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

Antispasmodics. XI. Basic 1,3-Dioxolanes

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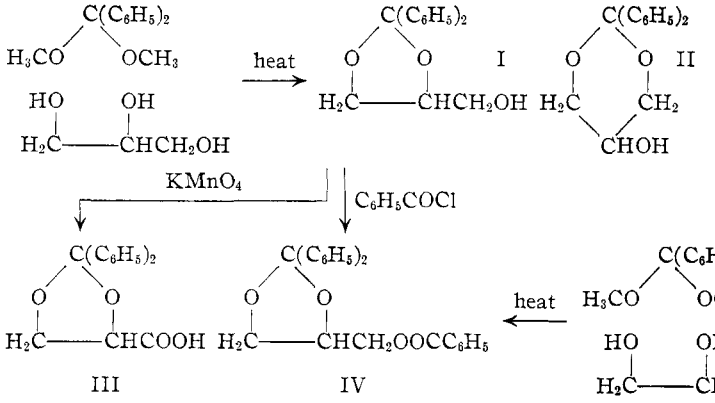
A series of basic 1,3-dioxolanes has been prepared and tested for pharmacological activity by the use of intestinal strips which had been stimulated with acetylcholine, barium chloride and histamine, respectively.

A further study of basic 1,3-dioxolanes, analogous to those which had been described previously,[3] seemed desirable in the hope that compounds might be obtained which would exhibit greater, as well as more selective, pharmacological activity.

Two general methods were used for the synthesis of the required 2-substituted 4-bromomethyl-1,3-dioxolanes: (A) condensation of a carbonyl compound with epibromohydrin in the presence of stannic chloride; (B) condensation of a carbonyl compound with glycerol α-bromohydrin in the presence of an acid catalyst, and continuous removal of the water formed by azeotropic distillation. The latter method was introduced by Salmi,[4] and has been used by Senkus[5] for the preparation of 1,3-dioxanes. The substituted 4-bromomethyl-1,3-dioxolanes were then aminated.

In order to obtain 1,3-dioxolanes in which the basic radical was attached to the ring through an ether linkage, a 4-hydroxymethyl compound, 2,2-diphenyl-4-hydroxymethyl-1,3-dioxolane (I), was prepared in the manner outlined



In order to prove that a dioxolane (I), and not a dioxane (II), had been formed, the reaction product was oxidized with potassium permanganate. The isolation of an acid (III) instead of a ketone and, furthermore, the formation of IV from the benzoylation of I, as well as from the interaction of benzophenone dimethyl ketal and glycerol α-monobenzoate, established the structure of I.

The alcohol (I) was converted into basic ethers, and the acid (III) into a basic ester by standard procedures.

The basic 1,3-dioxolanes, as well as their activity[6] on isolated muscle strips which had been stimulated by acetylcholine, barium chloride and histamine, respectively, have been reported in Table I.

Experimental Part

The crude substituted 4-bromomethyl-1,3-dioxolane, obtained from diphenylacetaldehyde,[7] dibenzyl ketone,[8] distyryl ketone,[9] cyclohexyl phenyl ketone,[10] benzophenone, di-*p*-tolyl ketone,[11] or di-*p*-chlorophenyl ketone,[12] by general method A or B, was heated on a steam-bath in a citrate bottle with 8–10 molecular equivalents of the required amine. Completion of amination was roughly estimated by the amount of amine hydrobromide which had precipitated.

The preparation of 2,2-diphenyl-4-bromomethyl-1,3-dioxolane was described previously.[3]

2,2-Pentamethylene-4-diethylaminomethyl-1,3-dioxolane. Method A.—A stirred solution of 20.0 g. (0.16 mole) of epibromohydrin and 13.5 g. (0.14 mole) of cyclohexanone in 100 cc. of dry carbon tetrachloride was maintained at 0–5° during the dropwise addition, over a 4-hour period, of 5 g. of stannic chloride in 100 cc. of carbon tetrachloride.[13] The mixture was then treated with 100 cc. of cold 10% sodium hydroxide solution, the organic layer separated, filtered, and the solvent removed.

Amination.—The crude bromomethyl compound, 73 g. (1 mole) of diethylamine and 100 cc. of dry benzene were heated in a citrate bottle at 100° for 90 minutes. After the addition of 50 cc. of 10% sodium hydroxide solution to the cold mixture, the benzene layer was separated, dried over anhydrous potassium carbonate, and the solvent removed. Fractionation of the residue yielded 24 g. of amine; b.p. 128–129° (0.01 mm.).

The hydrochloride was obtained by treatment of a solution of 12 g. of the crude amine in 300 cc. of dry ether with the calcd. amount of hydrogen chloride dissolved in the same solvent.

In order to prepare the methiodide, a solution of 5.7 g. (0.025 mole) of the amine and 37 g. (0.26 mole) of methyl iodide in 100 cc. of dry ether was allowed to remain at room temperature for 24 hours. The precipitated oil was washed with ether and, after solidification, the product was recrystallized from butanol–ether.

2-Cyclohexyl-2-phenyl-4-diethylaminomethyl-1,3-dioxolane. Method B.—A mixture of 11.3 g. (0.06 mole) of cyclohexyl phenyl ketone,[10] 9.3 g. (0.06 mole) of glycerol α-bromohydrin, 100 cc. of benzene and 0.1 g. of *p*-toluenesul-

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

(2) Wm. S. Merrell Company Fellow.

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

(4) E. J. Salmi, *Ber.*, **71**, 1803 (1938); E. J. Salmi and V. Rannikko, *ibid.*, **72**, 600 (1939).

(5) M. Senkus, THIS JOURNAL, **63**, 2635 (1941); M. Senkus, U. S. Patent 2,368,971.

(6) More extensive pharmacological data on some of the compounds has been published by B. B. Brown and H. W. Werner (*J. Pharmacol. Exp. Therap.*, **97**, 157 (1949)).

(7) S. Danilow, *Ber.*, **60**, 2390 (1927).

(8) H. Apitzsch, *ibid.*, **37**, 1428 (1904).

(9) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 167.

(10) P. Sabatier and A. Mailhe, *Compt. rend.*, **139**, 345 (1904).

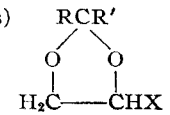
(11) Obtained from the Eastman Kodak Company.

(12) H. P. Newton and P. H. Groggins, *Ind. Eng. Chem.*, **27**, 1397 (1935).

(13) Chloroform or benzene may be used if the ketone to be employed is more soluble in one of these solvents.

TABLE I

BASIC 1,3-DIOXOLANES (SALTS)



Compounds 1, 2, 7, 10, 17 and 19 were recrystallized from ethyl acetate; 3, 8 and 11 from butanol–ether; 4 from ethyl acetate; 5 from isopropyl alcohol–ether; 9 from isopropyl alcohol–isopropyl ether; 12 from butanol–isopropyl ether; 13 and 14 from acetone–ether; 15 from toluene–petroleum ether (90–100°); 16 from ethanol–ether; 18 from ethyl acetate–ether.

	R	R′	X	M.p., °C.	Formula	Analyses, % Nitrogen Calcd.	Nitrogen Found	Halogen Calcd.	Halogen Found	Minimum effective concentration, μg./cc. Isolated rabbit jejunum Acetylcholine spasm 1:1,000,000	Isolated rabbit jejunum $BaCl_2$ spasm 1:10,000	Isolated guinea pig intestine Histamine spasm 0.1 μg. per cc.
A[a]	H	$(C_6H_5)_2CH$	$CH_2N(C_2H_5)_2 \cdot C_2H_2O_4$[b]	125–126[c]	$C_{23}H_{29}O_6N$	3.42	3.40	...	...	250,000	10,000	5
A	Pentamethylene		$CH_2N(C_2H_5)_2 \cdot HCl$	165–166[d]	$C_{13}H_{26}O_2NCl$	5.31	5.22	13.44	13.52	10,000	10,000	>20
A	Pentamethylene		$CH_2N(C_2H_5)_2 \cdot CH_3I$	98–100	$C_{14}H_{28}O_2NI$	3.79	3.78	34.36	34.10	10,000	10,000	>20
B	$C_6H_5CH_2$	$C_6H_5CH_2$	$CH_2N(C_2H_5)_2 \cdot HCl$	122–123[e]	$C_{22}H_{30}O_2NCl$	3.73	3.70	9.43	9.25	.....	.....	5
B	$C_6H_5CH_2$	$C_6H_5CH_2$	$CH_2N(C_2H_5)_2 \cdot CH_3I$	97–99	$C_{23}H_{32}O_2NI$	2.91	2.89	26.36	25.56	1,000,000	200,000	....
A	$C_6H_5CH{=}CH$	$C_6H_5CH{=}CH$	$CH_2N(C_2H_5)_2$	.....	$C_{24}H_{29}O_2N$[f]	3.85	3.81	...	...	.....	.....	....
A	$C_6H_5CH{=}CH$	$C_6H_5CH{=}CH$	$CH_2N(C_2H_5)_2 \cdot C_2H_2O_4$[b]	170–171	$C_{26}H_{31}O_6N$	3.23	3.37	...	...	500,000	500,000	20
A	$C_6H_5CH{=}CH$	$C_6H_5CH{=}CH$	$CH_2N(C_2H_5)_2 \cdot CH_3I$	151–152	$C_{25}H_{32}O_2NI$	..	..	25.05	24.54	.....	.....	....
B	C_6H_{11}	C_6H_5	$CH_2N(C_2H_5)_2 \cdot HCl$	155–157[g]	$C_{20}H_{32}O_2NCl$	..	..	10.02	9.76	1,000,000	100,000	>10
B	C_6H_{11}	C_6H_5	$CH_2N(C_2H_5)_2 \cdot CH_3I$	146–148	$C_{21}H_{34}O_2NI$	3.05	3.05	27.63	27.03	50,000,000	100,000	5
A	C_6H_5	C_6H_5	$CH_2NH_2 \cdot HCl$	192–193	$C_{16}H_{18}O_2NCl$	4.80	4.63	12.11	12.17	100,000	100,000	....
A	C_6H_5	C_6H_5	$CH_2NH(CH_3) \cdot HCl$	211–213[h]	$C_{17}H_{20}O_2NCl$	4.58	4.41	11.59	11.76	50,000	100,000	2
	C_6H_5	C_6H_5	$CH_2OCH_2CH_2N(CH_3)_2 \cdot HCl$[i]	95–97	$C_{20}H_{26}O_3NCl$	3.85	3.96	9.77	9.91	10,000	10,000	>10
	C_6H_5	C_6H_5	$CH_2OCH_2CH_2N(CH_3)_2 \cdot CH_3I$	140–141	$C_{21}H_{28}O_3NI$	2.98	3.06	27.04	26.71	>10,000	>10,000	>10
	C_6H_5	C_6H_5	$CH_2OCH_2CH_2N(C_2H_5)_2 \cdot HCl$[i]	80–82	$C_{22}H_{30}O_3NCl$	3.58	3.69	9.05	8.85	100,000	50,000	0.1
	C_6H_5	C_6H_5	$COOCH_2CH_2N(C_2H_5)_2 \cdot HCl$[i]	128–129	$C_{22}H_{28}O_4NCl$	3.45	3.53	8.74	8.68	100,000	100,000	2
A	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	$CH_2N(C_2H_5)_2 \cdot HCl$	173–174[j]	$C_{22}H_{30}O_2NCl$	3.73	3.72	9.43	9.57	500,000	500,000	5
A	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	$CH_2N(C_2H_5)_2 \cdot CH_3I$	130–131	$C_{23}H_{32}O_2NI$	2.91	2.86	26.36	26.66	1,000,000	1,000,000	10
A	p-ClC_6H_4	p-ClC_6H_4	$CH_2N(C_2H_5)_2 \cdot HCl$	141–142[k]	$C_{20}H_{24}O_2NCl_3$[l]	3.36	3.36	25.52	25.22	250,000	100,000	5

[a] Method used for the preparation of the 4-bromomethyldioxolane. [b] Tested as the hydrochloride. [c] Base, b.p. 170–180° (0.2 mm.). [d] Base, b.p. 128–129° (0.01 mm.). [e] Base, b.p. 141–144° (0.01 mm.). [f] $n^{20}D$ 1.5491. [g] Base, b.p. 147–151° (0.3 mm.). [h] Aminated for 6 days at 60°; base, b.p. 122–128° (0.01 mm.). [i] Hygroscopic. [j] Base, b.p. 175–177° (0.02 mm.). [k] Base, b.p. 153–160° (0.01 mm.). [l] Calcd. for Cl^-, 8.51. Found: 8.31.

fonic acid was refluxed in a flask to which a Dean-Stark[14] water trap and a condenser were attached. After the maximum amount of water had collected (about 3 hours), the cooled solution was washed with 10% sodium carbonate solution, then with water, and the benzene removed under reduced pressure.

Amination.—The crude bromomethyl compound, 44 g. (0.06 mole) of diethylamine and 100 cc. of dry benzene were heated on a steam-bath in a citrate bottle for 36 hours. After treatment in the described manner, 6.2 g. of the dioxolane was obtained; b.p. 147–151° (0.3 mm.).

2,2-Diphenyl-4-hydroxymethyl-1,3-dioxolane (I).—A mixture of 50 g. (0.21 mole) of diphenyldimethoxymethane[15] and 26.2 g. (0.28 mole) of anhydrous glycerol, in a small distillation flask, was heated at 250–255° (bath temperature) for 8 hours; the distilled methanol weighed 13.4 g. (100%). Upon fractionation, 32.5 g. (60%) of I was obtained; b.p. 133–137° (0.01 mm.). The product slowly solidified; m.p. 51–52° after recrystallization from petroleum ether (90–100°).

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 75.00; H, 6.29. Found: C, 74.91; H, 6.45.

The phenylurethan, after recrystallization from petroleum ether (90–100°), melted at 95–96°.

Anal. Calcd. for $C_{23}H_{21}O_4N$: N, 3.73. Found: N, 3.55.

2,2-Diphenyl-4-benzoyloxymethyl-1,3-dioxolane (IV).—A mixture of 5.8 g. (0.025 mole) of diphenyldimethoxymethane and 5 g. (0.025 mole) of glycerol α-monobenzoate was heated in a small distillation flask for 2 hours at 180–210° (bath temperature); the distilled methanol weighed 1.5 g. (89%). Trituration and then recrystallization of the product by the use of ethanol yielded 3.8 g. (41%) of the benzoate; m.p. 84–85°.

The benzoate was also prepared in 87% yield from I and benzoyl chloride in dry pyridine; m.p. and mixed m.p. 84–85°.

2,2-Diphenyl-4-(β-dimethylaminoethoxymethyl)-1,3-dioxolane Hydrochloride and Methiodide.—Ten grams (0.039 mole) of I, 1.8 g. (0.078 mole) of sodium and 30 cc. of dry toluene were refluxed for 4 hours. The mixture was cooled, decanted from the unreacted sodium, 4.2 g. (0.039 mole) of freshly distilled β-dimethylaminoethyl chloride added, and then refluxed for 4 hours. After the solution had been washed with water until it was neutral, the solvent was removed.

In order to prepare the hydrochloride, the crude amine, dissolved in dry ether, was treated with the calcd. amount of ethereal hydrogen chloride. The precipitated oil turned into a hygroscopic solid after several days in a refrigerator, and frequent triturations with dry ether. It was recrystallized from acetone–ether.

The methiodide was obtained when a mixture of 3.3 g. of the crude amine, 14.3 g. of methyl iodide and 35 cc. of chloroform was heated in a citrate bottle for 5 hours on a steam-bath. The solvent was removed, the residue triturated with dry ether until it became crystalline, the product extracted with hot ethyl acetate, and then recrystallized from acetone–ether.

2,2-Diphenyl-1,3-dioxolane-4-carboxylic Acid (III).—A solution of 13.0 g. (0.08 mole) of potassium permanganate and 2.8 g. (0.05 mole) of potassium hydroxide in 250 cc. of water was stirred and maintained at 50–60° during the portionwise addition of 15.0 g. (0.06 mole) of I. The mixture was then stirred for 1 hour, filtered, and extracted with ether. The aqueous solution was concentrated to a volume of 50 cc., cooled, and covered with 400 cc. of ether. The mixture was stirred vigorously while 10% hydrochloric acid was added, dropwise, until the solution reached a *p*H of 5–6. The ether layer was separated, dried over magnesium sulfate, the solvent removed, and the acid recrystallized from toluene–petroleum ether (90–100°); yield 3.7 g. (23%); m.p. 131–132°.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22; neut. equiv., 270.3. Found: C, 71.24; H, 5.51; neut. equiv., 270.5.

The β-diethylaminoethyl ester was obtained by the Horenstein and Pählicke procedure.[16]

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

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Synthetic Application and Mechanism of the Nef Reaction

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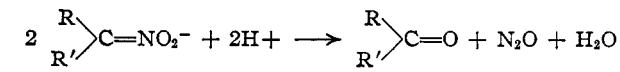
A convenient synthesis of apocamphenilone (V) is described. The sequence involves (i) a diene synthesis with cyclopentadiene and 1-nitropropene, (ii) hydrogenation of the double bond and (iii) transformation of the nitro group to carbonyl utilizing the Nef reaction. The stereochemistry of the intermediates and the final product are determined. A rational mechanism for the Nef reaction, along with supporting evidence, is presented.

The observation that aliphatic primary or secondary nitro compounds can be converted to aldehydes or ketones by adding the alkali salts of the former to aqueous mineral acid, was first recorded by Nef.[2] This reaction, which bears the name of its discoverer,[3] has been studied in a few simple cases[4–8]; in addition, it is the key step in a method of extending the aldose chain.[9] It is the purpose of this work to demonstrate further the utility of this remarkably simple transformation and to point out some pertinent features of a reasonable mechanism proposed herein.



The synthetic method we wish to illustrate consisted of the preparation of cyclic ketones *via* a

(1) Abstracted from a research report submitted by Robert J. Thiede in partial fulfillment of the Master of Science degree, University of Wisconsin.

(2) J. U. Nef, *Ann.*, **280**, 263 (1894).

(3) The reaction should be distinguished from that involving the addition of alkali acetylides to aldehydes and ketones, which is also known as the "Nef reaction."

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