_{10}H_{14}O_4$ | 60.59 | 60.92 | 7.11 | 7.25 |
| XXXIV | 3-(2-Methylcyclohexyloxy)-1,2-propanediol | | [b] | 10.0 | 133–136 | 2 | | $C_{10}H_{20}O_3$ | 63.79 | 63.44 | 10.70 | 10.20 |
| XXXV | 2-Methyl-3-(*o*-tolylmercapto)-1,2-propanediol | 1 | | 66.0 | 158–162 | 1 | | $C_{11}H_{16}O_2S$ | 62.22 | 61.89 | 7.59 | 7.56 |
| XXXVI | 2-Methyl-3-(*o*-toloxy)-1,2-propanediol | 1 | [c] | 50.0 | 142–144 | 2 | | $C_{11}H_{16}O_3$ | 67.32 | 66.95 | 8.21 | 8.21 |
| XXXVII | 2-Methyl-3-(*p*-toloxy)-1,2-propanediol | 1 | [c] | 66.0 | | | 101–102[ah] | $C_{11}H_{16}O_3$ | 67.32 | 67.62 | 8.21 | 8.07 |
| XXXVIII | 2-Methyl-3-(2,6-xylyloxy)-1,2-propanediol | 1 | | 27.0 | 149–150 | 2 | 64–65[ab] | $C_{12}H_{18}O_3$ | 68.54 | 68.38 | 8.63 | 8.75 |
| XXXIX | 2-Methyl-1-(*o*-toloxy)-2,3-butanediol | 4 | | 5.0 | 164–165 | 8 | 73–74[ab] | $C_{12}H_{18}O_3$ | 68.54 | 68.71 | 8.63 | 8.64 |
| XL | 3-(*o*-Methoxyphenoxy)-2-methyl-1,2-propanediol | 1 | [c] | 35.0 | | | 78–79[ac] | $C_{11}H_{16}O_4$ | 62.24 | 62.46 | 7.59 | 7.31 |
| XLI | 1-Methoxy-3-(*o*-toloxy)-2-propanol | 3 | | 51.0 | 175–176 | 33 | | $C_{11}H_{16}O_3$ | 67.32 | 67.32 | 8.21 | 8.16 |
| XLII | 1-(3-Methylbutoxy)-3-(*o*-toloxy)-2-propanol | 3 | | 25.2 | 142.0 | 1 | | $C_{15}H_{24}O_3$ | 71.39 | 71.31 | 9.58 | 9.67 |
| XLIII | 1-Methylamino-3-(*o*-toloxy)-2-propanol | | [b] | 60.0 | | | 78–79[ab] | $C_{11}H_{17}NO_2$ | | [as] | | |
| XLIV | *o*-Methylcarbanilic acid, O[1] ester with glycerol | | [b] | 42.0 | | | 74–75[ah] | $C_{11}H_{15}NO_4$ | 58.65 | 58.96 | 6.71 | 6.79 |
| XLV | 3-(2,3-Dihydroxy-*n*-propoxy)-4-methylphenylurea | 1 | | 38.9 | | | 160–161 | $C_{11}H_{16}N_2O_4$ | 54.98 | 55.25 | 6.71 | 6.75 [aw] |
| XLVI | 2-Methyl-3-(*o*-tolylsulfonyl)-1,2-propanediol | | [b] | 61.2 | | | 78[al] | $C_{11}H_{16}O_4S$ | 54.08 | 53.71 | 6.60 | 6.47 |
| XLVII | 3-(*o*-1-Propenylphenoxy)-1,2-propanediol | 1 | | 51.5 | 162–163 | 2 | 37–39[ab] | $C_{12}H_{16}O_3$ | 69.20 | 68.62 | 7.74 | 7.82 |
| XLVIII | 3-(*o*-Propylphenoxy)-1,2-propanediol | 1 | [c] | 40.0 | 150–151 | 1 | 52–53[ab] | $C_{12}H_{18}O_3$ | 68.54 | 68.90 | 8.62 | 8.55 |
| XLIX | 3-(*o*-Phenylenedioxy)-bis-1,2-propanediol | 1 | | 40.0 | 192–195 | 1.5 | 68–70[ac] | $C_{12}H_{18}O_6$ | 55.80 | 55.93 | 7.02 | 6.94 |
| L | 3-(*m*-Phenylenedioxy)-bis-1,2-propanediol | 1 | | 50.0 | 234 | 1 | | $C_{12}H_{18}O_6$ | 55.80 | 55.93 | 7.02 | 6.94 |
| LI | 3-(Phenylmercapto)-1,2-propanediol | 1 | | 70.0 | | | 72–73[ac] | $C_9H_{12}O_2S$ | | | [aq] | |
| LII | 3-(2-*n*-Propylphenoxy)-2-methyl-1,2-propanediol | 2 | | 63.5 | 152–155 | 2 | 61–62[ab] | $C_{13}H_{20}O_3$ | 69.61 | 69.87 | 8.99 | 9.18 |
| LIII | 4-(*o*-Toloxy)-2-butanone | | [f] | 16.0 | 141–145 | 1 | | $C_{11}H_{14}O_2$ | 74.12 | 73.76 | 7.91 | 7.73 |
| LIV | 3-(*o*-Toloxy)-1,2-propanediol | 1 | [c] | 70.0 | | | 71–72[aa] | $C_{10}H_{14}O_3$ | 65.91 | 65.79 | 7.74 | 7.72 |
| LV | 2-(*o*-Toloxy)-ethanol | 3 | [d] | 20.0 | 139 | 19 | | $C_9H_{12}O_2$ | 71.02 | 70.27 | 7.95 | 7.73 |
| LVI | 2-(*m*-Toloxy)-ethanol | 3 | [d] | 32.0 | 125–126 | 7 | | $C_9H_{12}O_2$ | 71.02 | 70.67 | 7.95 | 7.84 |
| LVII | 2-(*p*-Toloxy)-ethanol | 3 | [d] | 38.0 | 122–123 | 8 | 45–46[ab] | $C_9H_{12}O_2$ | 71.02 | 71.18 | 7.95 | 7.98 |
| LVIII | 1-(*o*-Toloxy)-2-propanol | 6 | [d] | 47.7 | 106–108 | 5 | | $C_{10}H_{14}O_2$ | 72.25 | 71.93 | 8.48 | 8.43 |
| LIX | 1-(*m*-Toloxy)-2-propanol | 6 | [d] | 19.0 | 127–129 | 12 | | $C_{10}H_{14}O_2$ | 72.25 | 72.58 | 8.48 | 8.34 |
| LX | 1-(*p*-Toloxy)-2-propanol | 6 | [d] | 20.5 | 126.5–128.0 | 12 | | $C_{10}H_{14}O_2$ | 72.25 | 72.44 | 8.48 | 8.19 |
| LXI | 2-(*o*-Toloxy)-3-buten-1-ol | 3 | | 31.9 | 125–126 | 8 | | $C_{11}H_{14}O_2$ | 74.12 | 73.75 | 7.91 | 7.67 |
| LXII | 2-(2-*o*-Toloxyethoxy)-ethanol | | [b] | 14.1 | 127 | 3 | | $C_{11}H_{16}O_3$ | 67.32 | 67.44 | 8.21 | 8.19 |
| LXIII | 3-(*o*-Toloxy)-1,2-propanediol, 1-ester with phosphoric acid, sodium salt | | [b] | 51.8<br>64.0 | | | | $C_{10}H_{13}Na_2O_6P$ | | | [ao](A)<br>[ap](B) | |
| LXIV | 3-(*o*-Tolylmercapto)-1,2-propanediol | 1 | | 75.2 | 169–172 | 2–3 | 39–40[ab] | $C_{10}H_{14}O_2S$ | 60.57 | 59.83 | 7.12 | 6.78 |

TABLE I (*Continued*)

| Compd. | Compound | Method of prepn. | Ref. | Yield, %[a] | B. p. (uncor.), °C. | Mm. | M. p., °C. (uncor.) | Empirical formula | Carbon, % Calcd. | Found | Hydrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LXV | 3-(*o*-Tolylsulfonyl)-1,2-propanediol | See XLVI | | 18.2 | Non-distillable oil | | | $C_{10}H_{14}O_4S$ | 52.16 | 51.73 | 6.13 | 6.32 |
| LXVI | 4-(*o*-Tolylsulfonyl)-2-butanone | | *f* | 87.6 | | | 36–38 | $C_{11}H_{14}O_3S$ | | | | |
| LXVII | 1-(*o*-Toloxy)-2,3-butanediol | 4 | | 35.5 | 141 | 1 | 110[ab] | $C_{11}H_{16}O_3$ | 67.32 | 66.75 | 8.21 | 7.88 |
| LXVIII | 3-(*o*-Toluidino)-1,2-propanediol hydrochloride | | *b* | 44.2 | | | 205[ag] | $C_{10}H_{16}ClNO_2$ | | | | |
| LXIX | 3-(*o*-Toloxy)-1-propanol | 1 | | 55.0 | 102–103 | 1 | | $C_{10}H_{14}O_2$ | 72.25 | 71.84 | 8.48 | 8.40 |
| LXX | (3-*o*-Toloxy-2-hydroxypropyl)-carbamate | | *b* | 76.0 | | | 93[ad] | $C_{11}H_{15}NO_4$ | 58.64 | 58.50 | 6.71 | 6.70 |
| LXXI | 2-Trichloromethyl-*m*-dioxane | | *b* | 17.8 | 103–106 | 10 | 72–73[ah] | $C_5H_7Cl_3O_2$ | 29.22 | 29.12 | 3.44 | 3.47 |
| LXXII | 3-Thymyloxy-1,2-propanediol | 1 | *c* | 45.0 | 164–166 | 2 | 67–68[ab] | $C_{13}H_{20}O_4$ | 69.61 | 69.33 | 8.98 | 8.54 |
| LXXIII | 3-Thymyloxy-2-methyl-1,2-propanediol | 1 | | 38.6 | 158–159 | 2 | | $C_{14}H_{22}O_4$ | 70.55 | 70.46 | 9.30 | 9.53 |
| LXXIV | 3-(3,5-Xylyloxy)-1,2-propanediol | 1 | | 30.0 | 165–170 | 2 | 66–67[ae] | $C_{11}H_{16}O_4$ | 67.32 | 66.95 | 8.21 | 8.12 |
| LXXV | 3-(2,5-Xylyloxy)-1,2-propanediol | 1 | | 25.0 | | | 69–70[ak] | $C_{11}H_{16}O_3$ | 67.32 | 67.51 | 8.21 | 7.89 |
| LXXVI | 3-(3,4-Xylyloxy)-1,2-propanediol | 1 | | 20.0 | | | 75–76[ae] | $C_{11}H_{16}O_3$ | 67.32 | 67.90 | 8.21 | 8.21 |
| LXXVII | 3-(2,6-Xylyloxy)-1,2-propanediol | 1 | | 40.0 | 145–146 | 1 | | $C_{11}H_{16}O_3$ | 67.32 | 67.08 | 8.21 | 8.27 |

[a] The yield figures do not take into account the recovery of any of the reagents. [b] The preparation of this compound is described later in this section. [c] Boyd and Marle, *J. Chem. Soc.*, **101**, 305 (1912), reported this compound but gave no physical constants or, if given, they differed from ours. [d] Boyd and Marle, *J. Chem. Soc.*, **105**, 2117 (1914), reported this compound but gave no physical constants. [e] The pharmacology of these compounds has been discussed[4]; however, in most instances, no mention was made of methods of preparation or physical constants. Where the latter were given, they differed from ours. [f] See ref. 9. [g] The procedure employed was the same as that used in preparing XXIII. [ae] Crystallized from carbon tetrachloride. [ab] From hexane. [ac] From ether. [ad] From water. [ae] From acetone–hexane. [af] From ether–hexane. [ag] From absolute ethanol–ether. [ah] From benzene. [ai] From ethanol–hexane. [ak] From acetone–ether. [al] From benzene–hexane. [am] Calcd. for $C_{11}H_{15}NO_4$: N, 6.22. Found: N, 6.40. [an] Calcd. for $C_9H_{14}N_2O_3$: N, 14.14. Found: N, 14.05. [ao] Calcd. for $C_{10}H_{13}Na_2O_6P$: Na, 15.02; P, 10.12. Found: (A) Na, 14.97; P, 9.93. [ap] Calcd. for $C_{10}H_{13}Na_2O_6P$: Found: (B) Na, 14.57; P, 9.71. [aq] Calcd. for $C_9H_{12}O_2S$: S, 17.38; Found: S, 17.19. [ar] Calcd. for $C_{11}H_{14}O_3S$: S, 14.17. Found: S, 14.43. [as] Calcd. for $C_{11}H_{17}NO_2$: N, 7.17. Found: N, 7.06. [at] Calcd. for $C_{18}H_{22}INO_2$: I, 36.13. Found: I, 36.11. [au] Calcd. for $C_{10}H_{16}ClNO_2$: N, 6.43; Cl, 16.29. Found: N, 6.54; Cl, 17.02. [av] Calcd. for $C_{10}H_{14}N_2O_4$: N, 12.38. Found: N, 12.20. [aw] Calcd. for $C_{11}H_{16}N_2O_4$: N, 11.66. Found: N, 11.62. [ax] Calcd. for $C_9H_{11}ClO_3$: Cl, 17.49. Found: Cl, 17.38.

nesium turnings and 47 g. (0.3 mole) of ethyl iodide in 200 ml. of anhydrous ether was added with stirring to a solution of 24.6 g. (0.15 mole) of *o*-toloxyacetone[12] in 200 ml. of anhydrous ether at about 5–10°. After the addition, the mixture was refluxed for one-half hour, cooled and poured on ice and dilute hydrochloric acid. The ether layer was separated, the aqueous layer was extracted twice with 100 ml. of ether, the combined ether extracts were washed with saturated sodium chloride solution, with saturated sodium bicarbonate solution, dried, concentrated, and distilled to give 17 g. of 2-methyl-1-(*o*-toloxy)-2-butanol, b. p. 133–135° (10 mm.).

**2-(2-*o*-Toloxyethoxy)-ethanol (LXII).**—To a solution of 99.3 g. (0.65 mole) of 2-(*o*-toloxy)-ethanol in 50 ml. of dry xylene was added 15.0 g. (0.65 mole) of sodium. The mixture was refluxed until all the sodium was dissolved. The reaction mixture was then heated on a steam-bath and 53.0 g. (0.65 mole) of ethylene chlorohydrin in 50 cc. of xylene was added dropwise, with stirring. After an additional half hour heating, the reaction mixture was cooled and filtered. The filtrate was distilled under reduced pressure to remove the xylene and the residue fractionated to give 18 g. of the product, b. p. 127–133° (3 mm.).

**3-(Cinnamyloxy)-1,2-propanediol (VIII).**—To a solution of 134 g. (1.0 mole) of cinnamyl alcohol in 600 ml. of benzene, was added 56.9 g. (1.0 mole) of sodium methoxide (95% purity). The suspension was refluxed for one hour, 250 ml. of benzene was removed by distillation, and 110.5 g. (1.0 mole) of glycerol-α-chlorohydrin was added, with stirring, during fifteen minutes. The heating and stirring was continued for an additional four hours. The mixture was then filtered, the filtrate was concentrated, and the residual oil fractionated to give 17.9 g. of the product, b. p. 184–189° (3 mm.).

**3-(2-Methylcyclohexyloxy)-1,2-propanediol (XXXIV).**—A solution of 115 g. (1.0 mole) of *o*-methylcyclohexanol in 400 ml. of xylene was treated with 23 g. (1.0 mole) of sodium and the mixture was heated and stirred until all of the sodium had reacted. At this time, 112 g. of glycerol α-chlorohydrin was added and the refluxing and stirring were continued for four hours. The product was isolated in the usual manner, b. p. 133–136° (2 mm.).

**2-Methyl-3-(*o*-tolylsulfonyl)-1,2-propanediol (XLVI).**—To a solution of 11 g. of 2-methyl-3-(*o*-tolylmercapto)-1,2-propanediol in 22 ml. of glacial acetic acid, was added 15 g. of 30% hydrogen peroxide, keeping the temperature below 50°. The mixture was allowed to stand for three days at room temperature and concentrated at 90° and 50 mm. The residue solidified, and was recrystallized from benzene-hexane to give 7.7 g. of the product, m. p. 78°.

**1,2-Dimethoxy-3-(*o*-toloxy)-propane (XVI).**—To a mixture of 51.1 g. (0.26 mole) of 1-methoxy-3-(*o*-toloxy)-2-propanol in 250 ml. of absolute ethanol, was added 5.98 g. (0.26 mole) of sodium. When the sodium had reacted, the ethanol was distilled and the final traces were removed *in vacuo* using an oil-bath at a temperature of 150°. Two hundred fifty ml. of anhydrous isopropyl ether was then added. To the mixture, 37 g. (0.26 mole) of methyl iodide was added slowly, with stirring. After the addition,

(12) Stoermer, *Ann.*, **312**, 288 (1900).

the mixture was stirred and refluxed for three hours, cooled and filtered. The filtrate was fractionated to give 31.1 g. of product, b. p. 149.5–150.5° (17 mm.).

**1-Methylamino-3-(*o*-toloxy)-2-propanol (XLIII).**—A mixture of 16.5 g. of glycide *o*-tolyl ether,[13] 50 ml. of 25% aqueous methylamine and 50 ml. of 95% ethanol was allowed to remain at room temperature for three days. The lower-boiling fractions were removed *in vacuo*, and the residue, which solidified, was recrystallized from hexane to give 12 g. of product, m. p. 78–79°.

**2-Hydroxy-3-(*o*-toloxypropyl)-trimethylammonium Iodide (XXIV).**—To a solution of 11 g. of 1-dimethylamino-3-(*o*-toloxy)-2-propanol[14] in 100 ml. of absolute ether, was added 8 g. of methyl iodide. The mixture was allowed to stand overnight, the precipitate was filtered and recrystallized from acetone–ether to give 12 g. of the product, m. p. 133°.

**3-(*o*-Hydroxymethylphenoxy)-1,2-propanediol (XXII): 3-(*o*-Formylphenoxy)-1,2-propanediol.**—To a stirred mixture of 97.6 g. (0.8 mole) of salicylaldehyde, 32 g. (0.8 mole) of sodium hydroxide and 320 ml. of water, at 85–90°, was added during fifteen minutes 90 g. (0.82 mole) of glycerol α-chlorohydrin. The mixture was heated and stirred for four hours, cooled and extracted with two 200 ml. portions of ethyl acetate. The ethyl acetate extracts were washed with saturated sodium chloride solution, dried and concentrated. The residue was recrystallized from acetone–hexane to give 45 g. (29.7%) of product, m. p. 87–88°. *Anal.* Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.45; H, 6.09.

A mixture of 5.5 g. (0.028 mole) of 3-(*o*-formylphenoxy)-1,2-propanediol, 90 ml. of absolute ethanol and 50 mg. of platinum oxide were shaken under hydrogen at 50 pounds pressure. Absorption was complete in thirty minutes. The catalyst was filtered, the filtrate distilled to dryness and the residue recrystallized from ethanol–hexane, to give 5 g. of product, m. p. 98–99°.

**3,6-Epoxy-2,3,4,6-tetrahydro-1,5-benzodioxocin.**—A mixture of 23.1 g. (0.117 mole) of 3-(*o*-formylphenoxy)-1,2-propanediol, 32.5 ml. of absolute ethanol, and 0.4 g. of ammonium chloride was refluxed and stirred for ten minutes. The mixture was cooled, made alkaline with a solution of 1 g. of sodium in 35 ml. of absolute ethanol, and distilled to dryness *in vacuo*. The residue was treated with 30 ml. of water, followed by 25 cc. of a saturated solution of sodium bisulfite partially neutralized with sodium bicarbonate. The resulting mixture was extracted twice with 150 ml. of ether, the extracts were washed with saturated sodium chloride solution, dried, concentrated, and the residue distilled, collecting the fraction, b. p. 113–114° (1 mm.). The distillate crystallized in the receiver and after triturating with hexane, was filtered, washed and dried, to give 13 g. (65%) of product, m. p. 63–64°. *Anal.* Calcd. for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66; mol. wt., 178.2. Found: C, 67.51; H, 5.56; mol. wt. (Rast), 188.

**3-(*o*-Toluidino)-1,2-propanediol Hydrochloride (LXVIII): N-(γ-Chloro-β-hydroxypropyl)-*o*-toluidine.**—To a solution of 32.1 g. (0.2 mole) of *o*-toluidine in 500 ml. of 95% ethanol was added slowly with thorough mixing, 27.8 g. of epichlorohydrin. The mixture was allowed to stand for three days at room temperature and the ethanol was rapidly removed *in vacuo* using a water-bath at 50–60°. The residual oil weighed 63 g. and was distilled immediately to give 26.3 g. (52%) of product, b. p. 145° (2 mm.). *Anal.* Calcd. for $C_{10}H_{14}ClNO$: N, 7.01. Found: N, 6.95.

A mixture of 48 g. of N-(γ-chloro-β-hydroxypropyl)-*o*-toluidine, 200 ml. of 10% sodium hydroxide and 150 ml. of ethanol was heated on the steam-bath for five hours. The solution was made slightly acidic with sulfuric acid, heated on the steam-bath for three hours, cooled, made alkaline and extracted with ether. After removing the ether there was obtained 37.5 g. of a residual oil. The hydrochloride was prepared by the addition of an excess of hydrogen chloride in ether to an ether solution of the free base. The crystalline, very hygroscopic hydrochloride was recrystallized from absolute ethanol–ether. It sintered at 160° and melted at 207°.

**N-(2,3-Dihydroxy-1-propyl)-*o*-methylcarbanilic Acid, Ethyl Ester (XIII).**—To a stirred mixture of 37.5 g. of 3-(*o*-toluidino)-1,2-propanediol, 100 ml. of water and 200 ml. of ether was added, at 0°, 22.5 g. of ethyl chlorocarbonate during one hour. The ether layer was separated, dried, concentrated and the residue distilled to give 6.0 g. of product, b. p. 215° (10 mm.).

The product is insoluble in acid while 3-*o*-(toluidino)-1,2-propanediol forms a stable hydrochloride. Consequently, the acetylation must have occurred on the nitrogen atom.

**(3-*o*-Toloxy-2-hydroxypropyl)-carbamate (LXX).**—To a stirred solution of 58.5 g. (0.32 mole) of Tolserol in 400 ml. of benzene was added dropwise a solution of 32 g. (0.3 mole) of phosgene in 200 ml. of benzene, maintaining the temperature at 30°. After the addition, the mixture was stirred one hour, 39 g. of dimethylaniline in 100 ml. of benzene was added and stirring was continued for an additional one-half hour. Ice water was added, the benzene layer was separated and stirred with 500 ml. of concentrated ammonia at 5° for six hours. The precipitated solid (55 g.) was recrystallized from water to give 53 g. of the product, m. p. 93°.

**3-(*o*-Toloxy)-1,2-propanediol, 1-Ester with Phosphoric Acid, Sodium Salt (LXIII).**—(A). A mixture of 72.8 g. of Tolserol and 39.2 g. of phosphoric acid was heated at 110–120° for twenty hours at 3 mm. The reaction mixture was dissolved in 200 ml. of water and the *p*H adjusted to 8.0 by the addition of 800 ml. of *N* sodium hydroxide. The solution was filtered and the filtrate freeze-dried. The salt was extracted with benzene, the benzene removed under reduced pressure and the residue dissolved in water and freeze-dried. The yield was 62 g. (51.8%). (B). A mixture of 2.17 g. (0.0153 mole) of phosphorus pentoxide, 5.56 g. (0.0306 mole) of Tolserol and 100 ml. of dry ether was kept for nine days at room temperature. Subsequently, 50 ml. of water was added with stirring, and dilute aqueous sodium hydroxide added until the *p*H of the aqueous phase was 9.0. The ether layer was separated, the water layer was extracted with fresh ether and, finally, the water layer was freeze-dried to give 6.0 g. of the hygroscopic sodium salt. From the ether extracts there was recovered 1.3 g. of Tolserol.

***o*-Methylcarbanilic Acid, O[1] Ester with Glycerol (XLIV): Allyl *o*-Methylcarbanilate.**—To a stirred solution of 26.6 g. of *o*-tolyl isocyanate in 100 ml. of dry benzene, was added 11.6 g. of allyl alcohol dissolved in 50 ml. of dry benzene, keeping the temperature below 20°. The mixture was refluxed for three hours, filtered, and the filtrate concentrated *in vacuo*. The residual solid was filtered, washed with cold benzene and recrystallized from benzene–hexane to give 21 g. (55%) of product, m. p. 39–41°. *Anal.* Calcd. for $C_{11}H_{13}NO_2$: N, 7.32. Found: N, 7.40. The oxidation of allyl *o*-tolylcarbamate was carried out as described above in Procedure 4, to give the product, m. p. 74–75°.

**α-Ethylcinnamic Acid, O[1] Ester with Glycerol (XXI): 2,2-Dimethyl-1,3-dioxolane-4-carbinol α-Ethylcinnamate.**—A mixture of 13.5 g. (0.07 mole) of α-ethylcinnamoyl chloride, 9.24 g. (0.07 mole) of isopropylidene glycerol and 7 ml. of pyridine was allowed to remain at room temperature for twenty-four hours. The mixture was then shaken with 100 ml. of water and extracted with two 200 ml. portions of ether. The ether extracts were combined, washed with 2% potassium carbonate solution, 1% hydrochloric acid and saturated sodium chloride solution. After drying, the ether was evaporated to give 16 g. (84%) of product,

Sixteen grams of α-ethylcinnamic acid isopropylidene glycerol ester was stirred with 188 ml. of 0.5 *N* hydrochloric acid at 60° for one hour. The mixture was cooled, neutralized with sodium bicarbonate and extracted with ether. The dried ether extracts were concentrated and

(13) Boyd and Knowlton, *J. Chem. Soc.*, **95**, 1802 (1909).

(14) Prepared by the same procedure employed with XLV; Brenans, *Bull. soc. chim.*, (4) **13**, 533 (1913), prepared this compound in benzene at 100°.

the residue fractionated to give 4.5 g. of product, b. p. 222–224° (5 mm.).

**1-(3-Methylbutoxy)-3-chloro-2-propanol.**—A mixture of 352 g. (4.0 moles) of 3-methylbutanol and 92.5 g. (1.0 mole) of epichlorohydrin was treated with 1.0 ml. of $SnCl_4$, and refluxed four hours. The mixture was then stirred with 20 g. of anhydrous sodium acetate, filtered and the filtrate fractionated to give 140.4 g. (78%) of product, b. p. 94° (5 mm.), $n^{25}D$ 1.4489. *Anal.* Calcd. for $C_8H_{17}ClO_2$: Cl, 19.62. Found: Cl, 19.10.

**3-(2,3-Dihydroxy-*n*-propoxy)-4-methylphenylurea (XLV).**—4-Nitro-2-hydroxytoluene was hydrogenated over 5% Pd on charcoal, in ethyl acetate, under 50 pounds pressure to give 82% **4-amino-2-hydroxytoluene**. The amine, 24.6 g. (0.2 mole), 48 ml. of concentrated hydrochloric acid and 200 ml. of water, cooled to 15°, was treated dropwise with 16.2 g. (0.2 mole) of potassium cyanate in 80 ml. of water. The urea separated quickly and was obtained in 87.1% yield, m. p. 185–186°. *Anal.* Calcd. for $C_8H_{16}N_2O_2$: N, 16.86. Found: N, 17.01. The condensation of the urea with glycerol α-chlorohydrin was carried out according to Procedure 1.

**2-Trichloromethyl-*m*-dioxane (LXXI).**—An ice cooled mixture of 180 g. (1.09 moles) of chloral hydrate and 76.1 g. (1.0 mole) of trimethylene glycol was treated gradually with 136 ml. of concentrated sulfuric acid, keeping the temperature below 40°. Subsequently, the mixture was heated one and one-half hours at 65–70°, cooled, diluted with water and extracted with 600 ml. of chloroform. The chloroform extracts were washed with water, aqueous sodium bicarbonate, dried, concentrated and distilled to give 48.1 g. of distillate, b. p. 103–6° (10 mm.), which partially solidified. After recrystallization from hexane, there was obtained 35.6 g. of product, m. p. 72–73°.

**Crotyl *o*-Tolyl Ether.**—To an ice-cooled solution of 54 g. (0.5 mole) of redistilled *o*-cresol, 100 ml. of dioxane and 20 g. of sodium hydroxide was added 68 g. (0.5 mole) of crotyl bromide in 100 ml. of dioxane. The mixture was stirred an additional hour at 0°, then an hour on the steam-bath. The sodium bromide was filtered, the dioxane distilled and the residue fractionated to give 20.8 g. of product, b. p. 109–111° (15 mm.). *Anal.* Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.04; H, 8.91.

## Summary

A series of aromatic ethers of polyhydroxy alcohols patterned after Tolserol [3-(*o*-toloxy)-1,2-propanediol] has been described. A number of related compounds, including sulfides, sulfones, amines, and carbamates, have been prepared.

NEW BRUNSWICK, N. J. RECEIVED DECEMBER 19, 1949

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[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

# Muscle-Relaxing Compounds Similar to 3-(*o*-Toloxy)-1,2-propanediol. II. Substituted Alkanediols[1]

BY HARRY L. YALE, EDWARD J. PRIBYL, WILLIAM BRAKER, JACK BERNSTEIN AND W. A. LOTT

In the first paper of this series[2] there was described the synthesis of a series of aromatic ethers of polyhydroxy alcohols related to Tolserol (3-*o*-toloxy-1,2-propanediol). In order to study further the relationship between chemical structure and muscle-relaxing properties, a series of substituted alkanediols were prepared.[3]

In general, substituted 1,3-propanediols were prepared by the reduction of the corresponding malonic ester with lithium aluminum hydride.[4] This method gave satisfactory yields with malonic esters, $RR'C(CO_2C_2H_5)_2$, where R was hydrogen or alkyl and R′ was alkyl or aryl. Yields were poorer when the ester was of the type $RR'OC(CO_2C_2H_5)_2$ or $RR'SC(CO_2C_2H_5)_2$. With diethyl ethyl-ethylmercaptomalonate, lithium aluminum hydride caused considerable degradation and none of the desired diol was obtained. An attempt to reduce diethyl ethyl-1-methylbutylmalonate according to the procedure of Hansley,[5] gave instead a product whose analysis agreed with the formula $C_9H_{20}O$; this compound is probably 2-ethyl-3-methylhexanol. The desired compound was prepared by the lithium aluminum hydride reduction. 2,2-Diethyl-1-phenyl-1,3-propanediol was prepared by the reduction of the corresponding β-hydroxy ester with lithium aluminum hydride.

Vicinal diols were prepared by the reaction of an α-hydroxy ester and a Grignard reagent.[6]

$$C_6H_5CHOHCO_2C_2H_5 + 3CH_2{=}CHCH_2MgBr \xrightarrow[\text{by HOH}]{\text{Followed}} C_6H_5CHOHC(CH_2CH{=}CH_2)_2OH$$

In addition, the triol, 1-phenyl-1,2,3-propanetriol (α-phenylglycerol) was prepared by the oxidation of cinnamyl alcohol with performic acid followed by saponification of the intermediate monoformate.[7] The diols are listed in Table I along with other pertinent data.

**Acknowledgment.**—The microanalyses were carried out by Mr. J. F. Alicino of this Institute.

## Experimental Part

All temperatures reported are uncorrected.

**2-Ethyl-2-phenylmercapto-1,3-propanediol.**—**Diethyl phenylmercaptomalonate**[8] was alkylated with ethyl bromide in the usual manner to give a 63.5% yield of **diethyl ethyl-phenylmercaptomalonate**, b. p. 151–153° (2 mm.), $n^{20}D$ 1.5265. *Anal.* Calcd. for $C_{15}H_{20}O_4S$: S, 10.82.

(1) Presented before the Division of Medicinal Chemistry, 116th Meeting of the American Chemical Society, Atlantic City, N. J., September 18–23, 1949.

(2) See the preceding paper, THIS JOURNAL, **72**, 3710 (1950). Tolserol is the registered name of E. R. Squibb & Sons for 3-*o*-toloxy-1,2-propanediol.

(3) The pharmacology of some of these compounds has been described recently by Berger, *Proc. Soc. Exptl. Biol. Med.*, **71**, 270 (1949).

(4) Nystrom and Brown, THIS JOURNAL, **69**, 1197 (1947).

(5) Hansley, *Ind. Eng. Chem.*, **39**, 55 (1947).

(6) Tiffeneau and Dolencourt, *Ann. chim. phys.*, [8] **16**, 247 (1909).

(7) Swern, Billen and Scanlan, THIS JOURNAL, **68**, 1504 (1946).

(8) Huntress and Olsen, *ibid.*, **70**, 2856 (1948).