2-(Hydroxymethyl)-piperidine.—Ethyl α-pipecolinate[11] (19 g.), in 100 cc. of ether, was reduced with 4.8 g. of lithium aluminum hydride in 300 cc. of ether. The mixture was refluxed for 6 hours; yield 12 g. (86%), b.p. 104–106° (10 mm.),[12] m.p. 67–69°.

The hydrochloride melted at 130–132° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_6H_{14}ONCl$: N, 9.25; Cl, 23.38. Found: N, 9.08; Cl, 23.38.

The picrate, obtained by adding an alcoholic solution of picric acid to an ethereal solution of the base, melted at 135–137°.[13]

1-Formyl-2-(hydroxymethyl)-piperidine.—2-(Hydroxymethyl)-piperidine (6.9 g.), 10 cc. of chloroform and 8.9 g. of chloral yielded 6.3 g. (73.4%) of product, b.p. 144–146° (2 mm.).

Anal. Calcd. for $C_7H_{13}O_2N$: N, 9.78. Found: N, 9.68.

1-Methyl-2-(hydroxymethyl)-piperidine.—Six grams of the formyl derivative, dissolved in 150 cc. of ether, was reduced with 2.4 g. of lithium aluminum hydride in 150 cc. of ether. The mixture was refluxed for 6 hours; yield 3.5 g. (65%), b.p. 96–98° (19 mm.).

The methiodide melted at 300–302° dec. after recrystallization from absolute ethanol.

Anal. Calcd. for $C_8H_{18}ONI$: N, 5.16; I, 46.83. Found: N, 5.07; I, 46.87.

(11) R. Willstätter, *Ber.*, **29**, 390 (1896).

(12) R. R. Renshaw, M. Ziff, B. Brodie and N. Kornblum (THIS JOURNAL, **61**, 638 (1939)), b.p. 80–83° (1 mm.).

(13) Reference 13, m.p. 128–129.5°.

(1-Methyl-2-piperidyl)-methyl *p*-Nitrobenzoate Hydrochloride.—A mixture of 3.0 g. of 1-methyl-2-(hydroxymethyl)-piperidine, 5.6 g. of *p*-nitrobenzoyl chloride and 50 cc. of benzene was refluxed for 5 hours. After the mixture had been cooled in a refrigerator, the precipitate was filtered and washed with ether; yield 7.4 g. (90%), m.p. 192–193°, after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{14}H_{19}O_4N_2Cl$: N, 8.91; Cl, 11.27. Found: N, 8.83; Cl, 11.10.

(1-Methyl-2-piperidyl)-methyl *p*-Aminobenzoate.—The nitro ester hydrochloride (3.1 g.) was reduced in the described manner; yield 2.5 g. (80%), m.p. 221–222° after recrystallization from methanol.

Anal. Calcd. for $C_{14}H_{21}O_2N_2Cl$: N, 9.85; Cl, 12.43. Found: N, 9.74; Cl, 12.40.

β-(2-Hydroxymethylpiperidino)-propiophenone Hydrochloride.—A mixture of 1.7 g. of 2-(hydroxymethyl)-piperidine hydrochloride, 0.9 g. of paraformaldehyde, 1.8 g. of acetophenone and 20 cc. of acetic acid was refluxed for 4 hours. The solvent was removed under reduced pressure, the residue was washed with ether, dissolved in water, the solution was made alkaline and the precipitate was extracted with ether. The extract was dried over magnesium sulfate and then treated with hydrogen chloride; the precipitate weighed 1.7 g. (50%), m.p. 191–192° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{15}H_{22}O_2NCl$: N, 4.93; Cl, 12.51. Found: N, 4.86; Cl, 12.43.

ANN ARBOR, MICHIGAN

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

Antispasmodics. XX. Basic 1,3-Dioxolanes and 1,3-Dioxanes

BY F. F. BLICKE AND G. R. TOY[1]

RECEIVED AUGUST 17, 1954

The preparation and antispasmodic activity of several 4-substituted 2,2-diphenyl- and 2-substituted 4,5-diphenyl-1,3-dioxolanes as well as of 5-substituted 2,2-diphenyl-5-methyl-1,3-dioxanes have been reported. In most instances the substituent was a (1-hexamethylenimino)-methyl or a (4-methyl-1-hexamethylenimino)-methyl group.

Earlier publications dealt with the preparation of basically-substituted 2,2-diphenyl-1,3-dioxolanes (I)[2,3] and 2,2-diphenyl-5-methyl-1,3-dioxanes (II).[4a,b] During this investigation we prepared compounds of types I and II and also basically substituted 4,5-diphenyl-1,3-dioxolanes (III) in which the basic substituent was a 1-hexamethylenimino or a 4-methyl-1-hexamethylenimino radical.

Interaction of 2,2-diphenyl-4-bromomethyl-1,3-dioxolane[2] with hexamethylenimine or 4-methylhexamethylenimine yielded compounds of type I. 2,2-Diphenyl-5-methyl-5-iodomethyl-1,3-dioxane[4a] reacted with the imines mentioned to form compounds of type II.

When hydrobenzoin was heated with bromoacetal, and the alcohol formed during the reaction was removed by distillation, 2-bromomethyl-4,5-diphenyl-1,3-dioxolane was obtained. Amination of this substance with piperidine, hexamethylenimine and 4-methylhexamethylenimine, respectively, produced compounds of type III.

The dioxolanes (Table I) and dioxanes were tested in The Wm. S. Merrell Company laboratories on the isolated rabbit jejunum against acetylcholine-induced spasm. The minimum effective concentrations were found to be as follows: 1:310,000 for 1 and 3; 1:200,000 for 4; 1:100,000 for 2 and 10; 1:31,000 for 5, 8 and 9; 1:10,000 for 6 and 7 (1:80,000,000 for atropine). The following minimum effective concentrations were found for barium chloride-induced spasm: 1:1,000,000 for 3; 1:500,000 for 4; 1:310,000 for 9 and 10; 1:31,000 for 1, 2, 5, 6 and 8; 1:10,000 for 7 (1:100,000 for papaverine).

Experimental

2-Bromomethyl-4,5-diphenyl-1,3-dioxolane.—A mixture of 21.4 g. of hydrobenzoin[5] and 19.7 g. of bromoacetal[6] was heated in a small distillation flask at 135–150° for 2 hours. During this time 9.2 g. (100%) of ethanol distilled from the mixture. The residue was recrystallized from 50 cc. of isopropyl alcohol with the addition of charcoal; yield 29.0 g. (91%), m.p. 89–90°.

Anal. Calcd. for $C_{16}H_{15}O_2Br$: Br, 25.04. Found: Br, 25.37.

The manner in which the compounds (1–8) listed in Table I were obtained is illustrated by the following procedure. The yields of the bases varied from 70–91%.

2,2-Diphenyl-4-(1-hexamethyleniminomethyl)-1,3-dioxolane Hydrochloride (1) and Methobromide (2).—A mixture of 25.0 g. (0.078 mole) of 2,2-diphenyl-4-bromomethyl-1,3-dioxolane,[2] 100 cc. of toluene and 39.6 g. (0.4 mole) of hexa-

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

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

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

(4) (a) F. F. Blicke and E. L. Schumann, *ibid.*, **76**, 1226 (1954); (b) *ibid.*, **76**, 3153 (1954).

(5) J. S. Buck and S. S. Jenkins, *ibid.*, **51**, 2163 (1929).

(6) S. M. McElvain and D. Kundiger, *Org. Syntheses*, **23**, 8 (1943).

TABLE I

1,3-DIOXOLANES

Compounds 1, 2, 5 and 7 were recrystallized from isopropyl alcohol; 3 from methyl ethyl ketone; 4 from acetone; 6 and 8 from ethanol

	Substituent	Salt	B.p., base °C.	Mm.	M.p., °C. salt	Formula	Nitrogen, % Calcd.	Found	Hydrogen, % Calcd.	Found
			4-Substituted 2,2-diphenyl-							
1	$CH_2NC_6H_{12}$[a]	HCl	175–177	.01	183–184	$C_{22}H_{28}O_2NCl$	3.75	3.69	9.48	9.45
2	$CH_2NC_6H_{12}$	CH_3Br			203–205	$C_{23}H_{30}O_2NBr$	3.24	3.35	18.48	18.50
3	$CH_2NC_7H_{14}$[b]	HCl	183–185	.01	173–175	$C_{23}H_{30}O_2NCl$	3.61	3.67	9.14	9.04
			2-Substituted 4,5-diphenyl-							
4	$CH_2NC_5H_{10}$[c]	HCl			201–202	$C_{21}H_{26}O_2NCl$	3.89	3.86	9.87	9.84
5	$CH_2NC_6H_{12}$	HCl	178–180	.05	163–165[d]	$C_{22}H_{28}O_2NCl$	3.75	3.77	9.48	9.40
6	$CH_2NC_6H_{12}$	CH_3Br			223–225[d]	$C_{23}H_{30}O_2NBr$	3.24	3.25	18.48	18.53
7	$CH_2NC_7H_{14}$	HCl	173–175	.05	157–159	$C_{23}H_{30}O_2NCl$	3.61	3.63	9.14	9.30
8	$CH_2NC_7H_{14}$	CH_3Br			226–228[d]	$C_{24}H_{32}O_2NBr$	3.14	3.20	17.90	18.07

[a] NC_6H_{12} = 1-hexamethylenimino. [b] NC_7H_{14} = 4-methyl-1-hexamethylenimino. [c] NC_5H_{10} = piperidino. [d] Melts with decomposition.

methylenimine[7] was heated in a pressure bottle on a steam-bath for 5 days. The mixture was washed with a solution of 10 g. of sodium hydroxide in 50 cc. of water. The organic layer was separated, dried over magnesium sulfate, the solvent and excess imine were removed by distillation and the residue was fractionated; yield 24.1 g. (91%).

The hydrochloride was prepared by addition of the calculated amount of ethereal hydrogen chloride to the base dissolved in ether.

In order to obtain the methobromide, excess methyl bromide was added to the base dissolved in ether.

2,2-Diphenyl-5-methyl-5-(1-hexamethyleniminomethyl)-(9) and 2,2-Diphenyl-5-methyl-5-(4-methyl-1-hexamethyleniminomethyl)-1,3-dioxane (10) Hydrochlorides.—By the process described above, 13.4 g. of 2,2-diphenyl-5-methyl-5-iodomethyl-1,3-dioxane,[4a] 16.9 g. of hexamethylenimine and 100 cc. of benzene yielded 5.0 g. (40.3%) of product after three recrystallizations from absolute ethanol; m.p. 68–70°.

The hydrochloride melted at 215–217° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{24}H_{32}O_2NCl$: N, 3.48; Cl, 8.82. Found: N, 3.55; Cl, 8.86.

From 15.0 g. of the iodomethyl compound, 43.0 g. of 4-methylhexamethylenimine and 100 cc. of benzene, 12.0 g. (83.3%) of product was obtained after recrystallization from methanol with the use of charcoal; m.p. 66–68° after recrystallization from absolute ethanol.

The hydrochloride melted at 214–215° dec. after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{25}H_{34}O_2NCl$: N, 3.37; Cl, 8.52. Found: N, 3.30; Cl, 8.47.

ANN ARBOR, MICHIGAN

(7) F. F. Blicke and N. J. Doorenbos, THIS JOURNAL, **76**, 2317 (1954).

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

Antispasmodics. XXI. Basic 1,3-Dioxolanes

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One series of basic 4,5-diphenyl-1,3-dioxolanes and two series of basic spiro-1,3-dioxolanes were prepared. In a number of these compounds the basic substituent was a hexa-, hepta- or octamethylenimino radical. The antispasmodic activity of some of the compounds has been reported.

Three types of basic 1,3-dioxolanes were prepared for pharmacological study.

Basic 4,5-diphenyl-1,3-dioxolanes (Table I) were obtained by interaction of 2-bromomethyl-4,5-diphenyl- (I) or 2-(β-chloroethyl)-4,5-diphenyl-1,3-dioxolane (II) with an amine. Among the amines employed were hexa-, hepta- and octamethylenimine. The required intermediate I was prepared from hydrobenzoin and bromoacetal by a described procedure.[3] The second intermediate II was synthesized by interaction of hydrobenzoin with β-chloropropionaldehyde diethylacetal.

Under the conditions described in the experimental part, a 1-alkyl-4-piperidone hydrochloride was heated with ethanol and then with hydrobenzoin with the formation of a basic spirodioxolane (Table II). For example, 1-methyl-3-phenyl-4-piperidone hydrochloride, after treatment with ethanol and hydrobenzoin, yielded 2,3,6-triphenyl-8-methyl-1,4-diox-8-azaspiro[4.5]decane. Presumably, a hemiketal is the first intermediate in this series of reactions.

Another type of basic spirodioxolane (Table III) was obtained by the use of 1-(hydroxymethyl)-cyclohexanol. Interaction of this substance with bromoacetal yielded 2-bromomethyl-1,3-dioxaspiro-[4.5]decane which condensed with amines to form the corresponding 2-basically substituted products; thus, reaction with dimethylamine produced 2-dimethylaminomethyl-1,3-dioxaspiro[4.5]decane.

Some of the compounds (Table I) were tested in the Wm. S. Merrell Company laboratories on the isolated rabbit jejunum against acetylcholine-induced spasm. The minimum effective concentra-

(1) This paper represents part of a dissertation submitted by H. E. Millson, Jr., in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1954.

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

(3) F. F. Blicke and G. R. Toy, THIS JOURNAL, **77**, 31 (1955).