The Synthesis of *dl*-Muscarine and *dl*-Allomuscarine[1,2]

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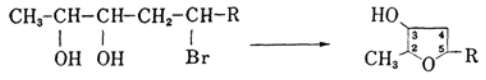
Since the structure and stereochemistry of muscarine (I) have been determined by X-ray analysis,[3] extensive studies of the synthesis of muscarine and its stereoisomers have been made by European workers.[4] However, none of them have completed the synthesis in a stereospecific manner. In the present paper, the authors would like to describe a new synthetic method in which hydroxyl and methyl groups are introduced in trans orientation by a stereospecific method.

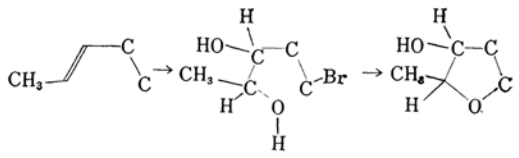
The principle underlying the present synthesis is as follows:



(A) (B)

Fig. 1

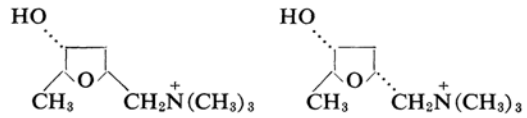
In the cyclization of A to form B (Fig. 1), the relative configuration of the methyl group at C_2 and of the hydroxyl group at C_3 in the tetrahydrofurane derivative, B, is determined by the stereochemistry of its precursors, the butane derivatives A. As is shown in Fig. 2,



(C) (D) (E)

Fig. 2

a trans compound, E, should be produced from an erythro compound, D, which, in turn, should be obtained by the dihydroxylation of a trans olefinic compound, C, with peracid. From the above considerations, ethyl crotylmalonate (III) was used as the starting material.



(I) (II)

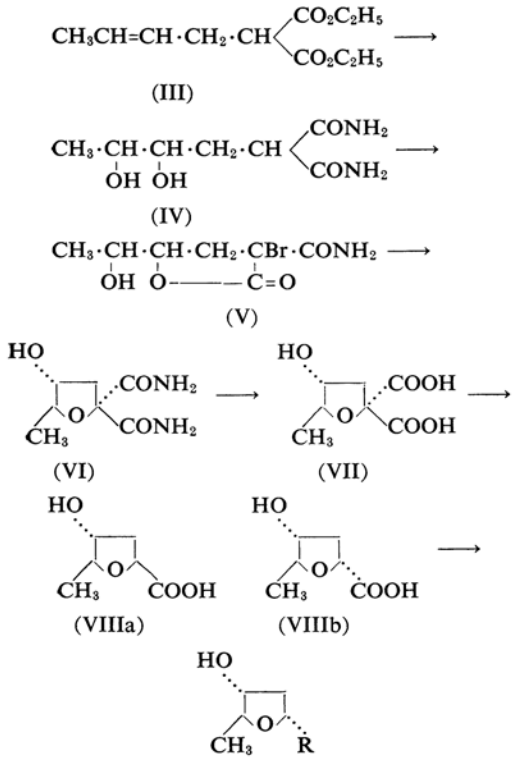
The oxidation of III with performic acid and the subsequent treatment of the product with alcoholic ammonia gave the dihydroxydiamide IV, m. p. 164—165.5°C, which is expected to be an erythro compound. On treatment with bromine in acetic acid, IV was converted to the bromolactone V, m. p. 110—111°C. Although two stereoisomers are possible for V, the relative configuration of methyl and hydroxyl groups in V should be independent of the stereochemistry of the α carbon atom of the bromolactone V and remain unchanged during the recyclization of V to VI. Therefore, no attempt was made to examine the configuration of the α carbon atom of V.

1) Preliminary communication: T. Matsumoto and H. Maekawa, *Angew. Chem.*, **70**, 507 (1958).

2) Nomenclature of muscarine isomers was assigned according to the convention of Hardegger, Eugster and Kögl. Cf. Ref. 4a.

3) F. Jellink, *Acta Cryst.*, **10**, 277 (1957); F. Kögl, C. A. Salemink, H. Schouten and F. Jellink, *Rec. trav. chim.*, **76**, 109 (1957).

4) a) H. Corrodi, E. Hardegger and F. Kögl, *Helv. Chim. Acta*, **40**, 2454 (1957); b) E. Hardegger, F. Lohse, ibid., **40**, 2383 (1957); c) C. H. Eugster, F. Häfliger, R. Denss and E. Girod, ibid., **41**, 205 (1958).



(III)

(IV)

(V)

(VI) (VII)

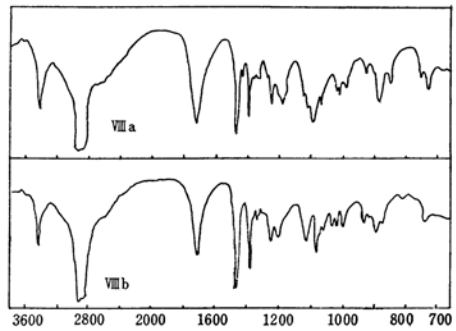
(VIIIa) (VIIIb)

IXa R= -$COOCH_3$
IXb R=···$COOCH_3$
Xa R= -$CON(CH_3)_2$
Xb R=···$CON(CH_3)_2$
XIa R= -$CH_2N(CH_3)_2$
XIb R=···$CH_2N(CH_3)_2$
XIIa R= -$CH_2N^+(CH_3)_3I^-$
XIIb R=···$CH_2N^+(CH_3)_3I^-$
XIIIa R= -$CH_2N^+(CH_3)_3(C_6H_5)_4B^-$
XIIIb R-···$CH_2N^+(CH_3)_3(C_6H_5)_4B^-$
XIVa R= -$CH_2N^+(CH_3)_3Cl^-$
XIVb R=···$CH_2N^+(CH_3)_3Cl^-$

Fig. 3

The ammonolysis of V in alcoholic ammonia proceeded smoothly to give the tetrahydrofurandiamide VI, m. p. 204—205°C. The hydrolysis of VI was carried out in a 10% sodium hydroxide solution to afford the acid VII, which was purified through the lead salt or by ion exchange chromatography.

The acid VII, m. p. 170—176°C, was then decarboxylated by heating it 15 min. at 175—180°C in a sealed tube to give an amorphous solid. The careful recrystallization of the solid from a large volume of dichloroethane gave a monocarboxylic acid VIIIa as needles, m. p. 145°C, after the concentration of the filtrate, an isomeric monocarboxylic acid VIIIb, m. p. 109—111°C, was obtained as granular crystals from the mother liquor. Since these two acids have the same molecular formula, $C_6H_{10}O_4$, and show similar infrared spectra (Fig. 4, VIIIa and VIIIb), they are clearly the expected two stereoisomers, VIIIa and VIIIb. However, no reliable evidence of their stereochemistry was obtained at this stage.



Wave number, cm^{-1}

Fig. 4. Infrared absorption spectra of VIIIa and VIIIb (Nujol).

The esterification of these two acids with diazomethane afforded extremely hygroscopic methyl esters, IXa and IXb respectively. The NMR spectra of these esters were different from each other, but no decisive information about the stereochemistry could be derived therefrom. On the other hand, the inspection of the infrared spectra of IXa and IXb in a high dilute condition showed that IXa has an absorption band at 3617 cm^{-1} (0.0024 mol. in carbon tetrachloride) due to a free hydroxyl group, while IXb has a rather broad absorption band at 3480 cm^{-1} (0.0024 mol. in carbon tetrachloride) attributable to an intramolecularly hydrogen-bonded hydroxyl group, as is shown in Fig. 5. Therefore, it may be concluded that

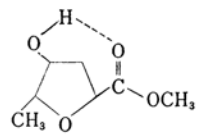


Fig. 5

the 145°C and 111°C compounds should be represented by VIIIa and VIIIb respectively.

By means of dimethylamine, IXa and IXb were converted to dimethylamides, Xa and Xb. In this reaction, the ester IXb, in which hydroxyl and methyl ester groups have the cis orientation, was converted to Xb about four times faster than the IXa isomer. At first, the slow reaction of IXa was attributed to the steric hindrance exerted by the bulky methyl group on the same side as the ester group. However, since the same phenomenon was also

observed in dimethyl ester series,[5] it is more reasonable to ascribe the acceleration to the neighboring participation of the hydroxyl group.[6,7]

The reduction of the dimethylamides Xa and Xb with lithium aluminum hydride gave normuscarine (XIa) and allonormuscarine (XIb). Finally *dl*-muscarine iodide (XIIa) and *dl*-allomuscarine iodide (XIIb) were prepared by the treatment of the noramines XIa and XIb with methyl iodide. Further, *dl*-muscarine chloride (XIVa) (m. p. 148—149°C) and *dl*-allomuscarine chloride (XIVb) (m. p. 143—144°C) were derived from the tetraphenylboronates (XIIIa and XIIIb) of the quarternery amines, and the chloride XIVa was shown to be identical with a sample prepared from natural material in infrared spectrum.[4c] *dl*-Muscarine chloride XIVa showed a marked physiological activity in the isolated heart of a frog, while that of *dl*-allomuscarine chloride was about one-half physiologically active as *dl*-muscarine.[1]

Experimental

Ethyl Crotylmalonate (III).—This was prepared by the method of Linstead.[8]

3, 4-Dihydroxypentane-1, 1-dicarbonamide (IV).—To a solution of 32 g. of III in 135 ml. of formic acid (80% solution), 73 g. of hydrogen peroxide (28% solution) was added slowly under ice-cooling. The mixture was stirred for 20 min. and then allowed to stand for 12 hr. at room temperature. After the solvent had been removed, the residue was mixed with 100 ml. of dry benzene and the solvent was slowly removed under reduced pressure. The residue was dissolved in 50 ml. of absolute ethanol, and the solution was added to 500 ml. of an ethanol solution saturated with ammonia at 0°C. The mixture was then swirled gently and allowed to stand overnight at room temperature. The resultant precipitates were recrystallized from ethanol (95%) to give 20 g. of IV, m. p. 164—165.5°C. Infrared spectrum: ν_{max}^{Nujol} 3430, 3420, 1665, 1040 cm^{-1}.

Found: C, 44.55; H, 7.43; N, 14.59. Calcd. for $C_7H_{14}O_4N_2$: C, 44.20; H, 7.42; N, 14.73%.

2-Bromo-2-carbamoyl-3, 4-dihydroxypentanoic Acid Lactone (1→4).—A solution of 20 g. of diamide (IV) in 100 ml. of glacial acetic acid was refluxed gently on an oil bath, and then 17 g. of bromine in 10 ml. of glacial acetic acid was added drop by drop. After the mixture had been cooled, the separated ammonium bromide was removed and the filtrate was concentrated under reduced pressure. The oily residue was washed several times with a small amount of benzene and allowed to stand overnight, thus giving an amorphous solid which was recrystallized from chloroform to give 25 g. of V, m. p. 110—111°C. Infrared spectrum: ν_{max}^{Nujol} 3430, 1788, 1758, 1683, 1599, 1206, 1003 cm^{-1}.

Found: C, 33.45; H, 3.86; N, 5.95. Calcd. for $C_7H_{10}O_4NBr$: C, 33.35; H, 4.00; N, 5.95%.

2-Methyl-3-hydroxy-5, 5-tetrahydrofurandicarbonamide (VI).—To a solution of 500 ml. of ethanol saturated with ammonia at 0°C, 25 g. of V in 50 ml. of ethanol was added; the mixture was then allowed to stand for 12 hr. at room temperature. After the solution had been cooled, the precipitated crystals were collected by means of a funnel and recrystallized from ethanol (95%) to give 16 g. of VI, m. p. 204—205°C. Infrared spectrum: ν_{max}^{Nujol} 3380, 3200, 1680, 1585, 1140, 1009 cm^{-1}.

Found: C, 45.05; H, 6.60; N, 14.87. Calcd. for $C_7H_{12}O_4N_2$: C, 44.68; H, 6.43; N, 14.88%.

2-Methyl-3-hydroxy-5, 5-tetrahydrofurandicarboxylic Acid (VII).—In 80 ml. of an aqueous solution (10%) of sodium hydroxide, 10 g. of VI was hydrolyzed on a water bath for 4 hr. After the reaction mixture had been cooled, the solution was acidified with acetic acid added to 25 g. of lead acetate dissolved in a small amount of water, and then allowed to stand for 10 hr. at −5°C. The resultant precipitates were collected and washed with a small amount of water. After the hydrogen sulfide was led into the suspension of the lead salts, the filtrate was concentrated to leave plates which were recrystallized from glacial acetic acid to give 7 g. of VII. Another purification was carried out by eluting the reaction mixture through an ion exchange resin IR-120 column. The removal of water from the eluted solution gave pure acid (VII), m. p. 175—176°C. Infrared spectrum: ν_{max}^{Nujol} 3385, 2650, 1702, 1202, 1087 cm^{-1}.

Found: C, 44.39; H, 5.33. Calcd. for $C_7H_{10}O_6$: C, 44.21; H, 5.30%.

2-Methyl-3-hydroxy-5-tetrahydrofurancarboxylic Acids (VIIIa) and (VIIIb).—A solution of 5 g. of VII in 50 ml. of water was heated at 175—180°C for 15 min. in a sealed tube, and then the solution was concentrated to leave an amorphous solid which was recrystallized from 100 ml. of ethylene dichloride to give needles of VIIIa, (m. p. 143—145°C, yield, 1.0 g.

Found: C, 49.12; H, 6.81. Calcd. for $C_6H_{10}O_4$: C, 48.97; H, 6.90%.

The further concentration of the solution yielded VIIIb as granules, m. p. 109—111°C, yield 0.9 g.

Found: C, 49.16; H, 7.00. Calcd. for $C_6H_{10}O_4$: C, 48.97; H, 6.90%.

Methyl 2-Methyl-3-hydroxy-5-tetrahydrofurancarboxylate (IXa).—One gram of VIIIa in 10 ml. of methanol was added to 36 ml. of an ethereal solution of diazomethane (ca. 4%), and then the mixture was allowed to stand for 2 hr. at room temperature. The solution was concentrated to leave a residue which was distilled under reduced pressure to yield 1.0 g. of IXa (hygroscopic; b. p. 113—115°C/3.5 mmHg). The infrared spectrum of IXa in carbon tetrachloride (0.0021 mol.) showed an absorption

5) A. Ichihara, T. Yamanaka and T. Matsumoto, This Bulletin, **38** 1165 (1965).

6) a) H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, **1957**, 1965; b) S. M. Kupchan, P. Slade, R. J. Youg and G. W. A. Milne, *Tetrahedron*, **18**, 499 (1962); c) T. C. Bruice and T. H. Fife, *J. Am. Chem. Soc.*, **84**, 1973 (1962).

7) The kinetic study will be published in another paper. T. Yamanaka, A. Ichihara, K. Tanabe and T. Matsumoto, in preparation.

8) E. N. Eccott and R. P. Linstead, *J. Chem. Soc.*, **1929**, 2153.

band at 3717 cm^{-1} due to a free secondary hydroxyl group; NMR spectrum: τ 8.80d (CH_3), 7.8q (CH_2), 6.27s (CO_2CH_3), 6.02s (OH), 5.48t (proton α to the ester group).

Methyl 2-Methyl-3-hydroxy-5-tetrahydrofurancarboxylate (IXb).—This was prepared in the same way as the cis acid VIIIb described above. The reaction of 0.9 g. of VIIIa with diazomethane gave 0.8 g. of ester (IXb), b. p. 109—111°C/3.5mmHg. IXb showed absorption bands at 3617 cm^{-1} (free OH) and 3480 cm^{-1} (broad, bonded OH) in carbon tetrachloride (0.0024 mol.); NMR spectrum: τ 8.82d (CH_3), 7.25—8.22 m (CH_2), 6.25s ($-CO_2CH_3$), 6.10s (OH), 5.53q (proton α to the ester group).

2-Methyl-3-hydroxy-5-tetrahydrofurancarboxylic Acid Dimethylamide (Xa).—One gram of IXa dissolved in 10 ml. of dry benzene was added to 50 ml. of a benzene solution of dimethylamine (ca. 30%) and allowed to stand for 25 hr. at 100°C in a sealed tube. The solvent was then evaporated to leave a residue which was washed with a small amount of ether to give Xa. Infrared spectrum: ν_{max}^{film} 3370, 1638, 1079 cm^{-1}.

2-Methyl-3-hydroxy-5-tetrahydrofuran Carboxylic Acid Dimethylamide (Xb).—To 40 ml. of a benzene solution of dimethylamine was added 0.8 g. of IXb in 10 ml. of benzene. The mixture was heated for 6 hr. at 100°C in a sealed tube. After the evaporation of the solvent, the resulting residue was washed with ether to give 0.7 g. of Xb. Infrared spectrum: ν_{max}^{film} 3360, 1640, 1071 cm^{-1}.

***dl*-Normuscarine (XIa).**—A solution of Xa (0.8 g.) in 5 ml. of tetrahydrofurane was added drop by drop to a solution of lithium aluminum hydride (1 g.) in 80 ml. of tetrahydrofurane and refluxed for 6 hr. on a water bath. After the excess lithium aluminum hydride had been decomposed by adding ethyl acetate, the reaction mixture was concentrated and the residue was dissolved in an aqueous solution of sodium hydroxide (20%). After several extractions with ether, the combined solution was dried over anhydrous potassium carbonate and evaporated to give Xa, b. p. 88—92°C/4 mmHg. Infrared spectrum: $\nu_{max}^{CCl_4}$ 3390, 1456, 1085, 1035 cm^{-1}. Reineckate of XIa: recrystallized from ethanol-water; m. p. 161—162°C (decomp.).

Found: C, 30.07; H, 5.23; N, 20.49. Calcd. for $C_{12}H_{24}O_2N_7S_4Cr$: C, 30.11; H, 5.54; N, 20.49%.

***dl*-Allonormuscarine (XIb).**—XIb was prepared in the same manner as XIa from 0.7 g. of Xb, b. p. 65—66°C/4 mmHg. Yield, 0.5 g. Infrared spectrum: $\nu_{max}^{CCl_4}$ 3200, 1460, 1158, 1105, 1063, 1033, 1015, 910, 858 cm^{-1}. Reineckate of XIb: recrystallized from ethanol-water, m. p. 164—165°C (decomp.).

Found: C, 29.99; H, 5.51; N, 19.70. Calcd. for $C_{12}H_{24}O_2N_7S_4Cr$: C, 30.11; H, 5.54; N, 20.49%.

***dl*-Muscarine Iodide (XIIa).**—To 0.1 g. of XIa in 1 ml. of ethanol, 0.3 g. of methyl iodide was added; the resultant solution was allowed to stand for 1 hr. at room temperature. After the excess methyl iodide and the solvent had been evaporated an oily residue was obtained. The rubbing of the residue with a glass rod gave crystals which were recrystallized from ether-isopropanol to yield 50 mg. of *dl*-muscarine iodide (XIIa), m. p. 116—118°C (the lit.[4c] has reported an m. p. of 107—108°C). Infrared spectrum: ν_{max}^{KBr} 3400, 1085, 1001, 970, 920 cm^{-1}.

Found: C, 36.14; H, 6.74; N, 4.64. Calcd. for $C_9H_{20}O_2NI$: C, 35.89; H, 6.69; N, 4.69%.

***dl*-Allomuscarine Iodide (XIIb.)**—By treating 0.3g. of XIb the same as XIa we obtained 0.2 g. of *dl*-allomuscarine iodide (XIIb), m. p. 131—132°C (Ref. 9 reported an m. p. of 131—132°C). Infrared spectrum: ν_{max}^{KBr} 3400, 1095, 1062, 995, 964, 910 cm^{-1}.

Found: C, 36.01; H, 6.66; N, 4.47. Calcd. for $C_9H_{20}O_2NI$: C, 35.89; H, 6.69; N, 4.65%.

***dl*-Muscarine Tetraphenylboronate (XIIIa).**—Recrystallized from acetone-ethanol; m. p. 174—175°C (lit.[4c] 173—174°C).

Found: N, 3.11. Calcd. for $C_{33}H_{40}O_2NB$: N, 2.84%.

***dl*-Allomuscarine Tetraphenylboronate (XIIIb).**—Recrystallized from acetone-ethanol; m. p. 176—177°C (lit.[9] 175—176°C).

Found: N, 3.04. Calcd. for $C_{33}H_{40}O_2NB$: N, 2.84%.

***dl*-Muscarine Chloride (XIVa).**—Upon treatment with cesium chloride, 0.3 g. of XIIIa was converted to muscarine chloride which was then recrystallized by ether-isopropanol; m. p. 148—149°C (lit.[4c] m. p. 147—148°C). The infrared spectrum was identical with those of a natural sample and of a synthetic specimen of Eugster. Infrared spectrum: ν_{max}^{KBr} 3250, 1485, 1105, 1075, 1056, 918 cm^{-1}.

Found: C, 51.29; H, 9.68; N, 6.72. Calcd. for $C_9H_{20}O_2NCl$: C, 51.54; H, 9.62; N, 6.68%.

***dl*-Allomuscarine Chloride (XIVb).**—XIIIa (0.4 g.) was converted to allomuscarine chloride. The recrystallization of the product from ether-isopropanol gave 0.2 g. of XIVb, m. p. 152.5—153.5°C (lit.[9] 153—154°C). Infrared spectrum: ν_{max}^{Nujol} 3300, 1090, 1065, 977, 959, 928 cm^{-1}.

Found: C, 51.33; H, 9.60; N, 6.47. Calcd. for $C_9H_{20}O_2NCl$: C, 51.54; H, 9.62; N, 6.68%.

Summary

The synthesis of *dl*-muscarine (I) and *dl*-allomuscarine (II) starting from ethyl crotylmalonate has been described. Trans oriented methyl and hydroxyl groups in these compounds have been introduced stereospecifically into the tetrahydrofurane ring.

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9) C. H. Eugster, F. Häflinger, R. Denss and E. Girod, *Helv. Chim. Acta*, **41**, 583 (1958).