MUSCARINE RESEARCH

I. SYNTHESIS OF A MIXTURE OF RACEMATES OF MUSCARINE AND ITS STEREOISOMERS

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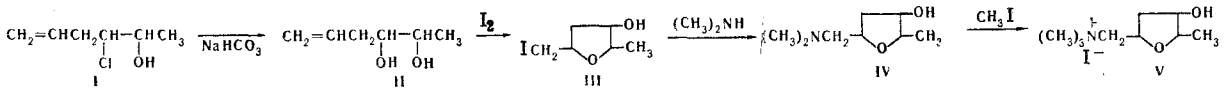
A mixture of racemates of muscarine and its stereisomers was synthesized by the reaction of 1-hexene-4,5-diol with iodine and subsequent conversion of the resulting 5-iodomethyl-3-hydroxy-2-methyltetrahydrofuran to the corresponding nor-base and methiodide. The presence of all the stereoisomers of muscarine was demonstrated by means of thin-layer chromatography and the IR spectrum. The sulfonium analog was also synthesized.

The ability of muscarine to selectively stimulate cholinoreceptors makes it a valuable preparation for pharmacological and physiological analysis [1]. Despite the large number of studies devoted to muscarine, from a preparative point of view, this alkaloid is still difficult to obtain, since almost all of the known methods for its synthesis involve many steps and give low yields [2-4].

Considering these circumstances, we felt it was necessary to propose a new preparative method for the preparation of muscarine from 4-chloro-1-hexen-5-ol (I) [5], which to a certain extent is free of the disadvantages of the previously described methods and can be used for the synthesis of other muscarine-like compounds. The synthesis was accomplished as follows:



The high yields in all stages of the synthesis make it possible to obtain a mixture of muscarine stereoisomers in an overall yield of ~50%. Moreover, the use of the iodination of II made it possible to combine the formation of the tetrahydrofuran ring and the iodomethyl group in one step. It is known that the existence of four stereoisomers—muscarine, allomuscarine, epimuscarine, and epiallomuscarine—is possible for (5-methyl-4-hydroxytetrahydrofurfuryl)trimethylammonium iodide (V). According to the synthetic scheme, one should have expected the formation of all of the stereoisomers. Diol II, obtained by the saponification of I, is apparently a mixture of the threo and erythro forms. The ring-forming reaction also is apparently not stereospecific. The broad range of the boilding point of the synthesized nor-base (IV) and the melting point of methiodide V, which differs from the melting points of all of the stereoisomers, may serve as a confirmation of these assumptions.

The IR spectrum of 2-methyl-3-hydroxy-5-dimethylaminomethyltetrahydrofuran (IV) contains bands that characterize the presence of intermolecular (3415 cm^{-1}) and intramolecular (3230 cm^{-1}) hydrogen bonds; this is due to the cis and trans orientations of the hydroxyl and dimethylaminomethyl groups.

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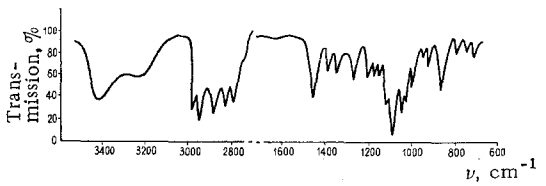

Fig. 1. IR spectrum of a mixture of stereoisomers of the nor-base of muscarine.

A. S. Serafimovich Volgograd State Pedagogical Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 579-581, May, 1970. Original article submitted July 23, 1968.

Thin-layer chromatography of V on KSK silica gel confirms the presence of all of the stereoisomers:

Stereoisomer	R_f*
Epiallonormuscarine	0.29 (0.24)
Normuscarine	0.36 (0.33)
Allonormuscarine	0.43 (0.43)
Epinormuscarine	0.58 (0.57)

The sulfonium analog of muscarine was obtained by means of the method described in [7] from 5-iodomethyl-2-methyl-3-hydroxytetrahydrofuran (III), thiourea, and methyl iodide.

EXPERIMENTAL

1-Hexane-4,5-diol (II). A mixture of 19.8 g (0.15 mole) of I and 50 g of potassium carbonate in 200 ml of water was refluxed for 15 h. The aqueous solution was saturated with sodium chloride and extracted thoroughly with ether. The ether extract was dried over anhydrous magnesium sulfate, the ether was removed, and the residue was vacuum distilled to give 14.8 g (85%) of II with bp 95-99 deg (19 mm), n_D^{20} 1.4593, and d_4^{20} 0.9824. Found: C 62.6; H 10.7%; MR_D 32.3. $C_6H_{12}O_2$. Calculated: C 62.1; H 10.4%; MR_D 32.5.

2-Methyl-3-hydroxy-5-iodomethyltetrahydrofuran (III). A solution of 29 g (0.25 mole) of II and 63.5 g (0.25 mole) of iodine in a mixture of 400 ml of methanol and 1200 ml of water was allowed to stand in the dark for a week. The mixture was worked up as in [5] to give 55.6 g (92%) of III with bp 100-105 deg (0.01 mm), n_D^{20} 1.5510, and d_4^{20} 1.7779. Found: C 30.1; H 4.7; I 52.1%; MR_D 43.4. $C_6H_{11}IO_2$. Calculated: C 29.8; H 4.6; I 52.5%; MR_D 43.6.

2-Methyl-3-hydroxy-5-dimethylaminomethyltetrahydrofuran (IV). A mixture of 49.2 g (0.22 mole) of III and 30.6 g (0.68 mole) of dimethylamine was heated in a sealed ampul at 50-60 deg for 4 h. The excess dimethylamine was removed in vacuo, and the residue was dissolved in dilute hydrochloric acid. The acid solution was washed with ether, and the aqueous solution was cooled and neutralized with concentrated potassium hydroxide solution, it was then saturated with solid potassium hydroxide and extracted with ether. The ether extract was dried over anhydrous potassium carbonate. The ether was removed, and the residue was vacuum distilled to give 96 g (75%) of IV with bp 60-90 deg (0.003 mm), n_D^{20} 1.4620, and d_4^{20} 0.9950. Found: C 59.8; H 10.8; N 8.6%; MR_D 43.9. $C_8H_{17}NO_2$. Calculated: C 60.4; H 10.7; N 8.8%; MR_D 44.0. IR spectrum (cm^{-1}): 1112, 1085, 1034, 1016, 915, 856, 2828, 2780, 2740, 3415, 3230.

Methiodide of IV (V). This compound was obtained as a white, crystalline substance with mp 121-123 deg (from isopropyl alcohol). Found: I 42.1%. $C_9H_{20}INO_2$. Calculated: I 42.2%.

2-Methyl-3-hydroxy-5-methylthiomethyltetrahydrofuran (VI). This compound [2 g (60%)], with bp 111-116 deg (2 mm), n_D^{20} 1.5025, d_4^{20} 1.1118, and a characteristic mushroom-like odor, was obtained, as in [7], from 4.8 g (0.02 mole) of III, 1.5 g (0.02 mole) of thiourea, 4.25 g (0.03 mole) of methyl iodide, and 4 g (0.1 mole) of sodium hydroxide. Found: C 51.9; H 8.9; S 19.6%; MR_D 43.2. $C_7H_{14}SO_2$. Calculated: C 51.8; H 8.6; S 20.0%; MR_D 43.4. IR spectrum (cm^{-1}): 873, 916, 1074, 1171, 620, 3376. The methiodide (90%) was obtained by the usual method as a viscous syrup.

Thin-layer chromatography was carried out on KSK silica gel using an acetone-chloroform-concentrated ammonium hydroxide system (70:25:5, by weight). The Dragendorf reagent was used to develop the chromatograms.

The IR spectra of films of the compounds were recorded with an IKS-14 spectrometer.

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*The data from [6] are given in parentheses.