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Studies in the Muscarine Series. VI. Muscarinic Activity of Some 1,3-Dioxolanes and 1,3-Dithiolanes

Z. Štefanac, N. Bregant, and K. Balenović

Chemical Laboratory, Faculty of Science, University of Zagreb, Strossmayerov trg 14, Zagreb, Croatia, Yugoslavia

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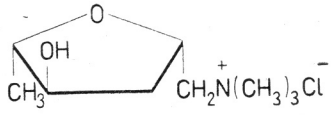
The synthesis of 1,3-dioxolanes Va-e and VIa-b, and the dithiolane III is described. A discussion is given of the structural relationship between these compounds and natural muscarine; their muscarinic activity was determined.

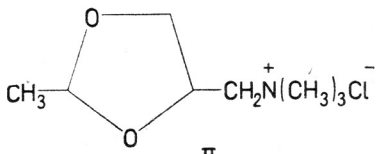
The physiological properties of muscarine I[1,2,3] and its stereoisomers[4] are highly stereospecific[5,6]. The anticholinesterase activities of muscarine and of its diastereoisomers and ketonic and unsaturated derivatives[7,8] have recently been described[9]. The complex physiological properties attributed through the years to crude muscarinic extracts were determined so for the first time on pure synthetic isomers and on highly purified enzyme preparations.



I

Recent pharmacological data[5,6,10] for these muscarine derivatives show that the muscarines are quite stereospecific in their actions on a number of pharmacological preparations, whereas the muscarones are not. This parallels the findings that the enzyme responds *in vitro* more sensitively to stereochemical differences in the muscarine than in the muscarone series. In contrast, the muscarones are much more active in stimulating smooth muscle[10] and with respect to nicotinic power[5,6,10] than are the muscarines.

The pharmacological behaviour of muscarones could possibly be used for the explanation of the powerful muscarinic activity of the 1,3-dioxolane derivative II[11,12,13,14,15] which differs from natural muscarine in that the secondary alcoholic function in the latter is substituted for the cyclic ether function.



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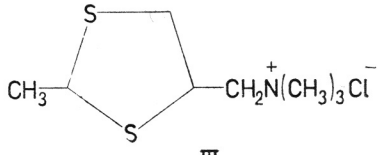


III

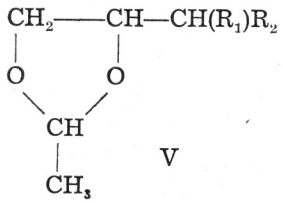
* Communication No. 80 from this Laboratory.

1,3-Dioxolanes with quaternary ammonium functions are therefore a very interesting class of compounds for the study of the correlation of chemical structure and biological activity. Furthermore, these compounds and their sulphur analogoues, 1,3-dithiolanes (*e. g.* III) can also be useful for the study of active centres on acetylcholinesterase surface*[16].

The present paper describes the synthesis of 1,3-dioxolanes Va-e and VIa-b.

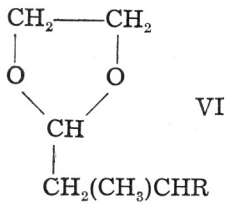
$HOCH_2CHOHCH(R_1)R_2$ IV

a, R_1 = *i*-propyl; $R_2 = C_6H_4(CO)_2N$
b, $R_1 = C_2H_5$ $R_2 = C_6H_4(CO)_2N$



V

a, R_1 = H; $R_2 = \overset{+}{N}(CH_3)_2C_2H_5I^-$
b, R_1 = *i*-propyl; $R_2 = C_6H_4(CO)_2N$
c, R_1 = *i*-propyl; $R_2 = NH_2$
d, R_1 = *i*-propyl; $R_2 = \overset{+}{N}(CH_3)_3Cl^-$
e, $R_1 = C_2H_5$; $R_2 = C_6H_4(CO)_2N$



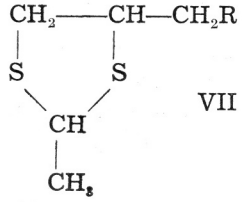
VI

a, $R = C_6H_4(CO)_2N$

b, $R = NH_2$

The starting material for the preparation of 2-methyl-4-methylenedimethylethyl ammonium 1,3-dioxolane iodide (Va) was 2-methyl-4-dimethylaminomethyl-1,3-dioxolane[13]. The muscarinic activity of Va was considerable (30×10^6 M. U./g) but lower than that of II (100×10^6 M. U./g) or I (238×10^6 M. U./g).

1,3-Dioxolanes of the type Vb-e were prepared from the corresponding amino acids *via* aminoglyoxal derivatives[18]. DL-Valine and DL-α-aminobutyric acid were used as starting materials for compounds of the type Vb-e and DL- and L-β-aminobutyric acid for those of the type VIa-b. The 1,3-dithiolane derivative III was prepared from 2,3-mercaptopropanol (BAL) through the reaction stages VIIa-d.



VII

a, R = OH
b, R = Br
c, $R = N(CH_3)_2$
d, $R = \overset{+}{N}(CH_3)_3I^-$

Muscarinic activity of III is low (as compared to the corresponding 1,3-dioxolane derivative II).

* For a summary of the work leading to the postulation of a bifunctional catalytic unit on the surface of acetylcholinesterase, refer to a review by Nachmansohn and Wilson[17]. For the explanation of the high stereospecificity of muscarines as inhibitors of acetylcholinesterase activity, a 3-pointed catalytic unit on the enzyme surface was proposed[5,9]

EXPERIMENTAL

4-Dimethylaminomethyl-2-methyl-1,3-dioxolane ethiodide (2-methyl-4--methylene-dimethylethylammonium-1,3-dioxolane iodide) (Va)

A liquid mixture of 2-methyl-4-dimethylaminomethyl-1,3-dioxolane (4.6 g.) prepared according to Fourneau *et al.*[13] and ethyl iodide (5 ml.) was left standing for one hour at room temperature and treated with ether (10 ml.). Crude 2-methyl-4-methylene-dimethylethylammonium-1,3-dioxolane iodide (Va) separated, in a yield of 7.1 g. (74.5%), showing the m. p. 106—109°. The analytical sample was obtained after two recrystallizations from a mixture of absolute ethanol and ether and consisted of colourless needles showing the constant m. p. 113—114°.

Anal. 9.273 mg. subst.: 12.248 mg. CO_2, 5.573 mg. H_2O
$C_9H_{20}O_2NI$ (301.034) calc'd.: C 35.91; H 6.65%
found: C 36.04; H 6.73%

4-Methyl-3-phthalimido-1,2-pentandiol (IVa)

Hydrogenation over previously reduced Adams' PtO_2 catalyst (215 mg.) was carried out at atmospheric pressure and 17° with a solution of 4-methyl-3-phthalimido-2-pentanonal (6.1 g., prepared from DL-valine[18]) in ethanol (50 ml.). 4-Methyl--3-phthalimido-2-pentanonal was distilled prior to hydrogenation at 120°/0.01 mm. After two moles of hydrogen were absorbed, the catalyst was filtered off, and 4-methyl-3-phthalimido-1,2-pentandiol was obtained from the filtrate in a quantitative yield by evaporation under reduced pressure. The thus obtained yellow oily diol was dissolved in ethanol, filtered through a column of alumina (1:5, activity IV) and evaporated to dryness. The analytical sample consisting of a colourless oil was prepared by precipitation from a mixture of dichloromethane and ether, and drying overnight at 100°/0.05 mm.

Anal. 9.625 mg. subst.: 22.446 mg. CO_2, 5.485 mg. H_2O
$C_{14}H_{17}O_4N$ (263.284) calc'd.: C 63.86; H 6.51%
found: C 63.64; H 6.38%

2-Methyl-4-(2-methyl-1-phthalimidopropyl)-1,3-dioxolane (Vb)

A mixture of 4-methyl-3-phthalimido-1,2-pentandiol (IVa) (5.26 g., 0.02 mole), paraldehyde (1.8 g., 0.04 mole) *p*-toluenesulphonic acid (0.15 g.) and benzene (400 ml.) was refluxed for 6 hours in a round-bottomed flask fitted with a total condensation take-off adapter. The cooled reaction mixture was washed twice with water and dried (Na_2SO_4). After the benzene was evaporated, the brown oily residue (5.7 g., 98.6%) of 2-methyl-4-(2-methyl-1-phthalimidopropyl)-1,3-dioxolane was dissolved in chloroform and filtered through a column of alumina (1:5, activity IV). The analytical sample was obtained by distillation at 95—100° (bath temp.)/0.025 mm.

Anal. 10.160 mg. subst.: 24.600 mg. CO_2, 6.492 mg. H_2O
$C_{16}H_{19}O_4N$ (289.320) calc'd.: C 66.42; H 6.62%
found: C 66.08; H 7.15%

2-Methyl-4-(1-amino-2-methylpropyl)-1,3-dioxolane (Vc)

A solution of 2-methyl-4-(2-methyl-1-phthalimidopropyl)-1,3-dioxolane (Vb, 1.134 g., 3.9 moles) and hydrazine hydrate (3.54 ml. of 1 *M* ethanolic solution) in ethanol (30 ml.) was refluxed for 3 hours on a steam bath. Dichloromethane (30 ml.) was added to the cooled reaction mixture and the phthalyl hydrazide filtered off. The filtrate was freed of the solvents *in vacuo;* the resulting 2-methyl-4-(1-amino-2--methylpropyl)-1,3-dioxolane distilled over powdered sodium hydroxide at 80—85°/15 mm. as a colourless oil.

Anal. 8.842 mg. subst.: 19.580 mg. CO_2, 8.550 mg. H_2O
$C_8H_{17}O_2N$ (159.224) calc'd.: C 60.34; H 10.76%
found: C 60.43; H 10.82%

2-Methyl-4-(1-dimethylamino-2-methylpropyl)-1,3-dioxolane methochloride (Vd)

A solution of 2-methyl-4-(1-amino-2-methylpropyl)-1,3-dioxolane (Vc, 0.6 g.) and methyl iodide (1.8 g.) in methanol (5 ml.) was refluxed for 2 hours. Finely powdered sodium hydroxide (0.6 g.) was added to the cooled reaction mixture, which was stirred for half an hour at room temperature. The same quantity of methyl iodide was added, and refluxing was continued for two more hours. Addition of sodium hydroxide and subsequent refluxing with methyl iodide was repeated once more, the reaction mixture evaporated to dryness, the dry residue dissolved in water, and treated with a freshly prepared aqueous suspension of silver chloride*. The mixture was left in the dark at room temperature for two days with occasional shaking. The reaction mixture was then filtered, the filtrate evaporated to dryness and the dry residue extracted with absolute ethanol. After evaporation of the ethanolic extract, crystallization from a mixture of absolute ethanol and ether gave 2-methyl-4-(1-dimethylamino-2-methylpropyl)-1,3-dioxolane methochloride (175 mg.).

For characterization and analytical purpose the chloroaurate of this compound was prepared with 30 per cent aqueous solution of Au (III) chloride (trace of hydrochloric acid). Repeated recrystallization from water gave the pure chloroaurate, m. p. 136—138°.

Anal. 7.298 mg. subst.: 6.248 mg. CO_2, 3.035 mg. H_2O, 2.662 mg. Au
$C_{11}H_{24}O_2NCl_4Au$ (541.138) calc'd.: C 24.41; H 4.47; Au 36.41%
found: C 23.36; H 4.65; Au 36.48%

3-Phthalimido-1,2-pentandiol (IVb)

Hydrogenation over previously reduced Adams' PtO_2 catalyst (50 mg.) was carried out at atmospheric pressure and 25° with a solution of freshly distilled 3-phthalimido-2-pentanonal (0.673 g. b. p. 130°/0.01 mm. prepared from α-aminobutyric acid[18]) in ethanol (8 ml.). After two moles of hydrogen were absorbed (24 hours), the catalyst was filtered off and 3-phthalimido-1,2-pentadiol was obtained from the filtrate in a quantitative yield by evaporation under reduced pressure. The diol distilled at 125—130°/0.025 mm. as a colourless oil.

Anal. 8.545 mg. subst.: 19.562 mg. CO_2, 5.070 mg. H_2O
$C_{13}H_{15}O_4N$ (249.258) calc'd.: C 62.63; H 6.07%
found: C 62.47; H 6.64%

2-Methyl-4-(1-phthalimidopropyl)-1,3-dioxolane (Ve)

A mixture of 3-phthalimido-1,2-pentandiol (IVb, 3.1 g., 0.012 mole), paraldehyde (1.08 g., 0.024 mole), *p*-toluenesulphonic acid (0.08 g.) and benzene (200 ml.) was refluxed for 6 hours in a round-bottomed flask fitted with a total condensation take-off adapter. The cooled reaction mixture was washed twice with water, and then dried (Na_2SO_4). After the benzene was evaporated the brown oily residue (3.3 g., 96.4%) was dissolved in benzene and filtered through a column of alumina (1:5, activity IV). From the benzene filtrates a pale yellow oil was isolated, which solidified after standing overnight.

Recrystallization from a mixture of dichloromethane and petroleum ether gave colourless prisms with the constant m. p. 114—116°.

Anal. 11.534 mg. subst.: 27.673 mg. CO_2, 6.552 mg. H_2O
$C_{15}H_{17}O_4N$ (275.294) calc'd.: C 65.44; H 6.22%
found: C 65.47; H 6.36%

(+)-2-(2-Phthalimidopropyl)-1,3-dioxolane (VIa)

A mixture of (+)-β-phthalimidobutyraldehyde (2.17 g., 0.01 mole, $[\alpha]_D^{18}$ +42°, prepared according to Balenović *et al.*[19]), ethylene glycol (2.5 ml., freshly distilled), *p*-toluenesulphonic acid (0.25 g.) and benzene (100 ml.) was treated in the previously

* The freshly prepared silver chloride precipitate was washed with bidistilled water by decantation until the chloride test was negative.

described manner. The cooled reaction mixture was washed with water and dried (Na_2SO_4). After evaporating the benzene, 2.4 g. (92%) of pale yellow oily (+)-2-(2-phthalimidopropyl)-1,3-dioxolane remained. Chromatography on alumina (1:5, activity IV, benzene) and distillation at 100—110°/0.025 mm. afforded the analytical sample as a colourless viscous oil, with $[\alpha]_D^{17}$ + 46° ± 0.5° (c, 0.656 in benzene).

Anal. 9.763 mg. subst.: 22.990 mg. CO_2, 5.090 mg. H_2O
$C_{14}H_{15}O_4N$ (261.168) calc'd.: C 64.38; H 5.75%
found: C 64.26; H 5.83%

(+)-2-(2-Aminopropyl)-1,3-dioxolane (VIb)

Hydrazinolysis of (+)-2-(2-phthalimidopropyl)-1,3-dioxolane (VIa, 1.8 g., 7 mmoles $[\alpha]_D$ + 45°) in the usual way with 1 *M* ethanolic hydrazine hydrate gave (+)-2-(2--aminopropyl)-1,3-dioxolane (0.55 g., 61%) consisting of a colourless liquid with the b. p. 71—73°/12 mm.

Anal. 14.992 mg. subst.: 30.040 mg. CO_2, 13.392 mg. H_2O
$C_6H_{13}O_2N$ (131.17) calc'd.: C 54.94; H 9.99%
found: C 54.68; H 9.99%

DL-*2-(2-Phthalimidopropyl)-1,3-dioxolane* (VIa)

was prepared in the same manner as the (+)-antipode, from DL-β-phthalimidobutyraldehyde (6.51 g., 0.03 mole) in a yield of 7.2 g (92%). Recrystallization from petroleum ether gave colourless needles wit the constant m. p. 63—64.5°. Sublimation at 90—95/0.025 mm. gave the analytical sample.

Anal. 9.904 mg. subst.: 23.470 mg. CO_2, 5.240 mg. H_2O
$C_{14}H_{15}O_4N$ (261.168) calc'd.: C 64.38; H 5.75%
found: C 64.67; H 5.92%

4-Hydroxymethyl-2-methyl-1,3-dithiolane (VIIa)

To a mixture of freshly distilled 2,3-dimercapto-1-propanol (BAL, 10 g., 0.081 mole) and acetaldehyde (3.5 g., 0.08 mole) chilled to —5°, a solution of 3% anhydrous hydrochloric acid in dioxane (100 ml.) was gradually added during half an hour. After the vigorous reaction subsided, the mixture was left at room temperature for 4 days. The solvent was evaporated *in vacuo* and the residue dissolved in benzene. After removing the benzene, the pale yellow liquid 4-hydroxymethyl-2-methyl-1,3-dithiolane (13.2 g.) remained. The analytical sample distilled at 125—145° (bath temp.)/0.01 mm., as a colourless oily liquid.

Anal. 8.547 mg. subst.: 12.684 mg. CO_2, 4.710 mg. H_2O
$C_5H_{10}OS_2$ (150.23) calc'd.: C 39.97; H 6.71%
found: C 40.50; H 6.17%

4-Bromomethyl-2-methyl-1,3-dithiolane (VIIb)

Bromination of 4-hydroxymethyl-2-methyl-1,3-dithiolane (VIIa, 5.2 g., 0.035 mole) was carried out with phosphorus tribromide (1.2 ml., 0.013 mole) in the usual manner[20], and afforded 4-bromomethyl-2-methyl-1,3-dithiolane (4.8 g., 65.1%). The analytical sample was prepared by distillation at 50—55°/0.01 mm. Colourless liquid.

Anal. 12.318 mg. subst.: 12.852 mg. CO_2, 4.832 mg. H_2O
$C_5H_9S_2Br$ (213.17) calc'd.: C 28.17; H 4.26%
found: C 28.47; H 4.41%

4-Dimethylaminomethyl-2-methyl-1,3-dithiolane (VIIc)

A mixture of freshly distilled 4-bromomethyl-2-methyl-1,3-dithiolane (VIIb, 2.6 g., 0.012 moles), anhydrous dimethylamine (2.8 g., 0.062 moles) and benzene (6 ml.) was heated in a sealed tube at 160° for 16 hours. The reaction mixture was alkalised with a concentrated sodium carbonate solution, extracted with ether, and the ethereal extracts washed with water and dried (K_2CO_3). After evaporation of the solvent

4-dimethylaminomethyl-2-methyl-1,3-dithiolane (2 g., 92.5%) remained as an oily liquid. Distillation at 95—100°/18 mm. gave the colourless liquid analytical sample.

Anal. 7.938 mg. subst.: 13.795 mg. CO_2, 5.929 mg. H_2O
$C_7H_{15}S_2N$ (177.29) calc'd.: C 47.41; H 8.52%
found: C 47.43; H 8.36%

4-Dimethylaminomethyl-2-methyl-1,3-dithiolane methiodide (VIId)

A mixture of freshly distilled 4-dimethylaminomethyl-2-methyl-1,3-dithiolane (VIIc, 0.3 g.), acetone (1 ml.) and methyl iodide (0.5 ml.) was left standing at room temperature for 2 hours, and afforded crystalline 4-dimethylaminomethyl-2-methyl-1,3-dithiolane methiodide (0.5 g., 92.5% m. p. 190°). Several recrystallizations from absolute ethanol yielded colourless needles with the m. p. 194—196° (decomp.).

Anal. 7.713 mg. subst.: 8.713 mg. CO_2, 4.115 mg. H_2O
$C_8H_{18}S_2NI$ (319.23) calc'd.: C 30.09; H 5.68%
found: C 30.83; H 5.97%

4-Dimethylaminomethyl-2-methyl-1,3-dithiolane methochloride (III)

An aqueous solution of 4-dimethylaminomethyl-2-methyl-1,3-dithiolane methiodide (VIId) was treated in the usual manner with an aqueous suspension of silver chloride. 4-Dimethylaminomethyl-2-methyl-1,3-dithiolane methochloride is very hygroscopic.

Anal. 7.073 mg. subst.: 10.736 mg. CO_2, 4.932 mg. H_2O
$C_8H_{18}S_2NCl$ (227.77) calc'd.: C 42.18; H 7.97%
found: C 41.42; H 7.80%

TABLE I

Determination of Muscarinic Activity

Compound	Muscarinic Activity for 1 g. Substance
4-Dimethylaminomethyl-2-methyl-1,3-dioxolane ethiodide (Va)	30×10^6 M. U.*
4-Dimethylaminomethyl-2-methyl-1,3-dioxolane methiodide (II)	100×10^6 M. U.
4-Dimethylaminomethyl-2-methyl-1,3-dithiolane methiodide (VIId)	10×10^4 M. U.

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* The biological test was carried out on eight isolated frog hearts *(Rana esculenta)* for each compound, following the technique and definition of muscarine unit (M. U.) of Kögl *et al.*[21]

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IZVOD

Studije u redu muskarina. VI. Muskarinska aktivnost nekih 1,3-dioksolana i 1,3-ditiolana

Z. Štefanac, N. Bregant i K. Balenović

Opisana je sinteza 1,3-dioksolana Va-e i VIa-b, kao i ditiolana III, te je određena njihova muskarinska aktivnost.

KEMIJSKI ZAVOD
PRIRODOSLOVNO-MATEMATIČKI FAKULTET
ZAGREB

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