melting point sample, after melting, was heated to 250° and cooled, the resolidified material remelted at 236–238° [lactone acetate].

Anal. Calcd. for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 72.08; H, 9.95.

Methyl 3β-Acetoxyallonor-16-cholenate (IV).—A solution of 11.3 g. of the acetoxy ester (III) in 114 ml. of dry pyridine was cooled in an ice–salt-bath and 11.4 ml. of redistilled thionyl chloride added. The mixture was allowed to stand for two hours in an ice–salt-bath and for one hour at room temperature, then poured into ice-water and stirred for one hour. The crystals were filtered and washed neutral with water to give 10.9 g., m.p. 94–170°. The crude product was dissolved in hot methanol, the solution concentrated to 55 ml., cooled and filtered to give 8.0 g., m.p. 103–180°. These crystals were dissolved in 300 ml. of ethyl ether, the volume reduced to 100 ml., cooled and the crystals filtered to give 1.6 g. of needles, m.p. 236–238°. A second crop of needles (0.25 g.) with the same melting point was obtained from the mother liquor at a volume of 35 ml. A mixture of these needles with a sample of the acetoxy lactone showed no depression in the melting point. It is apparent that relactonization occurs during the dehydration reaction. The mother liquor after removal of the lactone acetate was concentrated to dryness and the residue recrystallized several times from methanol and ethanol to give 3.1 g. of IV (fine needles) melting at 120.6–123.4°; $[\alpha]^{21}D$ +2.0° (2% in $CHCl_3$).

Anal. Calcd. for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68. Found: C, 74.70; H, 9.83.

Methyl 3β-Acetoxyallonorcholanate (V).—A solution of 2.0 g. of the unsaturated acetoxy ester (IV) dissolved in 300 ml. of absolute alcohol was hydrogenated at 760 mm. and 25° using 0.6 g. of 10% palladium-on-charcoal. The reduction was stopped when 109 ml. of hydrogen had been consumed (22 minutes). Fine needle-like crystals were formed during the reduction. The mixture of catalyst and crystals was removed by filtration and the filter cake washed thoroughly with chloroform to remove the sterol. The filtrate was concentrated to a small volume, the chloroform replaced completely with ethanol by distillation and the volume reduced to 40 ml. After cooling to 5°, the crystals were filtered to give 1.70 g. of V (needles), m.p. 157.5–159.0°. After recrystallization from acetone and methanol the analytical sample melted at 159.4–160.8°; $[\alpha]^{25}D$ +11.0° (2% in $CHCl_3$). This product corresponds in its properties to the methyl 3β-acetoxyallonorcholanate described by Wieland and Miescher[7] and by Plattner and Pataki.[2]

Anal. Calcd. for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.50; H, 9.95.

3β-Hydroxyallonorcholanic Acid.—The acetoxy ester (V) was saponified by refluxing with 2% methanolic potassium hydroxide. After recrystallization from ethyl acetate and acetone, the product melted at 226.0–226.8°; $[\alpha]^{24}D$ +22.8° (1% in ethanol). These constants agree with those reported by Plattner and Pataki.[2]

Acknowledgment.—We wish to thank Dr. W. B. Tarpley and Miss C. Vitiello of our Chemical Research Division for the infrared data herein reported.

(7) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **30**, 1876 (1947).

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β-Glycerol Ethers Isomeric with Mephenesin

BY W. A. WEST AND B. J. LUDWIG

RECEIVED APRIL 14, 1952

In a search for drugs that exhibit muscle-paralyzing activity more intense and with a longer duration of action than mephenesin (3-*o*-toloxy-1,2-propanediol), numerous compounds have been synthesized wherein variations were made in the nature and distribution of substituents in the aromatic nucleus, and modifications were made in the hydroxylated side chain.[1] Among the previously reported compounds are three isomers of mephenesin, 3-*m*-toloxy-1,2-propanediol, 3-*p*-toloxy-1.2-propanediol and 3-benzyloxy-1,2-propanediol, all of which have the formula $C_7H_7OCH_2CHOHCH_2OH$, but no reference has been made to the preparation of the corresponding β-glycerol ethers. This paper describes the preparation and physical constants of the four isomeric β-glycerol ethers having the formula $C_7H_7OCH(CH_2OH)_2$. These compounds are of interest not only because of their structural relationship to mephenesin but also because of their similarity to the anticonvulsant drug 2,2-diethyl-1,3-propanediol (DEP). The results of pharmacological studies carried out with these compounds will be reported elsewhere.

Synthesis of the 2-toloxy-1,3-propanediols was accomplished through the lithium aluminum hydride reduction of the corresponding toloxymalonic esters following the procedure described by Chaikin for the reduction of ethyl phenoxymalonate.[2] Since ethyl benzyloxymalonate could not be readily prepared by direct condensation of ethyl chloromalonate and sodium benzylate, 2-benzyloxy-1,3-propanediol was synthesized by the condensation of benzyl chloride and the sodium salt of 5-hydroxy-2-phenyl-*m*-dioxane followed by hydrolysis of the cyclic acetal.

The melting point of each of the 2-toloxy-1,3-propanediols is lower than that of the corresponding 3-toloxy-1,2-propanediol. However, the 2-benzyloxy derivative was isolated as a solid whereas the 3-benzyloxy compound has been reported to be a liquid.[3] The β-glycerol ethers reported here have water solubilities comparable to those of the corresponding α-glycerol ethers, with the exception of 2-*m*-toloxy-1,3-propanediol, which possesses an abnormally high water solubility.

Experimental[4]

Ethyl Toloxymalonates.—The three isomeric ethyl toloxymalonates were prepared by condensation of ethyl chloromalonate with the appropriate sodium cresolate in absolute ethanol following the procedure described for ethyl *m*-toloxymalonate by Niederl and Roth.[5]

2-Toloxy-1,3-propanediols.—The diols were obtained by reduction of the corresponding toloxymalonic esters with lithium aluminum hydride[2] followed by acid hydrolysis of the aluminate. The *o*-toloxy compound was purified by fractionation under diminished pressure, the meta- and para-isomers by crystallization from benzene–ligroin solution.

5-Benzyloxy-2-phenyl-*m*-dioxane (VII).—To a well-stirred suspension of 4.3 g. (0.11 mole) of sodium amide in 200 ml. of anhydrous toluene, there was added portionwise 18.0 g. (0.1 mole) of 1,3-benzylidene glycerol[6] and the mixture was refluxed until the evolution of ammonia had ceased. A solution of 16.0 g. (0.12 mole) of benzyl chloride in 50 ml. of anhydrous toluene was added over a period of 15 minutes and refluxing continued for six hours. The mixture was cooled, washed with two 50-ml. portions of water, dried over sodium sulfate and concentrated *in vacuo*.

(1) For a listing of the pertinent references in this field, see: B. J. Ludwig, W. A. West and W. E. Currie, THIS JOURNAL, **74**, 1935 (1952).

(2) S. W. Chaikin, *ibid.*, **70**, 3522 (1948).

(3) J. C. Sowden and H. O. Fischer, *ibid.*, **63**, 3244 (1941).

(4) All temperatures reported are uncorrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Middle Village, Long Island, New York.

(5) J. B. Niederl and R. T. Roth, THIS JOURNAL, **62**, 1154 (1940).

(6) H. Hibbert and N. M. Carter, *ibid.*, **51**, 1608 (1929).

TABLE I

Compd. no.	Compounds	Yield, %[a]	B.p., °C.	Mm.	$n^{25}D$	M.p., °C.[b]	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I	2-*o*-Toloxy-1,3-propanediol	60	150–153	2.0	1.5391	.....	$C_{10}H_{14}O_3$	65.95	66.16	7.69	7.81
II	2-*m*-Toloxy-1,3-propanediol	92	.....	..	....	66–67	$C_{10}H_{14}O_3$	65.95	66.22	7.69	7.81
III	2-*p*-Toloxy-1,3-propanediol	68	.....	..	....	68–69	$C_{10}H_{14}O_3$	65.95	65.98	7.69	7.59
IV	2-Benzyloxy-1.3-propanediol	87	185–187	10.0	....	38.5–40	$C_{10}H_{14}O_3$	65.95	65.88	7.69	7.59
V	Ethyl *o*-toloxymalonate	69	140–142	2.0	....	49.5–50	$C_{14}H_{18}O_5$	63.15	62.75	6.77	6.77
VI	Ethyl *p*-toloxymalonate	65	110–114	0.1	1.4908	.....	$C_{14}H_{18}O_5$	63.15	63.32	6.77	6.81
VII	5-Benzyloxy-2-phenyl-*m*-dioxane	60	.....	..	....	75.5–76.5	$C_{17}H_{18}O_3$	75.55	75.85	6.71	7.01

[a] Yields are based on material of reasonable purity and do not taken into account the recovery of starting materials. [b] M.p. data are for analytically pure samples.

The residual oil, which solidified on standing, was purified by crystallization from benzene–ligroin solution.

2-Benzyloxy-1,3-propanediol (IV).—A solution of 32.5 g. (0.12 mole) of 5-benzyloxy-2-phenyl-*m*-dioxane (VII), 170 ml. of ethanol, 60 ml. of water and 2.0 ml. of concentrated sulfuric acid was refluxed for two hours. Most of the ethanol was removed by distillation, the residue cooled and neutralized with sodium bicarbonate and the benzaldehyde steam distilled from the mixture. The aqueous solution of the diol was saturated with potassium carbonate and extracted with three 50-ml. portions of ether. After drying over magnesium sulfate, the ethereal solution was concentrated and the residual oil distilled under reduced pressure. The distillate solidified on cooling and was further purified by crystallization from benzene.

Table I summarizes the physical constants and analytical data for these compounds.

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The Reduction of 1,2-Isopropylidene-D-glucurono-lactone with Lithium Aluminum Hydride[1]

BY SAUL ROSEMAN

RECEIVED JULY 28, 1952

In the synthesis of 6-C^{14}-glucose described recently by Sowden,[2] the final step is the reduction of 6-C^{14}-1,2-isopropylidene-D-glucuronolactone with sodium borohydride followed by acid hydrolysis of the resultant mixture to yield glucose. With the particular lot of ion exchange resin (Duolite A-4) available for our first experiments, some difficulty was experienced in complete removal of the borate ion. A modification of the reduction step was therefore developed, utilizing lithium aluminum hydride. Although this reagent has a disadvantage in that it requires anhydrous conditions for its action, it possesses two advantages: (1) an increased yield of glucose, (2) it is possible to isolate the intermediate 6-C^{14}-1,2-isopropylidene-D-glucose in good yield.

Experimental

1,2-Isopropylidene-D-glucose.—The reaction vessel is a three-necked Grignard reaction flask into which are inserted a condenser and a dropping funnel, both protected with drying tubes. Stirring is performed with a magnetic stirrer, 8 ml. of a 1.6 *M* solution of lithium aluminum hydride (clear[3]) is added through the third opening in the flask followed by 10 ml. of anhydrous ether (stored over sodium) and the flask is stoppered; 1.08 g. of 1,2-isopropylidene-D-glucuronolactone is dissolved in 150 ml. of boiling anhydrous ether, the solution is allowed to cool, and is then added dropwise over a period of 30 minutes to the stirred lithium aluminum hydride solution. About 50 ml. more of ether is used to rinse in the last trace of lactone. The flask is placed in a water-bath at 50–60°, the solution is stirred and refluxed for 25 minutes, and is then cooled. Absolute alcohol is cautiously added at this point until the excess reagent is destroyed and then more rapidly with vigorous stirring until 25 ml. have been added. A clear, colorless solution should result. A solution of concentrated hydrochloric acid in alcohol is then added (4 parts concentrated hydrochloric acid to 10 parts absolute ethanol). The acid is added dropwise with stirring until a sample tested with phenolphthalein in alcohol shows that the mixture is barely acid (requires about 4 ml. of concentrated hydrochloric acid). The mixture should be essentially clear at this point. The solution is quickly cooled and is then poured into an iced mixture of 150 ml. of petroleum ether and 100 ml. of 0.01 *M* hydrochloric acid. The aqueous layer is separated and the ether layer is extracted once more with 100 ml. of 0.01 *M* hydrochloric acid. To deionize the solution, the combined aqueous extracts are passed through alternating layers of IR-120, H and IR-4B. In the isotope experiments where it is not desired to recover the resin, the two resins are mixed intimately before use—this being the most efficient procedure for maintenance of a neutral *p*H. The final resin layer is always the IR-120, H and the total volumes used are about 100 ml. of each resin (somewhat more in the case of the alternating layers). The neutral, colorless solution is concentrated at 50–55° *in vacuo* and yields 1.05 g. of slightly yellowish crystals, m.p. 153–157°. Recrystallization from ethyl acetate yields 0.70 g. of white crystals, melting at 161–162° and $[\alpha]^{24}D$ −12.0° (*c* 5.4, water). There was no depression of the melting point when the sample was mixed with an authentic specimen. A second crop was obtained upon the cautious addition of petroleum ether to the ethyl acetate mother liquors, 0.20 g., m.p. 158–160°, $[\alpha]^{24}D$ −12.2° (*c* 5.1, water).

D-Glucose.—The procedure described above for the reduction is followed up to, and including, the addition of alcohol to the reaction flask. The clear solution is then poured into a separatory funnel containing 200 ml. of water, 2 ml. of concentrated sulfuric acid, and 150 ml. of petroleum ether. The aqueous extract is removed and the ether layer washed once more with 50 ml. of 0.1 *M* sulfuric acid. The combined aqueous extracts are then heated for 1.5 hours on the steam-bath, and the colorless solution is cooled and treated with an excess of barium carbonate with shaking until the mixture is alkaline. The mixture is centrifuged and the precipitate is washed three times with water and finally with boiling water. Complete deionization is obtained by passing the solution through a 20-ml. layer of IR-120,H then 20 ml. of IR-4B and finally 10 ml. of IR-120,H. The combined eluate and washings are colorless, negative toward the naphthoresorcinol uronic acid test, and contain 0.85 g. of glucose according to a quantitative anthrone and reducing sugar analysis. The solution is concentrated, yielding a colorless sirup which is then treated with 4 ml. of 95% ethanol and seeded. After standing for one week, crystallization is complete, yielding 0.72 g. of anhydrous dextrose, m.p. 146°, $[\alpha]^{24}D$ 52.3°, equilibrium in

(1) This investigation was supported by grants from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service, and the Helen Hay Whitney Foundation.

(2) J. C. Sowden, THIS JOURNAL, **74**, 4877 (1952); preliminary report, 119th Meeting, ACS, Milwaukee, April, 1952. I would like to express my gratitude to Dr. Sowden for his many valuable suggestions.

(3) W. G. Brown, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 484.