[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. XIII. Basic 1,3-Dioxanes

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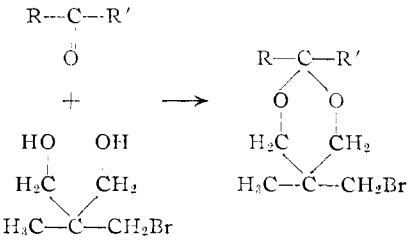
A series of 2-substituted and 2,2-disubstituted 5-methyl-1,3-dioxanes which contain a basic radical in the 5-position were prepared and tested for pharmacological activity.

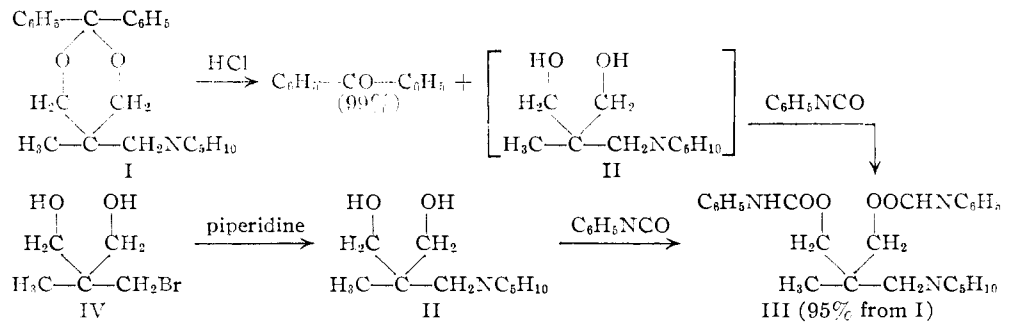
This paper deals with the preparation of basic 1,3-dioxanes with interesting pharmacological properties. Previously,[3,4] we have described the synthesis and properties of a number of basic 1,3-dioxolanes.

The required dioxane intermediates (Table I) were obtained by condensation of one of a variety of aldehydes and ketones with the readily prepared 2-methyl-2-bromomethyl-1,3-propanediol



In most cases the condensation was carried out by the use of the azeotropic distillation method described by Salmi[5] but when very volatile carbonyl compounds, such as acetaldehyde or acetone, were employed, special procedures were used which are described in the Experimental part. Since the intermediate bromomethyl compounds were difficult to aminate, they were converted into the corresponding iodomethyl derivatives before amination or they were aminated in the presence of sodium iodide.

In one instance the structure of a basic dioxane, 2,2-diphenyl-5-methyl-5-piperidinomethyl-1,3-dioxane, was determined in the following manner



Upon hydrolysis of the basic dioxane (I) with 18% hydrochloric acid, benzophenone precipitated in 99% yield. The 2-methyl-2-piperidinomethyl-1,3-propanediol (II), present in the filtrate, was obtained in the form of its diphenylurethan (III) in 95% yield. The urethan was synthesized by conversion of IV into II and treatment of the latter substance with phenyl isocyanate.

The basic dioxanes are listed in Table II together with the pharmacological data which were supplied by the research laboratories of The Wm. S. Merrell Company.

Experimental Part

The first four experiments described below illustrate the manner in which the compounds listed in Table I were obtained.

2,2-Diphenyl-5-methyl-5-bromomethyl-1,3-dioxane.—A mixture of 9.1 g. (0.05 mole) of benzophenone, 9.2 g. (0.05 mole) of 2-methyl-2-bromomethyl-1,3-propanediol,[6] 0.1 g. of *p*-toluenesulfonic acid and 100 cc. of benzene was refluxed for 24 hours in a flask to which a Dean–Stark water trap[7] and a condenser were attached. At the end of that time, 90% of the calculated amount of water had collected. The cooled mixture was washed thoroughly with 10% sodium carbonate solution and then with water. The benzene layer was separated, the solvent was removed under reduced pressure and the residue was cooled and rubbed to induce recrystallization; yield 17.2 g. (73%) after recrystallization from methanol.

5-Methyl-5-bromomethyl-1,3-dioxane.—2-Methyl-2-bromomethyl-1,3-propanediol (12.8 g., 0.07 mole), 14.0 g. (0.19 mole) of 40% aqueous formaldehyde and 7 g. of 85% phosphoric acid were heated in a small distillation flask until the temperature of the vapors reached 140°. The lower layer of the two-layer distillate was separated and distilled; yield 5.4 g. (40%), b.p. 126–127° (68 mm.).

2,5-Dimethyl-5-bromomethyl-1,3-dioxane.—A mixture of 12.8 g. (0.07 mole) of 2-methyl-2-bromomethyl-1,3-propanediol, 6.0 g. (0.14 mole) of acetaldehyde and 0.3 g. of phosphorus pentoxide was allowed to remain in a sealed tube, with occasional shaking, for 24 hours. The mixture was shaken with 100 cc. of benzene and 30 cc. of 10% sodium carbonate solution, the benzene layer was separated and the solvent removed. Upon distillation of the residue 12.5 g. (85%) of product was obtained; b.p. 64–66° (3 mm.).

2,2,5-Trimethyl-5-bromomethyl-1,3-dioxane was obtained when acetaldehyde was replaced by reagent grade acetone and the reaction mixture allowed to remain at ordinary temperature for 3 days.

(1) This paper represents part of a dissertation submitted by E. L. Schumann in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1949.

(2) The Wm. S. Merrell Company Fellow.

(3) F. F. Blicke and F. E. Anderson, THIS JOURNAL, **74**, 1733 (1952).

(4) F. F. Blicke and E. L. Schumann, *ibid.*, **74**, 2613 (1952).

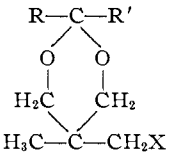
(5) E. J. Salmi, *Ber.*, **71**, 1803 (1938); E. J. Salmi and V. Rannikko, *ibid.*, **72**, 600 (1939). See also M. Senkus, THIS JOURNAL, **63**, 2635 (1941).

(6) J. Barbiere and J. Mattl, *Bull. soc. chim.*, [5] **5**, 1565 (1938).

(7) E. W. Dean and D. D. Stark, *J. Ind. Eng. Chem.*, **12**, 486 (1920).

TABLE I

1,3-DIOXANE INTERMEDIATES



R	R′	X	M.p. or b.p., °C.	Formula	Analyses, % Halogen Calcd.	Found	Yield, %
H	H	Br	126–127 (68 mm.)	$C_6H_{11}O_2Br$	40.97	40.78	40
H	CH_3	Br	64–66 (3 mm.)	$C_7H_{13}O_2Br$	38.22	37.63	85
H	C_6H_5	Br	147–149 (3 mm.)	$C_{12}H_{15}O_2Br$	29.47	29.31	90
CH_3	CH_3	Br	73–74 (2 mm.)	$C_8H_{15}O_2Br$	35.82	36.28	41
CH_3	CH_2CH_2CH–[a]	Br	100–102 (3 mm.)	$C_{10}H_{17}O_2Br$	32.08	32.79	54
CH_3	C_6H_5	Br	126–128 (3 mm.)	$C_{13}H_{17}O_2Br$	28.02	27.84	79
Pentamethylene		Br	112–113 (3 mm.)	$C_{11}H_{19}O_2Br$	30.37	29.96	88
$C_6H_5CH_2$	$C_6H_5CH_2$	Br	115–116[b]	$C_{20}H_{23}O_2Br$	21.29	21.10	74
$C_6H_5CH_2$	$C_6H_5CH_2$	I	119–120[b]	$C_{20}H_{23}O_2I$	30.05	29.95	96
C_6H_{11}	C_6H_5	Br	104–105[b]	$C_{18}H_{25}O_2Br$	22.62	22.86	47
C_6H_{11}	C_6H_5	I	118–119[b]	$C_{18}H_{25}O_2I$	31.71	32.22	73
C_6H_5	C_6H_5	Br	91–92[c]	$C_{18}H_{19}O_2Br$	23.01	22.91	76
C_6H_5	C_6H_5	I	114–115[b]	$C_{18}H_{19}O_2I$	32.19	32.64	87
p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	Br	135–136[b]	$C_{20}H_{23}O_2Br$	21.30	21.54	67
p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	I	124–125[b]	$C_{20}H_{23}O_2I$	30.05	29.52	97

[a] The required methyl cyclopropyl ketone was obtained from U. S. Industrial Chemicals, Inc., 60 E. 42nd St., New York, N. Y. Its preparation has been described by Bruylants, *Bull. soc. chim. Belg.*, **36**, 519 (1927). [b] Recrystallized from 95% ethanol. [c] Recrystallized from methanol.

2,2-Diphenyl-5-methyl-5-iodomethyl-1,3-dioxane.—A mixture of 60 g. (0.17 mole) of 2,2-diphenyl-5-methyl-5-bromomethyl-1,3-dioxane, 258 g. (1.7 moles) of sodium iodide and 900 cc. of absolute alcohol was heated in 6 citrate bottles at 100° for 48 hours. The precipitate was filtered and washed with water until it was free from inorganic halides; yield 59.7 g. (87%); the melting point (114–115°) was not changed by recrystallization from ethanol.

Amination procedures used to obtain compounds reported in Table II are illustrated below.

5-Methyl-5-diethylaminomethyl-1,3-dioxane Hydrochloride and Methiodide.—5-Methyl-5-bromomethyl-1,3-dioxane (5.2 g., 0.027 mole), 20 g. (0.13 mole) of sodium iodide, 4.3 g. (0.04 mole) of sodium carbonate, 29.2 g. (0.4 mole) of diethylamine and 55 cc. of absolute ethanol were heated at 100° in a citrate bottle for 6 days. The inorganic salts were removed by filtration, the alcohol evaporated, and the residue was shaken with 20 cc. of 10% sodium carbonate solution and 50 cc. of ether. The ether layer was separated, dried, the solvent was removed and the residue was fractionated. The amine (3.4 g.), b.p. 68–70° (3 mm.), was treated with an ethereal solution of the calculated amount of hydrogen chloride whereupon the hydrochloride (43%) precipitated.

The methiodide was prepared by heating a mixture of 1.5 g. of the amine, 11.4 g. of methyl iodide and 30 cc. of chloroform in a citrate bottle for 3 hours at 100°. The solvent was removed and the residue was triturated with dry ether; yield 1.5 g.

Aminations which yielded compounds 3–10, 18 and 25 (Table II) were carried out in the manner described above; the crude bromides were used to obtain compounds 8 and 25.

2,2-Diphenyl-5-methyl-5-dimethylaminomethyl-1,3-dioxane.—A mixture of 20.0 g. (0.051 mole) of 2,2-diphenyl-5-methyl-5-iodomethyl-1,3-dioxane, 23.0 g. (0.51 mole) of dimethylamine and 100 cc. of benzene was heated in a citrate bottle at 100° for 5 days. The cold mixture was treated with 50 cc. of 10% sodium carbonate solution, the benzene layer was separated, washed with water and the solvent was removed. The solid residue was recrystallized from methanol; yield 11.7 g. (74%).

The hydrochloride and methiodide, as well as compounds 20 and 21, were prepared in the manner described above.

Absolute ethanol, instead of benzene, was used as a solvent for the preparation of compounds 11, 12, 13, 14 and 24.

Amination of the required iodide with morpholine, in order to obtain compound 22, resulted in the formation of a solid mixture of the desired amine and unchanged iodide. Since separation of the compounds by recrystallization was not possible, the base was purified through the hydrochloride (compound 23).

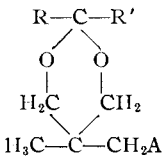
2,2-Di-α-thienyl-5-methyl-5-diethylaminomethyl-1,3-dioxane Hydrochloride.—The azeotropic distillation method was used to condense 9.7 g. (0.05 mole) of di-α-thienyl ketone[3] and 9.1 g. (0.05 mole) of 2-methyl-2-bromomethyl-1,3-propanediol. Refluxing was stopped after 24 hours because of apparent decomposition although only 62% of the calculated amount of water had collected. The cold mixture was washed with 10% sodium carbonate solution and then with water. After removal of the benzene, the black residue was triturated with 10 cc. of absolute ethanol and then filtered; 3.3 g. of unreacted ketone was obtained. The filtrate which contained the desired bromomethyl intermediate in, at most, a 0.0325 molar concentration was aminated with diethylamine. The mixture was filtered, the alcohol was removed, the oily residue was dissolved in benzene and the solution was washed with water until the water became neutral. After evaporation of the benzene, the residue was dissolved in ether and treated with an ethereal solution which contained 0.0325 mole of hydrogen chloride. The brown precipitate was filtered, dissolved in butanol, the solution was decolorized with Norite, and the hydrochloride was precipitated by the addition of diisopropyl ether; yield 1.8 g.

Hydrolysis of 2,2-Diphenyl-5-methyl-5-piperidinomethyl-1,3-dioxane.—A solution of 8.8 g. of the dioxane in 50 cc. of 18% hydrochloric acid became turbid almost immediately. After 12 hours the precipitated, oily benzophenone was rubbed to induce crystallization; yield 4.5 g. (99%), mixed m.p. 47–49°.

The acidic filtrate was evaporated to dryness, the residue was treated with 10 cc. of 50% aqueous sodium hydroxide and extracted thoroughly with ether. The dried extract was concentrated to a volume of about 100 cc., 7.1 g. of phenyl isocyanate was added, and the mixture was refluxed for 24 hours. After removal of the solvent, the residue became crystalline when rubbed under petroleum ether; the bisphenylurethan of 2-methyl-2-piperidinomethyl-1,3-propanediol (10.1 g., 95%) melted at 143–144° dec. but after recrystallization from isopropyl alcohol–water it melted at 148–149° dec.

Anal. Calcd. for $C_{24}H_{31}O_4N_3$: N, 9.88. Found: N, 9.54.

TABLE II: BASIC 1,3-DIOXANES



Cpd.[p] no.	R	R'	A	M.p., °C.	Formula	Analyses, % Nitrogen Calcd.	Nitrogen Found	Halogen Calcd.	Halogen Found	Yield, %	Maximal effective dilution: Isolated rabbit jejunum, Acetylcholine (1:1,000,000) spasm	Isolated rabbit jejunum, Barium chloride (1:10,000) spasm	Isolated guinea pig intestine, histamine (0.1 μg./cc.) spasm
1	H	H	$N(C_2H_5)_2 \cdot HCl$[a]	103-104	$C_{10}H_{22}O_2NCl$	6.26	6.08	15.85	15.48	43 B[b]	>10,000	>10,000	>10
2	H	H	$N(C_2H_5)_2 \cdot CH_3I$	155–156	$C_{11}H_{24}O_2NI$	4.26	4.23	38.55	38.80	38 B	>10,000	>10,000	>10
3	H	CH_3	$N(C_2H_5)_2 \cdot CH_3I$[c]	115–117	$C_{12}H_{26}O_2NI$	4.08	4.08	36.97	37.33	26 B	>10,000	>10,000	>10
4	H	C_6H_5	$N(C_2H_5)_2$[d]	.....	$C_{16}H_{25}O_2N$	5.32	5.26	...	...	13 B	10,000	10,000	..
5	CH_3	CH_3	$N(C_2H_5)_2 \cdot CH_3I$[e]	138–139	$C_{13}H_{28}O_2NI$	3.92	3.90	35.52	35.83	46 B	>10,000	>10,000	>10
6	CH_3	CH_2CH_2CH-	$N(C_2H_5)_2 \cdot CH_3I$[f]	104–107	$C_{15}H_{30}O_2NI$	4.65	3.73	33.11	33.63	21 B	>10,000	>10,000	>10
7	CH_3	C_6H_5	$N(C_2H_5)_2 \cdot HCl$[g]	124–126	$C_{17}H_{28}O_2NCl$	4.46	4.28	11.30	11.01	19 B	50,000	20,000	>10
8	CH_3	3-C_8H_5S[h]	$N(C_2H_5)_2 \cdot CH_3I$	195–196	$C_{20}H_{30}O_2NSI$	2.95	2.89	26.70	26.32	20 A	10,000	10,000	>10
9	Pentamethylene		$N(C_2H_5)_2 \cdot HCl$[i]	146–147	$C_{15}H_{30}O_2NCl$	4.80	4.64	12.15	11.72	40 B	10,000	10,000	>10
10	Pentamethylene		$N(C_2H_5)_2 \cdot CH_3I$	109–111	$C_{16}H_{32}O_2NI$	3.53	3.48	31.94	31.35	26 B	>10,000	>10,000	>10
11	$C_6H_5CH_2$	$C_6H_5CH_2$	$N(C_2H_5)_2 \cdot HCl$	189–190	$C_{24}H_{34}O_2NCl$	..	..	8.78	8.58	23 C	1,000,000	500,000	2
12	C_6H_{11}	C_6H_5	$N(C_2H_5)_2 \cdot HCl$	203–204[j]	$C_{22}H_{36}O_2NCl$	..	..	9.28	8.98	30 C	100,000	10,000	>10
13	C_6H_5	C_6H_5	$NH(CH_3) \cdot HCl$	226–227	$C_{19}H_{24}O_2NCl$	4.20	4.15	10.62	10.40	62 C	50,000	10,000	10
14	C_6H_5	C_6H_5	$NHCH(CH_3)_2 \cdot HCl$	227-228	$C_{21}H_{28}O_2NCl$	3.87	3.87	9.80	9.87	51 C	100,000	10,000	>10
15	C_6H_5	C_6H_5	$N(CH_3)_2$	86–87	$C_{20}H_{25}O_2N$	4.50	4.35	...	...	74 C	1,000,000	500,000	0.5
16	C_6H_5	C_6H_5	$N(CH_3)_2 \cdot HCl$	175-176	$C_{20}H_{26}O_2NCl$	4.03	3.88	10.19	10.07	100 D	500,000	500,000	0.2
17	C_6H_5	C_6H_5	$N(CH_3)_2 \cdot CH_3I$	228–230[j]	$C_{21}H_{28}O_2NI$	3.09	3.05	28.00	26.74	62 D	2,000,000	200,000	5
18	C_6H_5	C_6H_5	$N(C_2H_5)_2$	85–86	$C_{22}H_{29}O_2N$	4.13	4.09	...	...	37 B	.....	.....	..
19	C_6H_5	C_6H_5	$N(C_4H_9)_2 \cdot HCl$	189–190	$C_{22}H_{30}O_2NCl$	3.73	3.58	9.43	9.30	86 D	5,000,000	1,000,000	5
20	C_6H_5	C_6H_5	NC_5H_{10}[k]	93–94	$C_{23}H_{29}O_2N$	3.98	3.87	...	...	70 C	.....	.....	..
21	C_6H_5	C_6H_5	$NC_5H_{10} \cdot HCl$	141–142[j]	$C_{23}H_{30}O_2NCl$	3.61	3.41	9.14	8.99	100 D	10,000	100,000	2
22	C_6H_5	C_6H_5	NC_4H_8O[l]	122	$C_{22}H_{27}O_3N$	3.96	3.87	...	...	41 C	50,000	50,000	>10
23	C_6H_5	C_6H_5	$NH_4H_8O \cdot HCl$	197–199[j]	$C_{22}H_{28}O_3NCl$	3.59	3.40	9.09	8.82	100 D	.....	.....	..
24	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	$N(C_2H_5)_2 \cdot HCl$[m]	199–200	$C_{24}H_{34}O_2NCl$	3.47	3.42	8.78	8.75	17 C	200,000	500,000	5
25	C_6H_5	2-C_4H_3S[n]	$N(C_2H_5)_2 \cdot HCl$[o]	191–192	$C_{20}H_{28}O_2NSCl$	3.67	3.47	9.28	9.15	12 A	1,000,000	500,000	5
26	2-C_4H_3S	2-C_4H_3S	$N(C_2H_5)_2 \cdot HCl$	211–213[j]	$C_{18}H_{26}O_2NS_2Cl$	3.61	3.57	9.14	8.91	14 A	500,000	500,000	5
	Atropine										80,000,000	200,000	5,000,000
	Papaverine										100,000	100,000	..
	Benadryl										.....	.....	20,000

[a] Slightly hygroscopic. B.p. of base, 68–70° (3 mm.). [b] The letter indicates the intermediate on which the yield was based: A, the ketone; B, the bromide; C, the iodide; D, the amine base. [c] B.p. of base, 72–77° (2 mm.). [d] B.p. 144–146° (3 mm.). The picrate melted at 129–130° after recrystallization from ethyl acetate–ether. [e] B.p. of base, 71–72° (3 mm.). [f] B.p. of base, 108–111° (4 mm.). [g] B.p. of base 137–140° (3 mm.). [h] 3-Thianaphthenyl. B.p. of base, 155–158° (0.04 mm.). [i] B.p. of base, 123–125° (3 mm.). [j] Melts with decomposition. [k] Piperidino. [l] Morpholino. [m] B.p. of base, 167–170° (0.01 mm.). [n] 2-Thienyl. [o] B.p. of base, 145–147° (0.01 mm.). [p] Compounds 1, 9 and 19 were recrystallized from ethyl acetate; 2 and 5 from isopropyl alcohol; 3 and 6 from absolute ethanol–ether; 7, 12 and 24 from isopropyl alcohol–diisopropyl ether; 8 from acetone–ether; 10 from butanol–ether, then from acetone–ether; 11 from diisopropyl ketone–ether; 13 and 17 from absolute ethanol; 14 and 23 from ethanol–diisopropyl ether; 15, 20 and 22 from methanol; 16, 21 and 26 from butanol–diisopropyl ether; 18 from 95% ethanol; 25 from ethyl acetate–diisopropyl ether.

The hydrochloride melted at 195–196° dec. after recrystallization from absolute ethanol–diisopropyl ether.

Anal. Calcd. for $C_{24}H_{31}O_4N_3 \cdot HCl$: N, 9.10; Cl, 7.68. Found: N, 8.89; Cl, 7.46.

2-Methyl-2-piperidinomethyl-1,3-propanediol was synthesized in the following manner. A mixture of 8.5 g. of 2-methyl-2-bromomethyl-1,3-propanediol, 31.5 g. of piperidine and 50 cc. of benzene was heated at 100° in a citrate bottle for 4 days. After removal of the solvent, the residue was treated with alkali and then extracted with ether. The solvent was removed from the dried extract, and the residue was distilled; the amine (3.6 g.), which boiled at 123–126° (2 mm.), still contained unchanged bromide.

Two grams of the impure amine was mixed with 2.6 g. of phenyl isocyanate. After the reaction had subsided, the product was dissolved in dry ether and treated with the calculated amount of ethereal hydrogen chloride. After liberation of the amine from the salt, and recrystallization from petroleum ether (90–100°), the pure bisphenylurethan melted at 148–149° dec.; mixed m.p. 148–149° dec.

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL CHEMISTRY, NORTH DAKOTA AGRICULTURAL EXPERIMENT STATION, AND DEPARTMENT OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA]

The Isolation of β-Hydroxy-β-methylglutaric Acid from the Seed of Flax (*Linum usitatissimum*)[1]

BY HAROLD J. KLOSTERMAN AND F. SMITH

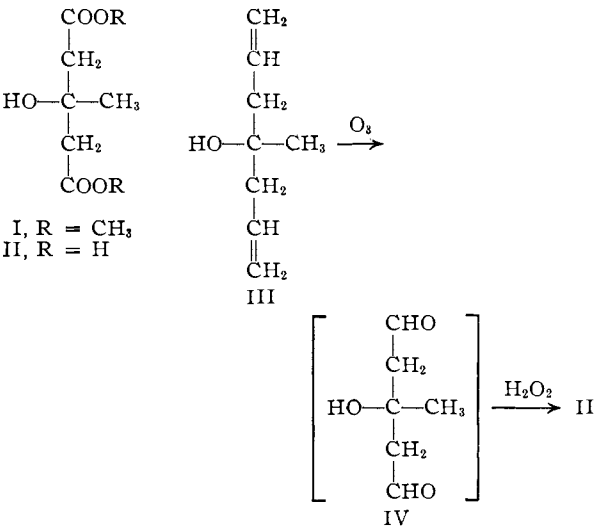
RECEIVED AUGUST 24, 1953

The amorphous product, extracted from fat-free linseed meal with ethanol–dioxane, yields upon treatment with sodium methoxide (a) a methyl ester, (b) a crystalline glucoside and (c) a non-crystalline glucoside. The ester is shown to be methyl β-hydroxy-β-methylglutarate (I) and the crystalline acid derived from it has been synthesized from diallylmethylcarbinol by ozonolysis and subsequent oxidation.

When linseed meal previously freed from fat is extracted with a mixture of equal parts of ethanol and dioxane a 2–4% yield of an amorphous tan powder (A) is produced[2]; this material appears to be a complex glucoside. It is shown herein that treatment of a solution of this powder (A) in methanol–dioxane with sodium methoxide affords three compounds: a colorless liquid methyl ester (I); a colorless crystalline glucoside; and a yellow powder which appears to be the glucoside of a polyhydroxy phenol. The constitution of compound I, the colorless liquid methyl ester, forms the subject of this paper. The two glucosides will be discussed in later communications.

The experimental basis for assigning formula I to the ester isolated from flaxmeal is as follows: The elementary analysis, molecular weight and equivalent weight determinations agreed with this formulation. Conversion of the ester I into the acid II by means of alkali was shown to involve the loss of two methyl groups thus showing that II is a dicarboxylic acid. One hydroxyl group was shown to be present in I by acetylation, and its tertiary character was indicated by the method of Murahashi.[3] Support for the presence of one side-chain methyl group was forthcoming from the observation that one mole of acetic acid was formed upon oxidation of I with chromic acid.[4]

Finally, β-hydroxy-β-methylglutaric acid, synthesized by the ozonization of diallylmethylcarbinol (III) followed by oxidation of the derived aldehyde IV, with hydrogen peroxide, was found to be identical with the acid II isolated from flax seed meal.



It is of some interest to note that the ethyl ester lactone of the acid I is said to be obtained by the action of ketene on acetoacetic ester[5] and since this work was completed a report has been given[6] of the synthesis of dicrotalic acid, which is also β-hydroxy-β-methylglutaric acid, isolated previously from *Crotalaria dura* and *Crotalaria globifera*.[7] The synthetic method used by these authors, which is similar to one formerly employed,[8] appears to be inferior as far as yield is concerned to that reported herein.

Experimental

Isolation of the Complex Linseed Glucoside.—Linseed meal freed from fat and ground in a ball mill (3 kg.) was extracted at room temperature by stirring with a mixture of equal parts of 95% ethyl alcohol and 1,4-dioxane (8 l.).

(1) Presented at the 124th National American Chemical Society Meeting, September, 1953. Paper No. 3046, Scientific Journal Series, Minnesota Agricultural Experiment Station. This work will form part of a thesis to be submitted to the graduate school of the University of Minnesota for the degree of Ph.D. Published by permission of the Director, North Dakota Agricultural Experiment Station.

(2) F. C. McIntyre, private communication.

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