[CONTRIBUTION FROM THE WARNER-LAMBERT RESEARCH INSTITUTE]

2,2-Disubstituted 1,3-Dioxolanes and 2,2-Disubstituted 1,3-Dioxanes

ROBERT I. MELTZER, ARNOLD D. LEWIS, JOSEPH VOLPE,[1] AND DAVID M. LUSTGARTEN

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In a search for central nervous system depressants there were prepared a number of 1,3-dioxolanes and 1,3-dioxanes substituted by a tertiary alcohol. The most active compound was 2-methyl-2-(3-hydroxy-3-ethylpentyl)-1,3-dioxolane (XIV).

It has been found possible to produce paralysis of the skeletal muscles by means of chemical agents which act either at the myoneural junction or which act on the central nervous system. In these laboratories we have been interested in agents of both types. Among the agents of the latter type, we have investigated a series of 1,3-dioxolanes and 1,3-dioxanes which are herewith reported.

Berger has reported[2] on a series of 1,3-dioxolanes synthesized by Boekelheide *et al.*[3] The compounds tested indicated that effective drugs were to be found in the series, but that the activity was of short duration and was accompanied by some undesirable side effects. The work was primarily concerned with 4-hydroxymethyl-1,3-dioxolane derivatives. There was, however, reported one compound which had a hydroxyl group on a substituent which was other than on the 4-position of the dioxolane ring. This compound, 2-methyl-2-(1-hydroxymethyl-*n*-amyl)-1,3-dioxolane, had a high order of activity.

The presently reported series of compounds was suggested by the following two considerations. As recognized by Berger,[2] the metabolism of the dioxolanes may, as in the case of mephenesin, proceed through an oxidation of the primary alcohol with resulting deactivation of the molecule. By introduction of the hydroxyl group in the form of a tertiary alcohol, such ready oxidation would be inhibited. Furthermore, tertiary alcohols may, in and of themselves, be expected to have central nervous system depressant activity. Boekelheide and his group had investigated a large number of 4-(hydroxyalkyl)-1,3-dioxolanes but had not followed the lead of the 2-(hydroxyalkyl)-1,3-dioxolane which they reported. We, therefore, prepared a series of 2-(hydroxyalkyl)-1,3-dioxolanes and 2-(hydroxyalkyl)-1,3-dioxanes in which the alcohols were tertiary.

Condensation of ethyl acetoacetate with ethylene glycol gave 2-methyl-2-carbethoxymethyl-1,3-dioxolane (I). By treatment of this ester with two moles of ethylmagnesium bromide there was obtained 2-methyl-2-(2-hydroxy-2-ethylbutyl)-1,3-dioxolane (II). This material showed an order of activity which was of interest. Reaction of the ester was therefore carried out with both methyl and propylmagnesium halides. The resulting tertiary alcohols (III and IV) both showed a lower activity than did the first prepared alcohol (II).

We prepared 2,2-diisopropyl-4-hydroxymethyl-1,3-dioxolane (V) (Promoxolane) for comparison and found that it, too, had an activity of shorter duration than that of compound II in our mouse test, although it possibly did show a better therapeutic index.

Because there was some thought that hydrolysis of II in the body to give ethylene glycol might not be desirable, condensation was carried out between ethyl acetoacetate and propylene glycol to give 2,4-dimethyl-2-carbethoxymethyl-1,3-dioxolane (VI). Treatment of this ester with ethylmagnesium bromide gave 2,4-dimethyl-2-(2-hydroxy-2-ethylpropyl)-1,3-dioxolane (VII), which proved to be less active than the previously prepared II. For the reason given for the preparation of VII we carried out the condensation between trimethylene glycol and ethyl acetoacetate to give 2-methyl-2-carbethoxymethyl-1,3-dioxane (VIII), which was converted by ethylmagnesium bromide to 2-methyl-2-(2-hydroxy-2-ethylbutyl)-1,3-dioxane (IX), which also was not as active as II.

We next considered that we might be able to increase the activity of the 1,3-dioxane compounds if we employed as a glycol 2,2-diethylpropane-1,3-diol, which itself is a central nervous system depressant. By carrying out the appropriate condensation to give ester X and treatment of this ester with ethylmagnesium bromide, the corresponding tertiary alcohol XI was obtained. This proved to be less active pharmacologically than was II.

At this point we thought it would be interesting to prepare a 1,3-dioxane which had its hydroxyalkyl group at a position other than at the 2-position. To this end we attempted to condense diisopropyl ketone with trishydroxymethylmethane in the way in which we had carried out our other similar condensations. In this we were unsuccessful. We were also unsuccessful when we changed to dioxane as a solvent in order to get a homogeneous reaction mixture and when we changed to dimethoxyethane or to diethoxyethane to get higher reaction temperatures. Anhydrous zinc chloride

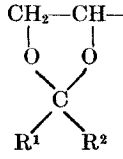
(1) Present address: National Starch Products, Plainfield, N. J.

(2) F. M. Berger, *Arch. intern. pharmacodynamie*, **85**, 474 (1951).

(3) V. Boekelheide, L. Liberman, J. Figueras, C. Krespan, F. C. Pennington, and D. S. Tarbell, *J. Am. Chem. Soc.*, **71**, 3303 (1949).

TABLE I

SUBSTITUTED 1,3-DIOXOLANES



Cmpd.	R^1	R^2	R^3	B.P. °C	B.P. Mm.	n_D at	°C	Yield, %	Empirical Formula	Analysis, % Calcd. C	Calcd. H	Found C	Found H
I	CH_3	$CH_2CO_2C_2H_5$	H	112–114	33[a]	1.4304	24	70					
II	CH_3	$CH_2C(C_2H_5)_2OH$	H	122–123	20	1.4489	24.5	30	$C_{10}H_{20}O_3$	63.79	10.71	63.81	10.94
III	CH_3	$CH_2C(CH_3)_2OH$	H	99	24	1.4401	25	34	$C_8H_{16}O_3$	59.97	10.07	59.85[b]	10.20
IV	CH_3	$CH_2C(n\text{-}C_3H_9)_2OH$	H	133	15[b]	1.4484	25	15	$C_{12}H_{24}O_3$	66.63	11.18	66.80	11.27
V	$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	CH_2OH	98–100	4[c]	1.4532	21	30					
VI	CH_3	$CH_2CO_2C_2H_5$	CH_3	75–76	4[d]	1.4275	25	37					
VII	CH_3	$CH_2C(C_2H_5)_2OH$	CH_3	104–108	9	1.4437	25	58	$C_{11}H_{22}O_3$	65.31	10.96	65.21	10.89
XIII	CH_3	$CH_2CH_2CO_2C_2H_5$	H	106–107	13[e]	1.4326	25	65					
XIV	CH_3	$CH_2CH_2C(C_2H_5)_2OH$	H	118–119	4	1.4575	25	75	$C_{11}H_{22}O_3$	65.31	10.96	65.27	11.14
XV	CH_3	$CH_2CH_2C(CH_3)_2OH$	H	110	10.5	1.4475	25	15	$C_8H_{16}O_3$	62.04	10.41	61.94	10.66
XVI	CH_3	$CH_2CH_2CH(OH)CH(CH_3)_2$	H	112.5–113	10.5	1.4412	25	7	$C_{10}H_{20}O_3$	63.79	10.71	63.91	10.80
XVII	CH_3	$CH_2CH_2CH_2CO_2C_2H_5$	H	128–129	15	1.4460	25	65	$C_{10}H_{18}O_4$	59.38	8.97	59.51	9.12
XVIII	CH_3	$CH_2CH_2CH_2C(C_2H_5)_2OH$	H	116–118	1.9	1.4572	24	70	$C_{12}H_{24}O_3$	66.83	11.42	66.63	11.18

[a] Kahn[4] reported b.p. 100° (17–18 mm.), n_D^{20} 1.4326. Salmi[5] reported b.p. 99.5–101° (17–18 mm.), n_D^{20} 1.43262. [b] 90° (1 mm.). [c] Boekelheide *et al.*[3] reported b.p. 115° (9 mm.), n_D^{21} 1.4502. [d] Salmi[5] reported b.p. 84.6–86° (6 mm.), n_D^{20} 1.4288. [e] Kahn[4] reported b.p. 110–112 (15 mm.).

(4) M. Kahn, *J. prakt. Chem.* (2) **156**, 103 (1940).
(5) E. J. Salmi, *Ber.*, **71**, 1803 (1938).

TABLE II

SUBSTITUTED 1,3-DIOXANES

Cmpd.	R^1	R^2	R^3	B.P. °C	B.P. Mm.	n_D^{25}	% Yield	Empirical Formula	Analysis, % Calcd. C	Calcd. H	Found C	Found H
VIII	H	H	$CH_2CO_2C_2H_5$	106–108	11	1.4432[a,b]	40	$C_{11}H_{22}O_3$	65.31	10.96	65.46	11.11
IX	H	H	$CH_2C(C_2H_5)_2OH$	126	11.5	1.4560	10	$C_{13}H_{28}O_4$	63.90	9.90	63.81	9.98
X	C_2H_5	C_2H_5	$CH_2CO_2C_2H_5$	94–96	0.4	1.4482	37	$C_{15}H_{30}O_3$	69.72	11.70	69.80	11.88
XI	C_2H_5	C_2H_5	$CH_2C(C_2H_5)_2OH$	121	1	1.4613	13	$C_{12}H_{24}O_3$	66.68	11.18	66.50	11.30
XII	CH_2OH	CH_3	n-C_6H_{11}	123	2	1.4560[c]	25.5					

[a] At 20°. [b] Salmi[5] reported b.p. 95° (4 mm.), n_D^{20} 1.44425. [c] At 25.5°.

was used instead of toluenesulfonic acid as condensing catalyst with no more success. The obvious difficulty was steric, coupled with the difficult formation of 1,3-dioxanes, as compared with the ready formation of 1,3-dioxolanes. To test this hypothesis, we tried a condensation between diisopropyl ketone and trimethylene glycol, using the same conditions under which water was readily eliminated in the condensation of the ketone with glycerine to give the 1,3-dioxolane (V). Water was eliminated only very slowly. This bears out what Boekelheide *et al.*[3] and Dworzak and Herrmann[6] had already indicated, namely that 1,3-dioxolanes are evidently more easily formed than are 1,3-dioxanes. Unlike Boekelheide *et al.*,[3] however, we found that methyl amyl ketone did condense with trimethylene glycol and so we tried the condensation between this less hindered ketone and trishydroxymethylmethane. The resulting compound, 2,5-dimethyl-2-amyl-5-hydroxymethyl-1,3-dioxane (XII), was no improvement pharmacologically over compound II.

We next carried out the condensation between ethyl levulinate and ethylene glycol. The resulting ester (XIII) was allowed to react with ethylmagnesium bromide to give 2-methyl-2-(3-hydroxy-3-ethylpentyl)-1,3-dioxolane (XIV). This compound showed an interesting order of activity which was of prolonged duration. The ester, XIII, was therefore allowed to react with methylmagnesium iodide and isopropylmagnesium bromide. The former reaction gave the expected tertiary alcohol XV, whereas the reaction with isopropylmagnesium bromide resulted in the product obtained by addition of one mole of Grignard to the ester, followed by reduction of the resulting ketone with a second mole of Grignard, to give 2-methyl-2-(3-hydroxy-4-methylpentyl)-1,3-dioxolane (XVI). Neither of these new alcohols was as interesting pharmacologically as was XIV, which in turn was longer acting than either II or V. In mice, XIV had the most advantageous ratio of effective dose to lethal dose of any of the compounds tested.

In view of the increase in activity obtained by introducing an additional methylene group between the tertiary alcohol and the dioxolane ring (XIV compared to II), it was of interest to ascertain the effect of another methylene group. By the procedure of Albertson,[7] ethyl 5-oxocaproate was prepared. Condensation with ethylene glycol gave XVII, which by reaction with ethyl Grignard reagent gave the desired 2-methyl-2-(4-hydroxy-4-ethylhexyl)-1,3-dioxolane (XVIII). This compound was not as active as was XIV.

We prepared one compound which had no hydroxyl group in it. This compound, 2,2-diisobutyl-4-chloromethyl-1,3-dioxolane was prepared to ascertain the effect on central nervous system depres-

(6) R. Dworzak and K. Herrmann, *Monatsh.*, **52**, 83 (1929).

(7) N. F. Albertson, *J. Am. Chem. Soc.*, **72**, 2594 (1950).

sion of replacing a hydroxyl group by a chlorine atom. Central nervous system depression was observed but the toxicity was high.

The pharmacological comparisons of the compounds were carried out by Miss Mary Lewis[8] of our Pharmacology Department.

EXPERIMENTAL[9,10]

As an example of the procedure used for the condensation of ketones with alcohols to give the cyclic acetals, I, V, VI, VIII, X, XII, XIII, and XVII, the following is an illustration.

2,5-Dimethyl-2-pentyl-5-hydroxymethyl-1,3-dioxane. A mixture of 60 g. (0.5 mole) of trishydroxymethylmethane, 250 ml. of toluene, and 0.5 g. of *p*-toluenesulfonic acid was allowed to reflux with a Dean-Stark trap until no water distilled. Methyl *n*-pentyl ketone, 57 g. (0.5 mole), was added, and refluxing was continued until no water distilled. The reaction mixture was cooled, and filtered if necessary from starting trishydroxymethylmethane. The filtrate was washed with 30 ml. of 10% sodium carbonate and then with water. After drying, the organic layer was distilled.

As an example of the procedure used for the reaction of the cyclic ketones with the Grignard reagents to give the products II, III, IV, VII, IX, XI, XIV, XV, XVI, and XVIII the following is illustrative.

2-Methyl-2-(3-hydroxy-3-ethylpentyl)-1,3-dioxolane. To methylmagnesium bromide prepared from 71 g. (0.65 mole) of ethyl bromide in 200 ml. of ether was added with cooling 47 g. (0.25 mole) of 2-methyl-2-(2-carbethoxyethyl)-1,3-dioxolane in 250 ml. of ether over a period of about 1 hr. When spontaneous refluxing ceased, the reaction mixture was refluxed for 1.5 hr. and then was decomposed with saturated aquecus ammonium chloride. The ether layer was dried over magnesium sulfate, filtered, and concentrated. The residue was allowed to reflux for 20 hr. with an equal volume of 20% aqueous sodium hydroxide, diluted with sufficient methanol to give a homogeneous solution, and then a volume equal to the added methanol was removed by distillation. The reaction mixture was extracted thoroughly with Skellysolve B and the extract was dried and distilled. The product, distilling at 147–149° (23–25 mm.), was carefully fractionated to give a pure product distilling at 118–119° (4 mm.), n_D^{24} 1.4575.

Ethyl 5-ketohexanoate. Condensation of ethyl acetoacetate and acrylonitrile was carried out according to the procedure of Albertson.[7] Our constants were in excellent agreement with those reported. Decarboxylation to 5-oxocapronitrile, however, found us in less satisfactory agreement. Our product, obtained in 79% yield, distilled at 98–99° (5.5 mm.), n_D^{25} 1.4287. Reported b.p. 86.5° (5.2 mm.), n_D^{25} 1.4790.

Anal. Calcd. for C_6H_9NO: C, 64.84; H, 8.16; N, 12.81. Found: C, 64.67; H, 8.32; N, 12.61.

On treatment of the nitrile with absolute alcoholic hydrogen chloride, followed by water in the usual way, a 62% yield of product b.p. 107° (15 mm.), n_D^{25} 1.4254 was obtained. Reported[11] b.p. 110–15° (12 mm.).

2,2-Diisobutyl-4-chloromethyl-1,3-dioxolane. Into a flask containing 100 ml. of carbon tetrachloride were added simultaneously from one dropping funnel 162 g. of freshly distilled diisobutyl ketone mixed with 95 g. of epichlorohydrin in 150 ml. of carbon tetrachloride and from another dropping funnel 13 g. of stannic chloride in 50 ml. of carbon tetrachloride at such rates as to finish both additions at once. By means of an ice bath the temperature of the reaction mixture was kept at 25–38°. After the addition was completed, the reaction was allowed to stand overnight and was then treated in an ice bath with 80 ml. of 20% sodium hydroxide dropwise with stirring. Layers were separated, and the aqueous layer was extracted with ether. The ether and carbon tetrachloride solutions were dried over magnesium sulfate and distilled. The product, b.p. 127–129° (20 mm.), n_D^{24} 1.4465 weighed 162 g. (67%).

MORRIS PLAINS, N. J.

(8) Present address: Pharmacological Research, Plympton, Mass.

(9) Temperatures are uncorrected.

(10) Analyses were carried out by Miss Linda Einstein.

(11) L. Ruzicka, *Helv. Chim. Acta.*, **2**, 144 (1919).

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Reactions of *p*-Hydroxybenzyl Alcohol Derivatives and Their Methyl Ethers with Molecular Chlorine[1]

K. V. SARKANEN AND C. W. DENCE

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Molecular chlorine displaces the carbinol group in a number of *p*-hydroxybenzyl alcohol derivatives and their methyl ethers forming an aldehyde and a chlorinated aromatic ring. The rate of displacement of a primary carbinol group is close to the same order of magnitude of comparable chlorine substitution and probably higher than the displacement rates of an aldehyde group.

In aqueous and partially aqueous media, molecular chlorine acts as a catalyst to hydrolyze aromatic methoxyl groups to phenolic hydroxyl groups and methanol under conditions where no proton-catalyzed hydrolysis is observed. The mechanisms involved in the displacement and hydrolysis reactions are discussed.

In common usage, the expression "aromatic substitution" mainly is used in cases where hydrogen attached to an aromatic nucleus is replaced by some other group, such as halogen. For this reason, reactions involving the replacement of a group other than hydrogen by an electrophilic reactant generally are not called substitution reactions, but rather "electrophilic aromatic displacements," the common aromatic substitution forming a subgroup of the latter reactions.[2] Examples of this sort in-