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Synthesis of Some Quaternary Bases Related to Tropine. Studies in the Muscarine Series. V*

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In connection with earlier work on muscarine from this laboratory[1] the following compounds have been synthesized: from DL-tropinic acid dimethyl ester (I) 1-methyl-2-hydroxymethyl-5-(2'-hydroxyethylpyrrolidine (II) and 1,1-dimethyl-2-hydroxymethyl-5-(2'-hydroxyethyl)pyrrolidinium iodide (III) were prepared; from 1,2,6-trimethyl-4-hydroxypiperidine and methyl iodide 1,1,2,6-tetramethyl-4-hydroxypiperidinium iodide (IV) was prepared; catalytic hydrogention of 1-methyl-3-hydroxypyridone-(4) gave 1-methyl-3,4-dihydroxypiperidine, from which, by reacting with methyl iodide, 1,1-dimethyl-3,4-dihydroxypiperidinium iodide (V) was obtained.

In the second communication of this series[1] the new formula for muscarine, $C_9H_{20}O_2N^+$, proposed by Eugster and Waser[2] was discussed, and in connection with the completely saturated nature of the compound it was stated that the muscarine molecule must contain a ring; it was also pointed out, with the well-known muscarine : atropine antagonism in mind[3], that this new formula for muscarine had the same carbon and hydrogen content as methylated tropine, and that fission of one ring in the tropine molecule, and addition of one molecule of water should lead to a compound of the same empirical formula as muscarine. It is also known that tropine itself shows an antagonistic action against muscarine on frog hearts[4].

We considered, therefore, to be of interest to synthesize some quaternary bases related to the tropine skeleton, containing pyrrolidine or piperidine nuclei.

DL-Tropinic acid, obtained by vigourous oxidation of tropine[5] was converted to DL-tropinic acid dimethyl ester (I)[6] and reduced with lithium aluminum hydride to 1-methyl-2-hydroxymethyl-5-(2'-hydroxyethyl)pyrrolidine (II). The diol II was then converted, using methyl iodide, to the quaternary salt III.

The quaternary salts IV and V were prepared from the corresponding pyrone derivatives. Reaction of 2,6-dimethylpyrone and meconic acid with methyl amine[8, 10], and subsequent catalytic hydrogenation gave 1,2,6-trimethyl-4-hydroxypiperidine[7] and 1-methyl-3,4-dihydroxypiperidine, respectively. These piperidine derivatives were converted to IV and V.

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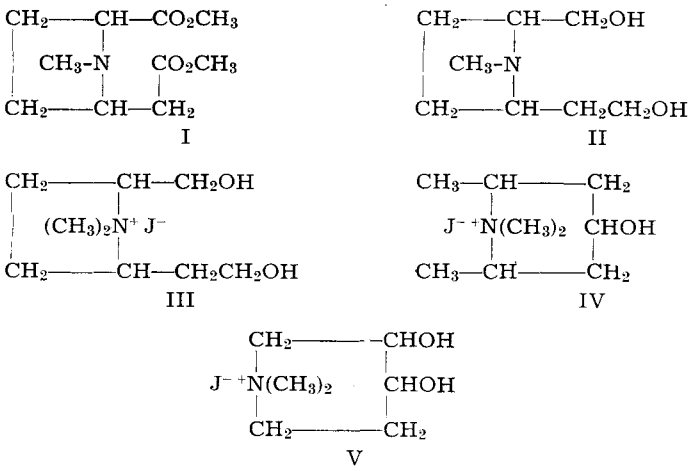

Results of the determination of muscarinic activities of compounds III, IV and V will be published elsewhere.

EXPERIMENTAL

All melting points are uncorrected.

DL-*Tropinic acid dimethyl ester*

The ester was prepared from tropine according to Merling[5] and Willstätter[6].

Reduction of DL-*tropinic acid dimethyl ester*

Into a four-necked reaction flask fitted with reflux condenser, thermometer, dropping funnel and calcium chloride tube, and containing absolute ether (20 ml.) and finely powdered lithium aluminum hydride (1 g.), a solution of DL-tropinic acid dimethyl ester (I, 1.5 g., 0.007 mole) in ether (20 ml.) was added dropwise during one hour, under continuous stirring. The addition of the ester was carried out gradually, the temperature of the reaction mixture remaining about 30—32°. After standing at room temperature for 6 hours, wet ether and water (20 ml.) were added to the reaction mixture. The aqueous layer together with the precipitate was extracted with ether in a liquid/liquid extractor during 24 hours. The combined ethereal extracts were dried (Na_2SO_4) and evaporated to dryness. *1-Methyl-2-hydroxymethyl-5-(2'-hydroxyethyl)-pyrrolidine* remained as a yellow hygroscopic oil, yield 0.7 g. (63%). For analysis the substance was distilled over powdered sodium hydroxide. The pure product was obtained as a colourless oil, b. p. 85—95°/0.0025 mm.

Anal. 8.47 mg. subst.: 18.69 mg. CO_2, 8.05 mg. H_2O
$C_8H_{17}NO_2$ (159.22) calc'd: C 60.34; H 10.76%
found: C 60.22; H 10.64%

1,1-Dimethyl-2-hydroxymethyl-5-(2'-hydroxyethyl)-pyrrolidinium iodide (III)

The quaternary salt was prepared from a solution of 1-methyl-2-hydroxymethyl-5-(2'-hydroxyethyl)-pyrrolidine (II, 100 mg.) in acetone (5 ml.), and methyl iodide (0.5 ml.). The crude *1,1-dimethyl-2-hydroxymethyl-5-(2'-hydroxyethyl)-pyrrolidinium iodide* separated as a viscous yellow oil which after removal of acetone *in vacuo* could be recrystallized from ethanol-ether (5:1). Colourless prisms, m. p. 103—104°.

Anal. 10.43 mg. subst.: 13.83 mg. CO_2, 6.40 mg. H_2O
$C_9H_{20}INO_2$ (301.18) calc'd.: C 35.89; H 6.69%
found: C 36.19; H 6.87%

1,2,6-Trimethylpyridone-(4)

The compound was prepared from 2,6-dimethylpyrone and methyl amine according to Campbell, Ackerman and Campbell[8].

1,2,6-Trimethyl-4-hydroxypiperidine

1,2,6-Trimethyl-4-hydroxypiperidine was first prepared by hydrogenation over platinum black of 1,2,6-trimethylpyridone-(4) in glacial acetic acid[7]. We prepared this compound by reduction of 1,2,6-trimethylpyridone-(4) (10 g.) with sodium (3.8 g.) and ethanol (300 ml.) under the conditions of Bouveault-Blanc reduction. From the reaction mixture *1,2,6-trimethyl-4-hydroxypiperidine* was isolated in the usual manner[9], yield 7.0 g. (67%) of pale yellow oil, b. p. 100—110°/12 mm. (B. p. 215—220° at atmospheric pressure[7]).

1,1,2,6-Tetramethyl-4-hydroxypiperidinium iodide (IV)

Methyl iodide (3 ml.) was added to a solution of 1,2,6-trimethyl-4-hidroxypiperidine (1.1 g.) in acetone (20 ml.). After standing for a few hours the separated quaternary salt was collected, yield 1.7 g. (77%) of *1,1,2,6-tetramethyl-4-hydroxypiperidinium iodide*. After repeated recrystallization from absolute ethanol, white prisms of the pure compound showed m. p. 282°.

Anal. 9.40 mg. subst.: 13.07 mg. CO_2, 5.89 mg. H_2O
$C_9H_{20}INO$ (285.18) calc'd: C 37.90; H 7.06%
found: C 37.95; H 7.01%

1-Methyl-3-hydroxypyridone-(4)

The compound was obtained from methyl amine and meconic acid according to Wibaut and Kleipool[10].

1-Methyl-3,4-dihydroxypiperidine

1-Methyl-3-hydroxypyridone-(4) (10 g., 0.8 mole) in ethanol (70 ml.) was hydrogenated in the presence of Raney-nickel catalyst (obtained from 10 g. of nickel-aluminum alloy, nickel content 40% prepared according to Paul and Hilly[11]) at 160° and 170 atm. pressure during 3 hours. The catalyst was removed by decanting off the reaction mixture through a filter. The filtrate was evaporated to dryness and extracted with acetone. The crude *1-methyl-3,4-dihydroxypiperidine* was obtained by evaporation of the solvent. Yield 6.5 g. (63%). The analytical sample was obtained by distillation of the crude compound at 90—100°/0.03 mm.; a colourless oil was obtained.

Anal. 10.03 mg. subst.: 20.06 mg. CO_2, 8.98 mg. H_2O
$C_6H_{13}NO_2$ (131.17) calc'd.: C 54.94; H 9.99%
found: C 54.57; H 10.02%

1,1-Dimethyl-3,4-dihydroxypiperidinium iodide (V)

To a solution of the crude 1-methyl-3,4-dihydroxypiperidine (2 g.) in acetone (30 ml.), methyl iodide (5 ml.) was added. After standing at room temperature for 24 hours, *1,1-dimethyl-3,4-dihydroxypiperidinium iodide* separated from the reaction mixture in theoretical yield, m. p. 254°. After repeated recrystallization from absolute ethanol, colourless prisms of the pure compound, m. p. 260° were obtained.

Anal. 8.95 mg. subst.: 10.21 mg. CO_2, 4.78 mg. H_2O
$C_7H_{16}INO_2$ (273.13) calc'd.: C 30.78; H 5.90%
found: C 31.11; H 5.97%

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IZVOD

Sinteza nekih kvaternih baza srodnih tropinu. Istraživanja o muskarinu. V

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U vezi s dosadanjim radovima o muskarinu[1], sintetizirani su ovi spojevi: iz dimetilnog estera DL-tropinske kiseline (I) priređeni su 1-metil-2-oksimetil-5-(2'-oksietil)pirolidin (II) i 1,1-dimetil-2-oksimetil-5-(2'-oksietil)pirolidinium jodid (III); iz 1,2,6-trimetil-4-oksipiperidina i metiljodida priređen je 1,1,2,6-tetrametil-4-oksipiperidinium jodid (IV); katalitičkim hidriranjem 1-metil-3-oksipiridona-(4) dobiven je 1-metil-3,4-dioksipiperidin, iz kojega je, reagiranjem s metiljodidom, dobiven 1,1-dimetil-3,4-dioksipiperidinium jodid (V).

Rezultati biološkog ispitivanja tih spojeva u pogledu muskarinskoga djelovanja bit će objavljeni na drugome mjestu.

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