Experimental[6]

The reduction has been carried out by procedures similar to those described in previous papers.[3,4] Thus a mixture of the starting material, diethylene or triethylene glycol (Note 1), alkali hydroxide and 85% hydrazine hydrate (Notes 2 and 3) was refluxed for about half an hour and the condenser was then removed to allow the aqueous liquor to evaporate and the temperature of the reaction mixture to rise to about 200°. In cases where either the starting material or the reduced product is volatile a take-off adapter was used instead of removing the condenser to evaporate aqueous liquor. After refluxing at this temperature for about two hours the reaction mixture was cooled, diluted with water (Note 4) and the separated reaction product was filtered or extracted with ether (Note 5). The results are summarized in Table I (Notes 6 and 7).

Catalytic reduction of Δ^5-pregnen-3(β)-ol (V) to allopregnan-3(β)-ol (VII): 0.2 g. of Δ^5-pregnen-3(β)-ol in 30 cc. of alcohol containing 3 drops of hydrobromic acid (48%) was shaken with hydrogen in the presence of 0.05 g. of Adams catalyst until the calculated amount of hydrogen was absorbed. The reaction mixture was filtered and the filtrate was concentrated in vacuum to a small volume. On dilution with water allopregnan-3(β)-ol (VII) separated in plates. It was recrystallized from methanol, m. p. 136–137, not depressed by admixture with the Wolff–Kishner reduction product from VI; yield 0.18 g.

NOTE 1.—The amount of diethylene glycol or triethylene glycol used can be varied according to the solubility of the carbonyl compound or its hydrazone formed during the reaction so that a clear or nearly clear reaction mixture is obtained during the heating period. Sometimes it is advisable to dissolve the carbonyl compound in alcohol before addition of glycol and other reagents, *e.g.*, in the case of cholestanone and cholestenone.

NOTE 2.—The amount of alkali hydroxide used is about 10% to the volume of the glycol used and the amount of 85% hydrazine hydrate used is always in excess (3 moles or more).

NOTE 3.—In reduction of alkali-sensitive compounds such as aldehydes, α,β-unsaturated ketones and those carbonyl compounds in which the carbonyl group is adjacent to an asymmetric center it is advisable to reflux the glycol solution of starting material with hydrazine hydrate for about half an hour and then add a concentrated aqueous solution of alkali hydroxide slowly as described previously.[4]

NOTE 4.—If the reduced product is acidic, it is obtained by acidifying the cooled reaction mixture with dilute hydrochloric acid.

NOTE 5.—In cases where the starting material contains methoxy group the crude reduced product was remethylated with dimethyl sulfate.

NOTE 6.—Most of the technical steroid ketones[7] were recrystallized before reduction, since otherwise the yield is sometimes unsatisfactory. The yields of reduced products given in Table I are on the basis of pure products for which the melting points are given.

NOTE 7.—In cases where the carbonyl compound is unstable and difficult to purify such as α-naphthaldehyde the hydrazone or semicarbazone can be taken as starting material for reduction.

(6) The microanalyses were carried out by Shirley Katz of this Laboratory.

Summary

1. The modified Wolff–Kishner method has been applied to the reduction of a number of steroid ketones and a few other carbonyl compounds giving excellent or comparatively good yields.

2. In the case of the steroids the reduction proceeds normally on the keto groups at positions C_3, C_7, C_{12}, C_{17} and C_{20}, but the C_{11} keto group remains unattacked.

(7) Steroid samples furnished through the courtesy of Merck & Co. and the Schering Corporation.

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

Drugs Effecting Muscular Paralysis. Some Substituted Dioxolanes and Related Compounds[1]

BY V. BOEKELHEIDE, L. LIBERMAN, J. FIGUERAS,[2a] C. KRESPAN,[2b] F. C. PENNINGTON AND D. S. TARBELL

The drugs which effect muscular paralysis may be divided into two classes, depending on whether the predominant action is peripheral or central in nature.[3] The usual curariform agents, including most natural alkaloids and certain quaternary ammonium salts, belong to the former class. The first important compounds to be discovered having a central action were *o*-toloxy-1,2-propanediol (myanesin) and certain related α-glyceryl ethers.[4] Recently,[5] it was found that another class of compounds, the 2-substituted-4-hydroxymethyl-1,3-dioxolanes, possessed an action similar to that of the α-glyceryl ethers. In fact, the results of testing in mice indicate that the best compounds of the dioxolane series exceed those of the α-glyceryl ether series both in degree of activity and in margin of safety. In an attempt to find the scope of activity and the effect of changes of structure on activity in the dioxolane series, a number of substituted dioxolanes have been prepared. In the present paper the synthesis of these dioxolanes is described and evidence is presented establishing the structures of several of the most active members of this series.[6]

The synthesis of the substituted dioxolanes was accomplished, in general, by heating the appropriate carbonyl compound with glycerol or ethylene glycol and an acid catalyst in the presence of a hydrocarbon solvent and with continuous removal

(1) Aided by a Grant from the National Foundation for Infantile Paralysis, Inc.

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(3) Craig, *Chem. Rev.*, **42**, 285 (1948).

(4) Berger and Bradley, *Brit. J. Pharmacol.*, **1**, 265 (1946).

(5) Berger, Boekelheide and Tarbell, *Science*, **108**, 561 (1948).

(6) The results of the physiological testing of these compounds will be reported separately by F. M. Berger, M.D., School of Medicine and Dentistry, University of Rochester, Rochester, New York.

TABLE I

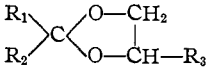
2,2-DIALKYL-4-HYDROXYMETHYL-1,3-DIOXOLANES (See Structure I)

Cpd.	R_1	R_2	B. p., °C.	Mm.	$n^{21}D$	d^{21}	M Calcd.[a]	M Obsd.	Yield, %	Formula	Composition, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
III	$-CH_3$	$-CH_2CH_2CH_3$	100	5	1.4427	1.024	41.66	41.46	65	$C_8H_{16}O_3$	59.97	59.74	10.07	10.01
IV	$-CH_3$	$-(CH_2)_3CH_3$	105	5	1.4450	1.006	46.28	46.25	75	$C_9H_{18}O_3$	62.03	61.08	10.41	10.30
V	$-CH_3$	$-C(CH_3)_3$	76	1	1.4493	1.021	46.28	45.82	70	$C_9H_{18}O_3$	62.03	61.49	10.41	9.90
VI	$-CH_3$	$-(CH_2)_4CH_3$	80	1	1.4464[b]	0.983	50.91	51.09	80	$C_{10}H_{20}O_3$	63.79	63.66	10.71	10.78
VII	$-CH_3$	$-CH(CH_3)(CH_2)_2CH_3$	95–100	2	1.4487				23	$C_{10}H_{20}O_3$	63.79	63.30	10.71	10.64
VIII	$-CH_3$	$-(CH_2)_5CH_3$	135	5	1.4486	.985	55.52	55.45	62	$C_{11}H_{22}O_3$	65.31	65.01	10.96	10.71
IX	$-CH_3$	$-(CH_2)_6CH_3$	113	1	1.4498	.967	60.14	60.11	66	$C_{12}H_{24}O_3$	66.63	66.30	11.18	11.19
X	$-CH_2CH_3$	$-CH_2CH_3$	95	4	1.4457	1.033	41.66	41.33	84	$C_8H_{16}O_3$	59.97	59.29	10.07	9.63
XI	$-CH_2CH_3$	$-(CH_2)_3CH_3$	106	2	1.4481	0.999	50.91	50.46	78	$C_{10}H_{20}O_3$	63.79	63.52	10.71	10.52
XII	$-CH_2CH_3$	$-(CH_2)_4CH_3$	121	4	1.4499	.990	55.52	54.82	68	$C_{11}H_{22}O_3$	65.31	65.04	10.96	10.60
XIII	$-CH(CH_3)_2$	$-CH(CH_3)_2$	115	9	1.4502	.995	50.91	50.75	24	$C_{10}H_{20}O_3$	63.79	63.50	10.71	10.52
XIV	$-CH_2CH(CH_3)_2$	$-CH_2CH(CH_3)_2$	103	2	1.4494	.980	60.14	59.86	47	$C_{12}H_{24}O_3$	66.63	66.67	11.18	11.09

[a] The value of 1.60 was used for ether oxygen; see Newman and Renoll, THIS JOURNAL, **67**, 1621 (1945). [b] Dupire, *Compt. rend.*, **214**, 359 (1942), reported the values: $n^{19}D$ 1.5132; d^{19} 1.100.

TABLE II

SUBSTITUTED 1,3-DIOXOLANES



Cpd.	R_1	R_2	R_3	B. p., °C.	Mm.	$n^{21}D$	d^{21}	M Calcd.	M Obsd.	Yield, %	Formula	Composition, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
XV	$-H$	$-(CH_2)_5CH_3$	$-CH_2OH$	106	4	1.4508	1.002	50.92	50.57	79	$C_{10}H_{20}O_3$	63.79	63.31	10.71	10.53
XVI	$-CH_3$	$-CH_2Cl$	$-CH_2OH$	112	10	1.4692	1.252	37.32	37.08	79	$C_6H_{11}O_3Cl$	43.25	42.99	6.66	6.62
XVII	$-CH_2Cl$	$-CH_2Cl$	$-CH_2OH$	110	3	1.4069	1.4919	42.16	41.63	65	$C_6H_{10}O_3Cl_2$	35.84	35.14	5.01	5.09
XVIII	$-CH_3$	$-CH(CO_2Et)(CH_2)_3CH_3$	$-CH_2OH$	131	2	1.4527	1.057	66.44	66.53	61	$C_{13}H_{24}O_5$	59.98	59.83	9.29	9.23
XIX	$-CH_3$	$-CH(CO_2Et)(CH_2)_3CH_3$	$-H$	112	5	1.4398				57	$C_{12}H_{22}O_4$	62.58	62.99	9.63	9.72
XX[a]	$-CH_3$	$-CH(CH_2OH)(CH_2)_3CH_3$	$-H$	106	5	1.4520	1.007	50.92	50.43	48	$C_{10}H_{20}O_3$	63.79	64.13	10.71	10.76
XXI	$-CH_3$	*o*-$CH_3CH_6H_4-$	$-CH_2OH$	118	1	1.5267	1.125	56.55	56.89	15	$C_{12}H_{16}O_3$	69.21	68.62	7.75	7.75

[a] See Experimental.

TABLE III

SUBSTITUTED DIOXASPIRANES AND 1,3-DITHIOLANES

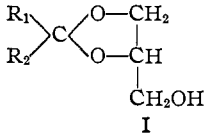
Cpd.	Name	B. p., °C.	Mm.	$n^{21}D$	d^{21}	Yield, %	Formula	Composition, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
XXII	2-M[a]-1,4-dioxaspiro-(4,4)-nonane	122	12	1.4730[c]	1.130	42	$C_8H_{14}O_3$	60.74	60.82	8.92	8.95
XXIII	2-M-6-methyl-1,4-dioxaspiro-(4,4)-nonane	122	11	1.4702[d]	1.099	25	$C_9H_{16}O_3$	62.74	61.94	9.37	9.13
XXIV	2-M-7-methyl-1,4-dioxaspiro-(4,5)-decane	102	2	1.4733	1.069	58	$C_{10}H_{18}O_3$	64.50	64.62	9.68	10.14
XXV	2-*n*-Amyl-2-methyl-4-M-1,3-dithiolane	93	1	1.5453		66	$C_{10}H_{20}OS_2$	54.04	53.75	9.14	8.70
XXVI	2,2-Dimethyl-4-M-1,3-dithiolanedisulfone[b]					79	$C_5H_{12}O_5S_2$	31.58	31.57	5.29	5.16

[a] M = hydroxymethyl. [b] See Experimental; m. p. 110–112°. [c] M calcd., 39.48; M obsd., 39.27. [d] M calcd., 44.10; M obsd., 43.74.

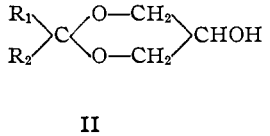
of the water formed. Those dioxolanes which were prepared and have not previously been reported, are listed in Tables I, II and III.

For the preparation of some of the compounds listed in Tables I, II and III, the general method could not be applied. Compound XX, 2-(1′-hydroxymethylamyl)-2-methyl-1,3-dioxolane, was prepared by the sodium and alcohol reduction of the corresponding ester, XIX. It was of interest that XX was the only compound prepared which had high physiological activity but did not have a hydroxymethyl group at the 4-position of the dioxolane ring. Compound XXV, 2-*n*-amyl-2-methyl-4-hydroxymethyl-1,3-dithiolane, was prepared by the condensation of methyl *n*-amyl ketone and 2,3-dimercapto-1-propanol (B. A. L.). Compound XXVI was obtained by the peroxide oxidation of 2,2-dimethyl-4-hydroxymethyl-1,3-dithiolane.

The condensation of a carbonyl compound with glycerol may yield either a dioxolane derivative (I) or a *m*-dioxane derivative (II). Although in



I



II

previous work[7–9] it has been assumed that ketones react with glycerol to give products having the dioxolane structure, this has apparently been established only for the condensation of acetone with glycerol.[10,11] An indication that ketones condense with glycerol to give dioxolane derivatives was obtained when it was found that methyl *n*-amyl ketone condensed readily with ethylene glycol but gave no product at all with trimethylene

(7) Dworzak and Herrmann, *Monatsh.*, **52**, 83 (1929).
(8) Kuhn, *J. prakt. Chem.*, **156**, 103 (1940).
(9) Dupire, *Compt. rend.*, **214**, 359 (1942).
(10) Irvine, Macdonald and Soutar, *J. Chem. Soc.*, **107**, 337 (1915).
(11) Hibbert and Morazain, *Can. J. Research*, **2**, 214 (1930).

glycol. Similar results have been cited by Dworzak and Herrmann[7] as evidence that ketones and glycerol give dioxolane derivatives. However, the work of Hibbert and his collaborators[12,13] has shown that such reasoning, when applied to the condensation of aldehydes with glycerol, is misleading. Therefore, the structures of the condensation products of glycerol with methyl *n*-amyl ketone and with methyl *n*-hexyl ketone were investigated and definitely shown to be of the dioxolane type.

The evidence for the dioxolane structure, I, was established as follows. The condensation product of glycerol and methyl *n*-hexyl ketone, on conversion to the corresponding methyl ether followed by acid hydrolysis, gave only α-methyl glyceryl ether. Thus, the condensation product must be 2-methyl-2-*n*-hexyl-4-hydroxymethyl-1,3-dioxolane, since the corresponding *m*-dioxane derivatives would yield a β-methyl glyceryl ether. Likewise the condensation product of glycerol and methyl *n*-hexyl ketone, on treatment with trityl chloride in pyridine under the usual conditions whereby primary but not secondary alcohol groups are etherified,[14] gave an 83% yield of the corresponding trityl ether. The condensation product of glycerol and methyl *n*-hexyl ketone must therefore be almost entirely 2-methyl-2-*n*-hexyl-4-hydroxymethyl-1,3-dioxolane.

Finally, a sample of 2-methyl-2-*n*-amyl-4-hydroxymethyl-1,3-dioxolane of known structure was prepared by the alkaline hydrolysis of the condensation product of methyl *n*-amyl ketone and 3-(3′,5′-dinitrobenzoxy)-1,2-propanediol. The infrared absorption spectrum of the 2-methyl-2-*n*-amyl-4-hydroxymethyl-1,3-dioxolane, thus prepared, was found to be identical within experimental error with that of the condensation product of glycerol and methyl *n*-amyl ketone. The absorption spectra are given in Fig. 1.

On the other hand, there is considerable evidence in the literature[15] that aldehydes condense with glycerol to give mixtures of the corresponding 4-hydroxymethyl-1,3-dioxolanes (I) and the corresponding 5-*m*-dioxanols (II). Since the condensation product of glycerol and heptanal possessed a fairly high degree of physiological activity, an investigation of its structure was made.

When the condensation product of glycerol and heptanal was allowed to react with trityl chloride in anhydrous pyridine, as before, there was obtained a 58% yield of the corresponding trityl ether. This rather low yield indicates that, while the product predominantly has structure I, there is also present some material having structure II.

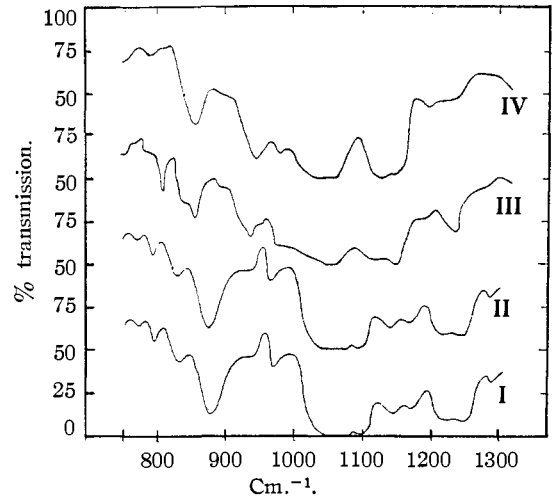


Fig. 1.—Infrared absorption spectra of the condensation product of glycerol and methyl *n*-amyl ketone (I); 2-*n*-amyl-2-methyl-4-hydroxymethyl-1,3-dioxolane (II); condensation product of glycerol and heptanal (III); and 2-*n*-hexyl-4-hydroxymethyl-1,3-dioxolane (IV). Spectra were obtained using 0.025 mm. cell.

Further evidence for this conclusion was obtained from infrared absorption spectra studies. A sample of 2-*n*-hexyl-4-hydroxymethyl-1,3-dioxolane of known structure was prepared by the alkaline hydrolysis of the condensation product of heptanal and 3-(3′,5′-dinitrobenzoxy)-1,2-propanediol. A comparison of the infrared absorption spectra (see Fig. 1) of this sample with that of the condensation product of glycerol and heptanal showed that, despite a close similarity of the two curves, there were certain real differences. The condensation product of glycerol and heptanal showed absorption peaks at 811 cm.$^{-1}$ and 1240 cm.$^{-1}$, which were not present in the spectra of the pure 2-*n*-hexyl-4-hydroxymethyl-1,3-dioxolane. However, until a pure sample of 2-*n*-hexyl-5-*m*-dioxanol is available for comparison, it is not possible to estimate accurately the amount of 2-*n*-hexyl-5-*m*-dioxanol present in the condensation product of glycerol and heptanal.

The infrared absorption spectra studies were initiated in the hope that some characteristic of the spectrum could be related to the dioxolane ring structure and that the infrared absorption spectra of these compounds could be used as a diagnostic test for the presence of the dioxolane ring. However, our knowledge of these spectra is still insufficient to allow such a diagnosis.

Experimental[16]

Formation of the Substituted Dioxolanes, Dioxaspiranes, and Dithiolanes Listed in Tables I, II and III.—With the

(12) Hibbert and Timm, THIS JOURNAL, **46**, 1283 (1924).

(13) Trister and Hibbert, *Can. J. Research*, **14**, 415 (1937).

(14) Helferich and Becker, *Ann.*, **440**, 1 (1924). Although it is realized that secondary alcohols may be etherified by trityl chloride [see Hockett and Hudson, THIS JOURNAL, **53**, 4456 (1931); **56**, 945 (1934)] and therefore this method is not an absolute criterion for the presence or absence of a secondary hydroxyl, it is felt that the method supplies supporting evidence since conditions highly unfavorable to etherification of a secondary hydroxyl were employed.

(15) (a) Van Roon, *Rec. trav. chim.*, **48**, 173 (1929); (b) Trister and Hibbert, *Can. J. Research*, **14**, 415 (1937); Hill, Wheeler and Hibbert, THIS JOURNAL, **50**, 2235 (1928); Hibbert and Sturrock, *ibid.*, **50**, 3376 (1928); and other papers in this same series.

(16) Analyses by Mrs. G. L. Sauvage; all melting points are uncorrected.

exceptions and additions noted below, the compounds listed in Tables I, II and III were prepared by the condensation of the appropriate carbonyl compound with glycerol, ethylene glycol, or 2,3-dimercapto-1-propanol (B. A. L.) according to the following procedure. A mixture of the appropriate carbonyl compound (0.20 mole), double-distilled glycerol (0.25 mole), toluenesulfonic acid (0.5 g.) and toluene (100 ml.) was heated in a three-necked flask with stirring and with provision for continuous removal of water.[17] When the expected amount of water had separated or when no further separation of water occurred, the reaction mixture was cooled, washed successively with a 25-ml. portion of a 5% potassium carbonate solution and three 50-ml. portions of water. The toluene was removed under reduced pressure and the residual oil distilled.

(A) Sodium α-(2-Methyl-4-hydroxymethyl-1,3-dioxolan-2-yl)-caproate.—A mixture of 21.0 g. of 2-(1'-carbethoxyamyl)-2-methyl-4-hydroxymethyl-1,3-dioxolane (XVIII) and 65 ml. of a 5% sodium hydroxide solution was boiled under reflux until the solution became clear (four hours). After evaporation of the solution to dryness, the residue was taken up in a minimum amount of alcohol and reprecipitated by addition of ether. Recrystallization of the crude material from a mixture of alcohol and ether yielded 15.1 g. (75%) of a white powder, m. p. 240–245°.

Anal. Calcd. for $C_{11}H_{19}O_5Na$: Na, 9.05. Found (as Na_2SO_4): Na, 9.09; 9.70.

(B) 2-(1'-Hydroxymethylamyl)-2-methyl-1,3-dioxolane (XX).—To a solution of 26.3 g. of 2-(1'-carbethoxyamyl)-2-methyl-1,3-dioxolane (XIX) in 150 ml. of absolute alcohol, a total of 23.0 g. of sodium and 170 ml. of absolute alcohol, was added alternately in small portions. When the reaction of sodium with alcohol was complete, 75 ml. of water was added and most of the alcohol was removed under reduced pressure. The organic residue was extracted with ether, washed, and the ether was removed. Distillation of the residue yielded 9.9 g. (48%) of a colorless oil, b. p. 106° at 5 mm.

(C) 2-Hydroxymethyl-8-methyl-8-aza-1,4-dioxaspiro-4,5-decane.[18]—A solution of 1.0 g. of 1-methyl-4-piperidone hydrochloride,[19] 0.65 g. of glycerol, and 25 ml. of chloroform was heated in such a manner that as the chloroform slowly distilled, fresh chloroform was added to maintain constant volume. After two hours, the reaction was stopped and the chloroform was removed *in vacuo*. An excess of 45% potassium hydroxide was added to the residue, and the organic layer was extracted with ether, dried, and distilled. There was obtained 0.5 g. of a light yellow oil, b. p. 104–106° at 1 mm.

A **picrate** of the oil was prepared in ether and was obtained as light yellow crystals, m. p. 154–157°.

Anal. Calcd. for $C_{16}H_{20}N_4O_{10}$: C, 43.27; H, 4.84. Found: C, 43.01; H, 4.83.

(D) 2,2-Dimethyl-4-hydroxymethyl-1,3-dithiolanedisulfone (XXVI).—To a solution of 2.3 g. of 2,2-dimethyl-4-hydroxymethyl-1,3-dithiolane[20] in 5 ml. of acetic acid, there was added dropwise 4.5 ml. of a 30% hydrogen peroxide solution. The mixture was allowed to stand overnight and was then poured into 50 ml. of water. On partial evaporation of the solution crystals separated and they were collected on a filter. Recrystallization of the crude material from a mixture of benzene and hexane yielded 2.4 g. (79%) of white crystals, m. p. 110–112°.

Evidence for the Structure of the Condensation Products of Glycerol and Ketones

(A) Preparation and Hydrolysis of 2-*n*-Hexyl-2-methyl-4-methoxymethyl-1,3-dioxolane.—A solution of 2-*n*-hexyl-2-methyl-4-hydroxymethyl-1,3-dioxolane (39.5 g., 0.195 mole) in toluene (20 ml.) was slowly added to an excess of sodium (0.20 mole) in boiling toluene (100 ml.). After the reaction with sodium was complete, the solution was removed from the excess sodium by decantation and methyl iodide (42.6 g., 0.30 mole) was slowly added with stirring. The reaction mixture was then boiled under reflux for one hour. The sodium iodide, which precipitated, was removed by filtration, the solvent was removed *in vacuo*, and the residue was distilled. There was obtained 22.9 g. (54%) of a colorless oil; b. p. 79° at 1 mm.; $n^{20}D$ 1.4350; d^{20} 0.9364.

Anal. Calcd. for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.30; H, 11.76.

Hydrolysis of a sample of 2-*n*-hexyl-2-methyl-4-methoxymethyl-1,3-dioxolane (22.9 g., 0.11 mole) was accomplished by heating it for several hours with 25 ml. of a 1% solution of hydrochloric acid containing sufficient alcohol to produce a homogeneous solution. The alcohol was then removed *in vacuo*, and the solution was extracted with ether to remove any methyl *n*-hexyl ketone present. After neutralization of the solution with lead carbonate followed by filtration, the water was removed *in vacuo* and the residue was distilled. There was obtained 5.4 g. (45%) of a viscous oil; b. p. 63° at 0.05 mm.; $n^{20}D$ 1.4463; d^{20} 1.1138. The oil formed a diphenylcarbamate, m. p. 119–120°. These properties agree well with those reported for α-methyl glycerol ether.[21]

The presence of methyl *n*-hexyl ketone in the ethereal extract was established by formation of the 2,4-dinitrophenylhydrazone, m. p. 57–58°.[22]

(B) Formation of 2-*n*-Hexyl-2-methyl-4-triphenylmethoxymethyl-1,3-dioxolane.—A sample of 2-*n*-hexyl-2-methyl-4-hydroxymethyl-1,3-dioxolane (29.9 g., 0.148 mole) was treated with trityl chloride (42.6 g., 0.148 mole) in anhydrous pyridine (30 ml.) according to the procedure of Seikel and Huntress.[23] The product obtained did not crystallize and could not be distilled without decomposition. Purification was finally effected as follows. The oil was treated with pentane (100 ml.) to precipitate any triphenylcarbinol, the pentane was removed, and the resulting oil was recrystallized from ethanol using a dry-ice cooling-bath. There was obtained 53.0 g. (83%) of a viscous, colorless oil, $n^{21}D$ 1.5607.

Anal. Calcd. for $C_{30}H_{36}O_3$: C, 81.03; H, 8.10. Found: C, 80.79; H, 7.86.

(C) Preparation of 2-*n*-Amyl-2-methyl-4-hydroxymethyl-1,3-dioxolane of Known Structure.—A mixture of 3-(3',5'-dinitrobenzoxy)-1,2-propanediol[24] (20.0 g., 0.07 mole), methyl *n*-amyl ketone (18.0 g., 0.14 mole), and benzene (70 ml.) was treated in the usual manner for preparing dioxolanes. The residual oil, which resulted, was treated with pentane and cooled to effect crystallization. There was obtained 19.3 g. (73%) of light yellow crystals, m. p. 43–48°. Repeated recrystallization of the crude material from a benzene–hexane mixture gave white crystals, m. p. 56–57°, liquid becomes clear at 60°.

Anal. Calcd. for $C_{17}H_{22}N_2O_7$: C, 53.40; H, 5.76. Found: C, 53.72; H, 5.66.

Since there are two diastereoisomeric forms possible for 2-*n*-amyl-2-methyl-4-(3',5'-dinitrobenzoxy-methyl)-1,3-dioxolane, it seemed probable that the crude product represented a mixture of both forms. Evidence for this was obtained from the fact that a sample of the crude product, which had been crystallized once from acetonitrile and melted at 52–54°, gave as good an analysis (Found: C, 53.59; H, 5.87) as did the highest melting product previously obtained.

Hydrolysis of the 2-*n*-amyl-2-methyl-4-(3',5'-dinitrobenzoxymethyl)-1,3-dioxolane was carried out on the crude mixture obtained above so that separation of diastereoisomers would not be effected by crystallization

(17) See "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 378.

(18) We are indebted to Dr. L. E. Craig for this experiment.

(19) Craig and Tarbell, THIS JOURNAL, **71**, 465 (1949).

(20) Stocken, *J. Chem. Soc.*, 592 (1947).

(21) Hibbert, Whelen and Carter, THIS JOURNAL, **51**, 303 (1929), give $n^{17}D$ 1.4463, d^{17} 1.1197; and a diphenylcarbamate derivative, m. p. 118–119°.

(22) Allen, *ibid.*, **52**, 2955 (1930).

(23) Seikel and Huntress, *ibid.*, **63**, 593 (1941).

(24) Fairbourne and Foster, *J. Chem. Soc.*, **127**, 2763 (1925).

and so that the hydrolysis product would be comparable for an infrared absorption study to that obtained by direct synthesis. A mixture of 2-*n*-amyl-2-methyl-4-(3′,5′-dinitrobenzoxymethyl)-1,3-dioxolane (9.7 g., 0.25 mole), potassium hydroxide (2.8 g.) and water (100 ml.) was boiled gently for one hour. The basic solution was dried, the ether was removed, and the residual oil was distilled yielding 3.0 g. (62.5%) of a colorless oil; b. p. 70–72° at 0.5 mm., $n^{21}D$ 1.4468, d^{21} 0.988. These physical properties and the infrared absorption spectra of this compound (see Fig. 1) are essentially identical with those obtained for the product from the direct reaction of methyl *n*-amyl ketone and glycerol.

Evidence for the Structure of the Condensation Product of Glycerol and Heptanal

(A) Treatment of the Condensation Product with Trityl Chloride in Pyridine.—The condensation product was treated with trityl chloride in anhydrous pyridine according to the procedure of Seikel and Huntress.[23] The reaction mixture was heated on the steam-bath for five minutes. From 18.8 g. of condensation product there was obtained, after one crystallization from alcohol, 26.0 g. (58%) of white crystals, m. p. 56–58°. This crude material apparently represents a mixture of the diastereoisomeric racemates, which are possible for 2-*n*-hexyl-4-(triphenylmethoxymethyl)-1,3-dioxolane. By repeated recrystallization of this material from alcohol a pure sample of white crystals, m. p. 70–71°, was obtained.

Anal. Calcd. for $C_{29}H_{34}O_3$: C, 80.93; H, 7.90. Found: C, 81.03; H, 7.81.

(B) Preparation of a Sample of 2-*n*-Hexyl-4-hydroxymethyl-1,3-dioxolane of Known Structure

2-*n*-Hexyl-4-(3′,5′-dinitrobenzoxymethyl)-1,3-dioxolane.—A mixture of 25.0 g. of 3-(3′,5′-dinitrobenzoxy)-1,2-propanediol,[24] 18.2 g. of heptanal and 80 ml. of benzene was heated in a flask connected to an ordinary water-eliminator. When the expected quantity of water had separated, the benzene was removed and the residue was triturated with hexane. The fluffy, white crystals, m. p. 65–68°, which separated, were collected on a filter and weighed 16.0 g. (48%). Since this crude material probably represents a mixture of the two possible diastereoisomeric racemates, it was employed without further purification in the hydrolysis experiment described below. Repeated recrystallization of the crude material from a mixture of benzene and hexane gave a pure sample of one of the racemates, m. p. 74–75°.

Anal. Calcd. for $C_{17}H_{22}N_2O_8$: C, 53.41; H, 5.76. Found: C, 53.43; H, 5.67.

2-*n*-Hexyl-4-hydroxymethyl-1,3-dioxolane.—A mixture of 14.0 g. of the crude 2-*n*-hexyl-4-(3′,5′-dinitrobenzoxymethyl)-1,3-dioxolane, m. p. 65–68°, and 90 ml. of a 5% potassium hydroxide solution was boiled under reflux for three hours. The organic layer was then extracted with ether, washed, dried, and the ether was removed. Distillation of the residue yielded 4.0 g. (58%) of a colorless oil; b. p. 80° at 0.2 mm.; $n^{21}D$ 1.4492; d^{21} 0.988; *M* calcd. 50.92; $M_{obsd.}$ 51.05.

Anal. Calcd. for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.83; H, 10.78.

Summary

Some substituted dioxolanes, dioxaspiranes and dithiolanes of possible interest as agents for effecting muscular paralysis have been prepared. On the basis of chemical evidence and infrared absorption spectra data, the condensation products of glycerol with methyl *n*-amyl ketone and methyl *n*-hexyl ketone have been assigned the structures of 2,2-dialkyl-4-hydroxymethyl-1,3-dioxolanes.

On the basis of similar evidence the condensation product of glycerol and heptanal is thought to be a mixture of which the predominant constituent is 2-*n*-hexyl-4-hydroxymethyl-1,3-dioxolane.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Analogs of Dibenzylacetic Acid[1]

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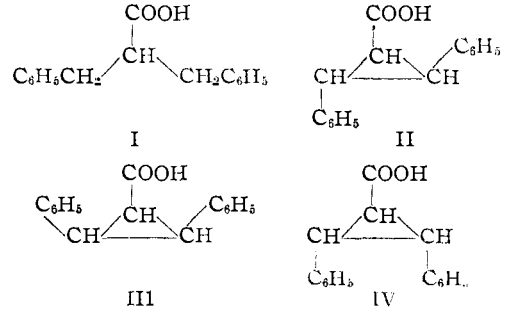
Certain dialkylaminoalkyl esters of dibenzylacetic acid abolish spasm produced by barium chloride or histamine several times as effectively as papaverine while their atropine-like activity against spasm caused by acetylcholine is generally low.[5] A comparison of analogous compounds in which the benzyl groups have been altered by cyclization or isosteric replacements promised to clarify further this relationship.

The first of our variations of the structure of dibenzylacetic acid (I) was concerned with a steric fixation of the two benzyl carbon atoms by incorporating them in a cyclopropane ring. The required 2,3-diphenylcyclopropanecarboxylic acids were prepared by adding ethyl diazoacetate to *cis*- and *trans*-stilbene, respectively, decomposing the intermediate pyrazoline derivative without isolation, and hydrolyzing the resulting esters. *trans*-Stilbene gave only one racemic acid (II), and only one of the two meso forms (III and IV) expected from *cis*-stilbene could be isolated from the reaction mixture. For further comparison, 2,2-diphenylcyclopropanecarboxylic acid (V) was



(1) Presented in part before the 114th Meeting of the American Chemical Society, Washington, D. C., August 31, 1948.

(2) Charles C. Haskell Postdoctorate Fellow, 1947.

(3) Du Pont Senior Fellow, 1948.

(4) Smith, Kline and French Fellow, 1947.

(5) Wagner-Jauregg, Arnold and Born, *Ber.*, **72**, 1551 (1939).