

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<sub>4</sub> 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*<sub>D</sub><sup>25</sup> 1.4489. *Anal.* Calcd. for C<sub>8</sub>H<sub>17</sub>ClO<sub>2</sub>: 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<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>: N, 16.86. Found: N, 17.01. The condensation of the urea with glycerol  $\alpha$ -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<sub>11</sub>H<sub>14</sub>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

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

## Muscle-Relaxing Compounds Similar to 3-(*o*-Toloxyl)-1,2-propanediol. II. Substituted Alkanediols<sup>1</sup>

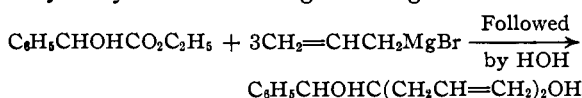
BY HARRY L. YALE, EDWARD J. PRIBYL, WILLIAM BRAKER, JACK BERNSTEIN AND W. A. LOTT

In the first paper of this series<sup>2</sup> 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.<sup>3</sup>

In general, substituted 1,3-propanediols were prepared by the reduction of the corresponding malonic ester with lithium aluminum hydride.<sup>4</sup> This method gave satisfactory yields with malonic esters, RR'C(CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>, 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<sub>2</sub>C<sub>2</sub>H<sub>5</sub>)<sub>2</sub> or RR'SC(CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>. With diethyl ethyl-ethylmercaptomalonic, 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,<sup>5</sup> gave instead a product whose analysis agreed with the formula C<sub>9</sub>H<sub>20</sub>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  $\beta$ -hydroxy ester with lithium aluminum hydride.

Vicinal diols were prepared by the reaction of an  $\alpha$ -hydroxy ester and a Grignard reagent.<sup>6</sup>



In addition, the triol, 1-phenyl-1,2,3-propanetriol ( $\alpha$ -phenylglycerol) was prepared by the oxidation of cinnamyl alcohol with performic acid followed by saponification of the intermediate monoformate.<sup>7</sup> 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 phenylmercaptomalonic**<sup>8</sup> was alkylated with ethyl bromide in the usual manner to give a 63.5% yield of **diethyl ethyl-phenylmercaptomalonic**, b. p. 151–153° (2 mm.), *n*<sub>D</sub><sup>20</sup> 1.5265. *Anal.* Calcd. for C<sub>14</sub>H<sub>20</sub>O<sub>2</sub>S: S, 10.82.

(6) Tiffeneau and Dolencourt, *Ann. chim. phys.*, [8] **18**, 247 (1909).

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

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

(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*, **73**, 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.*, **36**, 55 (1947).

TABLE I

		SUBSTITUTED ALKANEDIOLS									
Compounds 1,3-Propanediols		Yield, %	B. p. (uncor.) °C.	Mm.	M. p., °C. (uncor.)	Empirical formula	Carbon, %		Hydrogen, %		
							Calcd.	Found	Calcd.	Found	
I	2,2-Diethyl- <sup>a</sup>	50.0	110-113	5	57 <sup>b</sup>	C <sub>7</sub> H <sub>16</sub> O <sub>2</sub>	63.59	63.69	12.20	12.25	
II	2-Ethyl-2-phenyl-	45.0	151-152	1.5	78-79	C <sub>11</sub> H <sub>16</sub> O <sub>2</sub>	73.30	73.48	8.95	8.87	
III	2-Methyl-2-ethyl-	23.4	110-115	5	45-48 <sup>b</sup>	C <sub>8</sub> H <sub>14</sub> O <sub>2</sub>	60.98	60.68	11.95	11.80	
IV	2-Methyl-2- <i>n</i> -butyl-	60.5	116-117	5	.....	C <sub>9</sub> H <sub>18</sub> O <sub>2</sub>	65.72	65.09	12.41	11.81	
V	2-Methyl-2- <i>n</i> -propyl-	44.2	.....	.....	62-63 <sup>c</sup>	C <sub>7</sub> H <sub>16</sub> O <sub>2</sub>	63.59	63.68	12.20	12.32	
VI	2-Ethyl-2-isopropyl-	29.4	110-115	5	.....	C <sub>8</sub> H <sub>16</sub> O <sub>2</sub>	65.71	65.19	12.41	12.31	
VII	2-Methyl-2-isopropyl-	31.8	.....	.....	64-65 <sup>c</sup>	C <sub>7</sub> H <sub>16</sub> O <sub>2</sub>	63.59	63.48	12.20	12.42	
VIII	2-Ethyl-2-(1-methylbutyl)-	62.0	125-126	15	.....	C <sub>10</sub> H <sub>22</sub> O <sub>2</sub>	68.91	69.16	12.72	12.58	
IX	2,2-(Dimethylcyclohexenyl)- <sup>d</sup>	48.3	118-120	1	58-60 <sup>c</sup>	C <sub>10</sub> H <sub>18</sub> O <sub>2</sub>	70.55	70.34	10.66	10.34	
X	2,2-Di- <i>n</i> -propyl-	40.5	.....	.....	60-61 <sup>c</sup>	C <sub>9</sub> H <sub>20</sub> O <sub>2</sub>	67.46	67.06	12.58	12.48	
XI	2-Ethyl-2-phenoxy- <sup>e</sup>	27.6	115-120	2	.....	C <sub>11</sub> H <sub>16</sub> O <sub>3</sub>	67.33	67.43	8.22	8.22	
XII	2-Ethoxy-2-ethyl- <sup>e</sup>	20.2	119-120	19	.....	C <sub>7</sub> H <sub>16</sub> O <sub>3</sub>	56.73	56.91	10.88	11.15	
XIII	2,2-Di- <i>n</i> -butyl-	48.0	125-130	1	.....	C <sub>11</sub> H <sub>24</sub> O <sub>2</sub>	70.16	70.31	12.85	12.69	
XIV	2,2-Diethyl-1-phenyl	80.0	160	2	.....	C <sub>13</sub> H <sub>20</sub> O <sub>2</sub>	75.04	74.94	9.67	9.45	
Vicinal diols											
XV	2-Allyl-1-phenyl-1,2-(4-pentene)- diol	76	144	3	.....	C <sub>14</sub> H <sub>18</sub> O <sub>2</sub>	77.03	77.07	8.31	8.27	
XVI	1-Phenyl-2- <i>n</i> -propyl-1,2-pentane- diol	54.0	.....	.....	103-104 <sup>c</sup>	C <sub>14</sub> H <sub>22</sub> O <sub>2</sub>	75.63	75.68	9.98	10.00	
XVII	2- <i>n</i> -Butyl-1-phenyl-1,2-hexane- diol	52.8	.....	.....	102-103 <sup>b</sup>	C <sub>16</sub> H <sub>26</sub> O <sub>2</sub>	76.75	76.86	10.33	10.40	
XVIII	2-(3-Methylbutyl)-1-phenyl-5- methyl-1,2-hexanediol	60.0	.....	.....	110-111	C <sub>18</sub> H <sub>30</sub> O <sub>2</sub>	77.85	77.65	10.81	10.86	
XIX	3-Ethyl-6,8,8-trimethyl-3,4-non- anediol <sup>f</sup>	65.7	114-116	5	41-42 <sup>c</sup>	C <sub>14</sub> H <sub>30</sub> O <sub>2</sub>	72.98	72.78	13.13	12.27	
XX	2-Ethyl-1-( <i>p</i> -isopropylphenyl)-1,2- butanediol <sup>f</sup>	70.0	.....	.....	109-110 <sup>c</sup>	C <sub>15</sub> H <sub>24</sub> O <sub>2</sub>	76.22	76.41	10.24	10.65	
XXI	1-Methyl-2-phenyl-1,2-propane- diol	45.0	.....	.....	62-63 <sup>c</sup>	C <sub>10</sub> H <sub>14</sub> O <sub>2</sub>	72.26	71.87	8.49	8.33	
XXII	1-Phenyl-1,2,3-propanetriol <sup>f</sup>	16.9	194	6	.....	C <sub>9</sub> H <sub>12</sub> O <sub>3</sub>	64.26	64.66	7.19	7.01	

<sup>a</sup> Shortridge, *et al.*, THIS JOURNAL, 70, 946 (1948), prepared this compound from ethylbutyraldehyde and formaldehyde, m. p. 61.0-61.6°. Monocarbamate, m. p. 69-70° (see Experimental Part). <sup>b</sup> Recrystallized from benzene-hexane. <sup>c</sup> Recrystallized from hexane. <sup>d</sup> The dimethyltetrahydrobenzaldehyde used was furnished by the Shell Development Co. It consisted of the mixture of two isomers obtained by the condensation of methylpentadiene and acrolein. The procedure was that of French and Gallagher, THIS JOURNAL, 64, 1497 (1942). <sup>e</sup> See Experimental Part. <sup>f</sup> Moureu and Gallagher, *Bull. soc. chim.*, 29, 1009 (1921), prepared this compound by a different method and give a b. p. 185-186° (5 mm.).

Found: S, 10.89. To 13.0 g. (0.35 mole) of lithium aluminum hydride in 700 ml. of anhydrous ether was added dropwise and with stirring a solution of 94.1 g. (0.317 mole) of diethyl ethyl-phenylmercaptomalonate, at such a rate as to maintain a steady reflux. The mixture was then stirred an additional fifteen minutes, cooled in an ice-bath and decomposed by the careful addition of water. The mixture was then made acid with 10% hydrochloric acid. The ether layer was separated, the water layer was extracted with ether and the combined ether solutions were dried. The ether was evaporated and the residue distilled to give 27.0 g. of a pale yellow oil, b. p. 161-165° (3 mm.). Analyses indicated the oil to be a slightly impure 2-ethyl-2-phenylmercapto-1,3-propanediol. Repeated fractionation gave a slightly better product which was still impure.

*Anal.* Calcd. for C<sub>11</sub>H<sub>16</sub>O<sub>2</sub>S: C, 62.33; H, 7.60; S, 14.97. Found: C, 62.88; H, 6.39; S, 14.69.

**2-Ethyl-2-phenoxy-1,3-propanediol.**—Diethylphenoxy-malonate<sup>6</sup> was converted to diethyl ethyl-phenoxy-malonate in 90.2% yield by the usual procedure, b. p. 133-134° (2 mm.), *n*<sub>D</sub><sup>20</sup> 1.4872. *Anal.* Calcd. for C<sub>15</sub>H<sub>20</sub>O<sub>5</sub>: C, 64.26; H, 7.19. Found: C, 63.85; H, 7.26. Reduction with lithium aluminum hydride gave the diol, *n*<sub>D</sub><sup>20</sup> 1.5120.

**2-Ethoxy-2-ethyl-1,3-propanediol.**—Diethyl ethoxy-malonate,<sup>9</sup> *n*<sub>D</sub><sup>22</sup> 1.4215, was alkylated in 64.8% yield

to diethyl ethoxy-ethylmalonate. b. p. 110-115° (10 mm.), *n*<sub>D</sub><sup>22</sup> 1.4227. *Anal.* Calcd. for C<sub>11</sub>H<sub>20</sub>O<sub>5</sub>: C, 56.88; H, 8.68. Found: C, 56.82; H, 8.53. The diol was obtained in the usual manner, *n*<sub>D</sub><sup>20</sup> 1.4496.

**Attempted Preparation of 2-Ethyl-2-ethylmercapto-1,3-propanediol.**—Sodium ethyl mercaptide was prepared in 750 ml. of dry toluene from 46 g. (2.0 mole) of sodium sand and 124 g. (2.0 mole) of ethyl mercaptan and treated with 245 g. of ethyl chloroacetate to give 214 g. (72.3% yield) of ethyl ethylmercaptoacetate, b. p. 98-103° (35 mm.), *n*<sub>D</sub><sup>20</sup> 1.4562. *Anal.* Calcd. for C<sub>8</sub>H<sub>12</sub>O<sub>2</sub>S: S, 21.64. Found: S, 22.10. By reaction with ethyl oxalate in the presence of sodium ethoxide<sup>9</sup> this intermediate was converted to the oxalacetate which was not isolated but was pyrolyzed directly by heating in an oil-bath at 190-230°. The residue from the pyrolysis was distilled to give a 34.6% yield of diethyl ethylmercaptomalonate b. p. 140-144° (15 mm.), *n*<sub>D</sub><sup>20</sup> 1.4577. *Anal.* Calcd. for C<sub>9</sub>H<sub>16</sub>O<sub>4</sub>S: C, 49.07; H, 7.32. Found: C, 49.27; H, 7.49. Alkylation with ethyl bromide in the usual manner gave diethyl ethyl-ethylmercaptomalonate in 24.7% yield, m. p. 83-85°, after recrystallization from hexane. *Anal.* Calcd. for C<sub>11</sub>H<sub>20</sub>O<sub>4</sub>S: C, 53.20; H, 8.12; S, 12.91. Found: C, 53.15; H, 8.19; S, 12.67. Reduction of the malonate with lithium aluminum hydride appeared to proceed normally; however, no material was obtained boiling above 100°. Apparently degradation to volatile products had occurred.

(9) Wislicenus and Scheidt, *Ber.*, 24, 432 (1891).

**3-Ethyl-6,8,8-trimethyl-3,4-nonanediol.**—A solution of 133 g. (0.75 mole) of 2-hydroxy-4,6,6-trimethylheptanoic acid [ $\alpha$ -hydroxydecanoic acid (Rohm and Haas)] in 750 ml. of absolute ethanol was saturated with dry hydrogen chloride at 0° and worked up in the usual way to give 109.1 g. (67.3%) of the ethyl ester, b. p. 89–94° (2 mm.),  $n_D^{25}$  1.4346. *Anal.* Calcd. for  $C_{12}H_{24}O_3$ : C, 66.63; H, 11.18. Found: C, 67.09; H, 11.43. Reaction with ethylmagnesium bromide gave the diol,  $n_D^{25}$  1.4518.

**2,2-Diethyl-1-phenyl-1,3-propanediol.**—Ethyl 2,2-diethyl-3-hydroxy-3-phenylpropionate was prepared in 72.0% yield by the reaction of benzaldehyde, ethyl diethylbromoacetate and zinc dust; the product distilled at 121–122° (0.6 mm.),  $n_D^{25}$  1.5050. *Anal.* Calcd. for  $C_{15}H_{22}O_3$ : C, 71.92; H, 8.86. Found: C, 71.68; H, 8.82. The diol,  $n_D^{25}$  1.5253, was obtained by reduction with lithium aluminum hydride.

**2,2-Diethyl-3-hydroxypropyl Carbamate.**—To a stirred solution of 66 g. (0.5 mole) of 2,2-diethyl-1,3-propanediol, 75 g. of dimethylaniline and 500 ml. of benzene, at 5 ± 2°, was added a solution of 50 g. of phosgene in 250 ml. of benzene. After an additional two hours of stirring at 5°, the liquid was decanted from dimethylaniline hydrochloride, treated with 250 ml. of concentrated ammonia, and stirred two additional hours at 5°. The benzene layer was separated, washed with water, dried and concentrated. The residual oil solidified and was recrystallized from benzene-hexane to give 2 g. (2.7%) of the product, m. p. 69–70°. *Anal.* Calcd. for  $C_8H_{17}NO_3$ : N, 7.99. Found: N, 7.88.

**1-Phenyl-1,2,3-propanetriol.**—A mixture of 40.2 g. (0.3 mole) of cinnamyl alcohol and 253.8 g. of 98–100% formic acid was cooled to 5° and treated all at once with 41.4 g. of 30% hydrogen peroxide. The mixture was

warmed to 35° and kept at 35–40° for 22 hours, concentrated *in vacuo* and the residue saponified with a solution of 21 g. of potassium hydroxide in 95% ethanol. The ethanol was distilled and the residue extracted with ether. The dried ethereal solution was concentrated and distilled to give 8.5 g. (16.9%) of the product, b. p. 194° (6 mm.).

**The  $C_9H_{20}O$  Compound.**—The sodium reduction procedure described by Hansley<sup>5</sup> was followed. A mixture of 210 g. of dry xylene, 80 g. of dry "Isobutylcarbinol" (Sharples) and 50 g. of diethyl ethyl-1-methylbutylmalonate was fed into a refluxing stirred suspension of 36.2 g. of sodium sand in 50 ml. of dry xylene contained in a 3-liter 3-necked flask equipped with a copper water cooled condenser and air stirrer. The addition required fifty minutes during which 4.34 liters of gas was evolved. After standing overnight the mixture was hydrolyzed by the cautious addition of 300 ml. of water, and then steam distilled. The organic layer in the steam distillate was separated and the water layer extracted with three 200-ml. portions of ether. The ether and organic layers were combined, dried and distilled to remove xylene and "Isobutylcarbinol," after which the residue was fractionated to give 9.5 g. (34%) of what is presumed to be 2-ethyl-3-methylhexanol, b. p. 76° (6 mm.). *Anal.* Calcd. for  $C_9H_{20}O$ : C, 74.93; H, 13.97. Found: C, 74.93; H, 13.91.

### Summary

The preparative methods for a series of substituted alkanediols have been described.

NEW BRUNSWICK, NEW JERSEY

RECEIVED DECEMBER 19, 1949

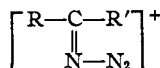
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

## The Effect of Structure on the Course of the Schmidt Reaction on Unsymmetrical Ketones<sup>1</sup>

By P. A. S. SMITH AND JEROME P. HORWITZ

The Schmidt reaction of hydrogen azide with ketones under the influence of strong acids is known to give amides:  $R-CO-R + HN_3 \rightarrow R-CO-NH-R + N_2$ .<sup>2</sup> We have undertaken an investigation of the behavior of unsymmetrical ketones in this reaction and report here our observations on substituted benzophenones and certain aryl alkyl ketones, together with the interpretation according to one of the mechanisms recently proposed.<sup>3</sup>

A feature of that mechanism is the intermediate occurrence of a species formulated as



whose structure indicates the possibility of geomet-

(1) Presented at the Meeting of the American Chemical Society, San Francisco, California, March 28–April 2. Part of this work was taken from part of the doctoral thesis of Jerome P. Horwitz, University of Michigan, 1949. This article antedates the paper of Smith and Ashby, *THIS JOURNAL*, **73**, 2503 (1950), which is a sequel to the present work. Reference 1 in that paper was intended to refer to the present article, but through error refers to an unrelated article.

(2) H. Wolff, "The Schmidt Reaction," in R. Adams, "Organic Reactions," Vol. III, John Wiley and Sons, New York, N. Y., 1946.

(3) P. A. S. Smith, *THIS JOURNAL*, **70**, 320 (1948); cf. M. S. Newman and H. Gildenhorn, *ibid.*, **70**, 317 (1948).

rical isomerism of the same type as encountered in oximes. If, as in the Beckmann rearrangement, the *trans* group (R) migrates from C to N, then the ratios of the *syn* and *anti* configurations of this intermediate would determine the relative extents of migration of R and R'. In the absence of such a geometrical effect, the factor determining the relative extents of migration would be expected to be the relative intrinsic rates of migration of R and R'. These different rates, commonly referred to as "migration aptitudes," are presumably the result of different activation energies of different groups undergoing the required transition. An indication as to their relative magnitudes is available from studies of the pinacol rearrangement<sup>4</sup> and the rates of migration of different groups in the Beckmann rearrangement.<sup>5</sup>

In order to obtain evidence as to whether the geometrical configuration of the intermediate or

(4) For a summary of the work of various authors, see H. Adkins in Gilman, "Organic Chemistry," 2nd ed., John Wiley and Sons, New York, N. Y., 1943, p. 1067, and G. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, New York, N. Y., 1949, p. 513.

(5) A. W. Chapman and F. A. Fidler, *J. Chem. Soc.*, 448 (1936).