Studies in the Muscarine Series. III*. Acetals of Betaine Aldehyde and Their Muscarinic Activity; Some Views on the Structure of Muscarine

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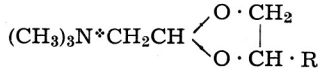
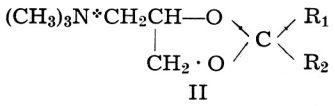
A description is given of the preparation of cyclic acetals of betaine aldehyde: (formyl-methyl)-trimethyl ammonium iodide - 1,3 - butylene acetal [IV] and (formyl-methyl)-trimethyl ammonium iodide dibenzyl acetal [V]; results of the investigation of their muscarinic activity are also given. The structure of muscarine is discussed, especially in connection with the new empirical formula for this compound proposed by Eugster and Waser[4].

Some years ago, E. Fourneau and coworkers[1] described a series of synthetic products of very high muscarinic activity, which had formulae I and II.



I a, R = H



II a, $R_1 = H$; $R_2 = CH_3$

The cyclic acetal of betaine aldehyde [Ia; R = H] has a much higher muscarinic activity than the free betaine aldehyde. In the first communication of this series[2], we described the preparation and the muscarinic activity of the homologs of Ia, derived from optically active amino acids, to be able to prove, on simple synthetic models, Kögl's claim for the very high stereospecificity of muscarine[3]. In the meantime, Eugster and Waser[4] have proposed a new formula for muscarine: $C_9H_{20}O_2N^+$ (simplest formula). The same authors have pointed out that muscarine contains neither the aldehyde group, nor C = O or C = C groups.

We should like to point out that the completely saturated character of muscarine, in connection with the formula $C_9H_{20}O_2N^+$ leads to the conclusion that the muscarine molecule contains one ring. Furthermore, it may be of considerable interest, with the well-known muscarine-atropine antagonism in mind[5], that the new (simplest) empirical formula for muscarine has the same carbon and nitrogen content as methylated tropine, and that the breaking of one ring in tropine and the addition of one molecule of water leads to

* Paper I, see reference[2].

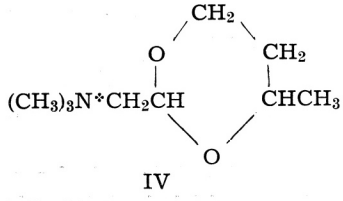
a compound with the same empirical formula as muscarine. Moreover, tropine itself shows an antagonism against muscarine on frog's heart[6].

On the other hand, synthetic products of the formula II show the highest muscarinic activity of all synthetic products [IIa, $R_1 = H$, $R_2 = CH_3$]. The lethal dose for dogs is 2 μg./kg.; the dose of 0.1 μg./kg. results in a considerable lowering of blood pressure.

The same compound, but with free hydroxy groups [III] has a low physiological activity, the lethal dose for white mice being 1700 μg./g.[7].

$(CH_3)_3N^*CH_2CHOHCH_2OH$
III

All the synthetic cyclic acetals with high muscarinic activity have five-membered rings. Their homologs with six-membered rings have not been described, and we, therefore, synthesized derivatives IV and V.



IV

$(CH_3)_3N^*CH_2CH(OCH_2Ph)_2$
V

The results of our studies on natural muscarine will be the subject of other communications.

EXPERIMENTAL

Phthalimido-acetaldehyde - 1,3 - butylene acetal

A mixture of phthalimido-acetaldehyde (6.3 g., 0.03 mole), 1,3-butanediol (3.5 g., 0.03 mole) and p-toluenesulfonic acid (0.2 g.) in benzene (350 ml.) was refluxed in a flask provided with a total condensation take-off adapter. After 7 hours the theoretical quantity of water had distilled. The reaction mixture was cooled, washed with water, dried (Na_2SO_4) and evaporated to dryness. The crystalline residue of *phthalimido-acetaldehyde - 1,3 - butylene acetal*, yield 8.6 g. (98%), m. p. 118—120°, was recrystallized from dichlorometane-petroleum ether (1 : 1). The white prisms of the pure compound had the m. p. 139—140°.

Anal. 9.44 mg. subst.: 22.20 mg. CO_2, 4.90 mg. H_2O
$C_{14}H_{15}NO_4$ (261.27) calc'd: C 64.35; H 5.79%
found: C 64.15; H 5.81%.

Amino acetaldehyde - 1,3 - butylene acetal

A mixture of phthalimido acetaldehyde - 1,3 - butylene acetal (7.83 g. 0.03 mole), an ethanolic 1 *M* solution of hydrazine hydrate (60 ml., 0.033 mole) and ethanol (80 ml.) was refluxed for 3 hours. After cooling the reaction mixture, the phthalyl hydrazide was filtered off, dichloromethane added to the filtrate, and an additional quantity of phthalyl hydrazide filtered off (total phthalylhydrazide 78%). The filtrate was distilled, and the *amino acetaldehyde - 1,3 - butylene acetal* distilled at 60—70°/18 mm. Yield 2.6 g. (66.6%).

Picrate, yellow needles from methanol, m. p. 199°.

Anal. 10.00 mg. subst.: 14.74 mg. CO_2, 4.07 mg. H_2O
$C_{12}H_{16}N_4O_9$ (360.28) calc'd: C 40.00; H 4.47%
found: C 40.22; H 4.46%.

(Formyl-methyl)-trimethyl ammonium iodide - 1,3 - butylene acetal. Betaine aldehyde - 1,3 - butylene acetal [IV]

A mixture of aminoacetaldehyde (1,3)-butylene acetal (1.4 g., 0.011 mole), methyl iodide (1.9 g., 0.033 mole), sodium hydroxide (0.7 g., 0.02 mole), and ethanol (8 ml.) was slowly heated in a round-bottomed flask with reflux condenser for 2 hours. The reaction mixture was cooled, finely powdered sodium hydroxide (0.7 g.) added, and the suspension shaken until the sodium hydroxide dissolved. (At this moment separation of sodium iodide began.) The same quantity of methyl iodide as above (1.9 g.) was then added, and the mixture heated under reflux for 2 hours. This entire procedure was repeated twice. After cooling the reaction mixture and leaving it to stand overnight, the crude *(formyl-methyl)-trimethyl ammonium iodide-1,3-butylene acetal* separated, yield 3,2 g., m. p. 197—199°. Recrystallization from absolute ethanol yielded 2.3 g. (74.5%) of sodium iodide-free product, m. p. 200—202°. The analytical sample was recrystallized from absolute ethanol, white needles, m. p. 208°.

Anal. 8,29 mg. subst.: 10.88 mg. CO_2, 4.99 mg. H_2O
$C_9H_{20}INO_2$ (301.18) calc'd: C 35.89; H 6.69%
found: C 35.82; H 6,74%.

Phthalimido acetaldehyde dibenzyl acetal

By treating a mixture of phthalimido acetaldehyde (9.45 g. 0.05 mole), benzyl alcohol (12.6 g. 0.1 mole) and p-toluenesulfonic acid (0.4 g.) in benzene (400 ml.) in the same manner as described in the preparation of phthalimido acetaldehyde - 1,3 - butylene acetal, crude *dibenzyl acetal* was obtained in a yield of 19 g. (99%), m. p. 95—100°. Recrystallization from dichloromethane-petroleum ether (1 : 1) yielded white needles of the pure product, m. p. 108—109°.

Anal. 10.24 mg. subst.: 27.90 mg CO_2, 5.07 mg. H_2O
$C_{24}H_{21}NO_4$ (387.42) calc'd: C 74.40; H 5.46%
found: C 74.34; H 5.54%.

Aminoacetaldehyde dibenzyl acetal

By treating a mixture of phthalimido acetaldehyde dibenzyl acetal (19.4 g., 0,05 mole), an ethanolic 1 *M* solution of hydrazine hydrate (200 ml.), and ethanol (200 ml.) in the same manner as described in the preparation of aminoacetaldehyde-1,3-butylene acetal, 85% of phthalyl hydrazide could be separated, and 10.3 g. (80%) of crude *aminoacetaldehyde dibenzyl acetal* was obtained as a yellow viscous oil. The pure product was obtained by distillation at 110—115°/0.03 mm. as a colorless oil.

Anal. 12.35 mg. subst.: 33.93 mg. CO_2, 8.31 mg. H_2O
$C_{16}H_{19}NO_2$ (257.32) calc'd: C 74.68; H 7.44%
found: C 74.97; H 7,53%.

Picrate, yellow needles from ethyl acetate-petroleum ether, m. p. 123—124°.

Anal. 8.94 mg. subst.: 17.87 mg. CO_2, 3.70 mg. H_2O
$C_{22}H_{22}N_4O_9$ (486.43) calc'd: C 54.32; H 4,56%
found: 54.54; H 4.63%.

(Formyl-methyl)-trimethyl ammonium iodide dibenzyl acetal. Betaine aldehyde dibenzyl acetal [V]

A mixture of aminoacetaldehyde dibenzyl acetal (1.8 g., 0.007 mole), methyl iodide (2.4 g.), and methanol (10 ml.) was treated in the same manner as described in the preparation of compound IV. Crude *(formyl-methyl)-trimethyl ammonium iodide dibenzyl acetal* [V] was obtained, m. p. 120—130°. Recrystallization from absolute ethanol gave white needles of the pure product, yield 2.2 g. (76%), m. p.

144—145°. The analytical sample was recrystallized from ethanol, and had the m. p. 146°.

Anal. 9.29 mg. subst.: 18.12 mg. CO_2, 5.11 mg. H_2O
$C_{19}H_{26}JNO_2$ (427.33) calc'd: C 53.40; H 6.13%
found: C 53.22; H 6.15%.

The biological test was carried out on eight isolated frog hearts *(Rana esculenta)* for each compound, following the technique of Kögl *et al.*[7] The results of the measurements are summarized in Table 1.

TABLE 1

Compound	Muscarinic activity for 1 g. substance*
(Formyl-methyl)-trimethyl ammonium iodide-1,3-butylene acetal (IV)	19.000 M. U.
(Formyl-methyl)-trimethyl ammonium iodide dibenzyl acetal (V)	—
Cyclic acetal of betaine aldehyde (Ia)	78.000 M. U.**
Natural muscarine	200.10^6 M. U.*** 238.10^6 M. U.****

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* Muscarine units according to Kögl *et al.*[7]
** Our determination of muscarinic activity of the compound first prepared by E. Fourneau *et al.*[1]
*** Determinations carried out by Kögl *et al.*[7] on *Rana esculenta.*
**** Determinations carried out by Eugster and Waser[4] on *Rana temporaria.*

IZVOD

Istraživanja o muskarinu. II. Acetali betainaldehida i njihovo muskarinsko djelovanje; prilog određivanju strukture muskarina

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Opisano je priređivanje cikličkih acetala betainaldehida: (formil-etil)-trimetil-amoniumjodid-1,3-butilenacetala [IV] i (formil-etil)-trimetil-amoniumjodid dibenzil-acetala [V], kao i rezultati ispitivanja muskarinskog djelovanja tih acetala. Diskutirana je struktura muskarina, osobito u vezi s novom empiričkom formulom za ovaj spoj, koju su predložili Eugster i Waser[4].

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