The Synthesis of *cis*- and *trans*-Demethylmuscarines[1]

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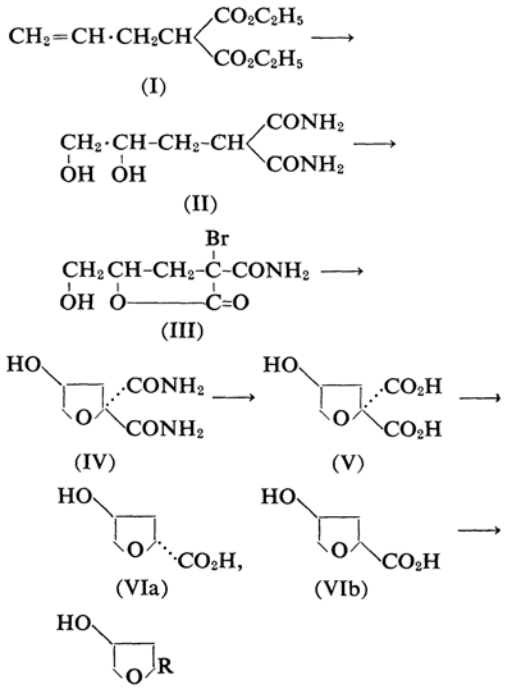
In previous papers[2,3] we reported the synthesis and pharmacological activities of *dl*-muscarine and its stereoisomers. Since the activities were found to depend sensitively upon the structure, it appeared of interest to synthesize *dl*-demethylmuscarines and investigate their physiological activities.

The route previously described for the synthesis of *dl*-muscarine and *dl*-allomuscarine was applied to the preparation of *dl*-demethylmuscarine, starting with ethyl allylmalonate (I).



VIIa R=···CO_2CH_3
VIIb R=-CO_2CH_3
VIIIa R=···$CON(CH_3)_2$
VIIIb R=-$CON(CH_3)_2$
IXa R=···$CH_2N(CH_3)_2$
IXb R=-$CH_2N(CH_3)_2$
Xa R=···$CH_2N^+(CH_3)_3I^-$
Xb R=-$CH_2N^+(CH_3)_3I^-$

Fig. 1

The oxidation of ethyl allylmalonate (I) with performic acid gave an oily product which was without purification, allowed to react with ammonia in ethanol to form dihydroxydiamide II. Bromolactonamide III, prepared by the reaction of dihydroxydiamide with bromine,[4] was then subjected to ammonolysis in order to give tetrahydrofurandicarboxylic acid diamide IV, which was subsequently hydrolyzed to dicarboxylic acid V.

The decarboxylation of this acid, V, by heating it at 150—160°C in a sealed tube gave an amorphous solid, from which two acids were isolated in the ratio 1 : 1; one of these acids was crystallized from ethyl acetate as rhombic crystals, m. p. 127—129°C, while the other acid was obtained as a granular crystals, m. p. 142—143°C, by further concentration of the filtrate. These two compounds have the same molecular formula, $C_5H_8O_4$, and similar absorption bands in infrared spectra (Fig, 2, VIa and VIb). Therefore, these are the

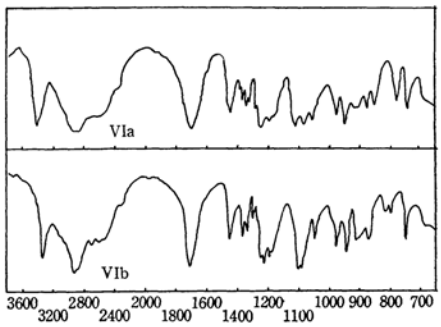


Fig. 2. Infrared absorption spectra of VIa and VIb (Nujol).

expected stereoisomers VIa and VIb. The treatment of these acids, VIa and VIb, with ethereal diazomethane gave the corresponding methyl esters, VIIa and VIIb respectively. The infrared spectrum of VIIb exhibited a broad absorption band at 3482 cm^{-1} (0.077 mol. in carbon tetrachloride) attributable to the presence of an intramolecular hydrogen bond between the carbonyl group and the secondary hydroxyl group. On the other hand, the compound VIIa showed two absorption bands at

1) Short communication: T. Matsumoto and A. Ichihara, This Bulletin, 33, 1015 (1960).
2) a) T. Matsumoto and H. Maekawa, *Angew. Chem.*, 70, 507 (1958); b) H. Maekawa, A. Ichihara and T. Matsumoto, This Bulletin, 38, 1161 (1965).
3) T. Matsumoto and A. Ichihara, *Biochem. Z.*, 331, 589 (1959).
4) W. Traube, *Ber.*, 37, 4540 (1904).

3620 cm^{-1} (sharp, free OH) and 3485 cm^{-1} (broad, bonded OH, 0.068 mol. in carbon tetrachloride); the intensity of the band at 3620 cm^{-1} relative to the band at 3485 cm^{-1} is increased with further dilution. Therefore, VIa is a trans compound and VIb is cis compound. The tetrahydrofurancarboxylic acid esters, VIIa and VIIb, were then converted with dimethylamine to tetrahydrofurancarboxylic acid dimethylamides, VIIIa and VIIIb. In these reactions an interesting difference in the rate of reaction was observed; the cis ester was converted to VIIIb about three or four times faster than the trans isomer. The effect of acceleration in cis-ester should be ascribed to the presence of an hydroxyl group near the ester group.[5] A similar facilitation by hydroxyl groups has been reported in other compounds.[6]

The reduction of the dimethylamides VIIIa and VIIIb with lithium aluminum hydride gave the dimethylamines IXa and IXb respectively. A stereoisomeric mixture of cis and trans amines, IXa and IXb, resulting from the sequence of reactions VIa and VIb to IXa and IXb, is also easily separable by chromatography on alumina.

Since the infrared spectrum of the cis isomer IXb also exhibits a broad absorption band at 3194 cm^{-1} (0.0072 mol. in carbon tetrachloride) ascribed to the intramolecular hydrogen bond between dimethylamino and hydroxyl groups, it has been ascertained that the reactions in the sequence VI to IX proceeded without any configurational changes.

Finally, by means of methyl iodide, the IXa and IXb amines were converted to *trans-dl*-demethylmuscarine (Xa) (m. p. 119—120°C) and *cis-dl*-demethylmuscarine (Xb) (m. p. 117—118°C) respectively, whose infrared spectra were identical with those of Eugster's specimens.[7] In physiological activity for an isolated heart of a frog, *trans*-demethylmuscarine is slightly stronger than the cis-isomer, but rather weaker than *dl*-muscarine itself.

Experimental.[8]

Ethyl Allylmalonate (I).—This was prepared by the procedure of Linstead.[9]

3, 4-Dihydroxybutane-1, 1-dicarbonamide (II). — To a solution of 120 g. of ethyl allylmalonate in 540 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 allowed to stand for 12 hr. at room temperature. After removal of the solvent, the residue was mixed with 200 ml. of dry benzene, and the benzene was slowly removed under reduced pressure. The residue was then added to 2 l. of ethanol saturated with ammonia at 0°C, and the mixture was swirled gently and allowed to stand overnight at room temperature. The precipitated crystals were recrystallized from ethanol (95%) to give 72 g. of II, m. p. 157—158°C; infrared spectrum: ν_{max}^{Nujol} 3330, 1765, 1664, 1593, 1178, 1070 cm^{-1}.

Found: C, 40.76; H, 6.84; N, 15.66. Calcd. for $C_{16}H_{12}O_4N_2$: C, 40.90; H, 6.78; N, 15.90%.

The compounds III, IV and V were prepared by the method of Traube.[4] 3-Hydroxy-5, 5-tetrahydrofurandicarboxylic acid (V) recrystallized from glacial acetic acid showed a m. p. of 138—140°C.

Found: C, 41.13; H, 4.67. Calcd. for $C_6H_8O_5$: C, 40.91; H, 4.58%. (Ref. 3 described an m. p. of the hydrate but not of the anhydrous compound).

***trans*- and *cis*-4-Hydroxy-2-tetrahydrofurancarboxylic Acid (VIa and VIb).** — A solution of 10 g. of tetrahydrofurandicarboxylic acid V in 100 ml. of water was heated for 1 hr. in a sealed tube at 150—160°C. The removal of water under reduced pressure left a residue which was solidified by rubbing it with glass rod to give 6.8 g. of an amorphous solid, m. p. 108—111°C. The solid was carefully recrystallized from 50 ml. of ethyl acetate to afford 2.6 g. of VIb as rhombic crystals, m. p. 127—129°C, infrared spectrum: Fig. 2, VIa.

Found: C, 45.59; H, 5.99. Calcd. for $C_5H_8O_4$: C, 45.45; H, 6.10%.

The trans acid VIa, m. p. 142—143°C, was obtained as granular crystals by concentrating the above filtrate. Infrared spectrum: Fig. 2, VIb.

Found: C, 45.50; H, 6.10. Calcd. for $C_5H_8O_4$: C, 45.45; H, 6.10%. (Ref. 4 reports a mixture of VIa and VIb, m. p. 110°C).

***trans*-Methyl-4-hydroxy-2-tetrahydrofurancarboxylate (VIIa).** — A solution of 0.9 g. of *trans* acid (VIa) in 10 ml. of methanol was added slowly to 100 ml. of ethereal solution (ca. 8%) of diazomethane at room temperature. A reaction took place, smoothly evolving nitrogen. After the mixture had been allowed to stand for 1 hr., the solvent was evaporated and the residue was distilled under reduced pressure to give 0.8 g. of *trans*-methyl ester (VIIa), b. p. 110—115°C/7 mmHg.

The infrared spectrum of VIIa in carbon tetrachloride (0.068 mol.) showed absorption maxima at 3620 and 3485 cm^{-1} attributable to free hydroxyl and intermolecularly-associated hydroxyl groups respectively. With further dilution (0.0024 mol.), the intensity of the former band relative to the latter one was increased.

Found: C, 49.27; H, 7.15. Calcd. for $C_6H_{10}O_4$: C, 49.31; H, 7.15%.

***cis*-Methyl-4-hydroxytetrahydrofuran-2-carboxylate (VIIb).** — This was prepared, in the way described above, from 0.6 g. of *cis*-tetrahydrofurancarboxylic acid, VIb. The distillation of the crude

5) T. Yamanaka, A. Ichihara, K. Tanabe and T. Matsumoto, *Shokubai* (*Catalyst*), **6**, 304 (1964); *Tetrahedron*, in press.

6) For further examples see Ref. 2b.

7) Guido Zwicky, P. G. Waser and C. H. Eugster, *Helv. Chim. Acta*, **42**, 1177 (1959).

8) Melting points are uncorrected. The infrared spectra in high dilution condition were measured on a Nippon Bunko grating infrared spectrometer model DS-401G, using 50 mm. KBS cell under high resolution condition.

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

product gave 0.5 g. of the *cis*-ester VIIb, b. p. 105—110°C/7 mmHg, whose infrared spectrum showed an absorption band at 3482 cm^{-1} due to an intramolecularly-hydrogen-bonded hydroxyl group in carbon tetrachloride (0.077 mol.).

Found: C, 49.22; H, 6.87. Calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.90%.

***trans*-4-Hydroxy-2-tetrahydrofurancarboxylic Acid Dimethylamide (VIIIa).** — The *trans*-methyl ester (0.5 g.) was added to 35 ml. of a solution (30%) of dimethylamine in absolute ethanol, and the mixture was heated for 25 hr. in a sealed tube at 80—90°C. The cooled reaction mixture was then concentrated to leave an oily residue, whose infrared absorption showed bands at 3350, 1638, 1105, 1077 cm^{-1} for amide VIIIa and a rather weak absorption at 1730 cm^{-1} for the unchanged ester (VIIa), which was removed by extracting it with ether.

***cis*-4-Hydroxy-2-tetrahydrofurancarboxylic Acid Dimethylamide (VIIIb).** — *cis*-Amide (VIIIb) was prepared in a way similar to that used for the trans-isomer described above. *cis*-Methyl ester (0.47 g.) was added to 30 ml. of an ethanolic solution (30%) of dimethylamine, and the mixture was heated for 8 hr. in a sealed tube at 80—90°C. The oily residue obtained by the evaporation of the solvent exhibited the following bands in the infrared spectrum: ν_{max}^{film} 3370, 1640, 1092, 1075 cm^{-1}. No absorption bands attributable to the ester VIIb were observed.

***trans*-(4-Hydroxy-2-tetrahydrofurfuryl)methyldimethylamine (IXa).** — To a solution of 0.6 g. of lithium aluminum hydride in 21 ml. of dried tetrahydrofuran, *trans*-dimethylamide (0.7 g.) in 5 ml. of tetrahydrofurane was added drop by drop under ice cooling; the mixture was then refluxed for 4 hr. on a steam bath. After the excess lithium aluminum hydride had been decomposed by adding 20 ml. of ethyl acetate to the cooled reaction mixture, the solvent was evaporated and the residue was treated with a solution (20%) of sodium hydroxide. The undissolved material was extracted several times with ethyl acetate. The extracts were combined, dried over anhydrous potassium carbonate, and evaporated to leave an oily residue. The residue was then chromatographed on 40 g. of deactivated alumina, using a mixture of benzene and methanol (0.5—10%) as a developer. Elution with benzene-methanol (5%) gave 0.45 g. of the *trans*-dimethylamine IXa. Infrared spectrum: $\nu_{max}^{CCl_4}$ 3400, 1103, 1070, 1035, 976 cm^{-1}. Reineckate of IXa: m. p. 167—187°C (decomp.)

Found: C, 28.55; H, 5.01; N, 20.91. Calcd. for $C_{12}H_{25}O_2N_7S_4Cr$: C, 28.44; H, 4.77; N, 21.10%.

***cis*-(4-Hydroxy-2-tetrahydrofurfuryl)methyldimethylamine (IXb).**—The cis-isomer IXb was prepared by exactly the same procedure as was the trans-isomer. The *cis*-dimethylamide VIIIb (0.7 g.) gave 0.42 g. of the *cis*-dimethylamine IXb, b. p. 75—80°C/4 mmHg, the infrared spectrum of which in high diluted conditions exhibited a broad band at 3194 cm^{-1} ascribed to the intramolecularly-hydrogen-bonded hydroxyl group in carbon tetrachloride (0.0072 mol.). Infrared spectrum: $\nu_{max}^{CCl_4}$ 3220, 1110, 1086, 1062, 1037, 1027 cm^{-1}. Reineckate of IXb: m. p. 183—184°C (decomp.).

Found: C, 28.40; H, 5.05; N, 20.94. Calcd. for $C_{12}H_{25}O_2N_7S_4Cr$: C, 28.44; H, 4.77; N, 21.10%.

***trans*-Demethylmuscarine (Xa).**—To a solution of 0.2 g. of *trans*-amine IXa in ethanol an excess of methyl iodide was added, and the mixture was allowed to stand for 1 hr. at room temperature. The reaction mixture was then evaporated under reduced pressure to leave a solid which was recrystallized twice from ethanol-water to give 0.2 g. *trans*-demethylmuscarine (Xa), m. p. 119—120°C; infrared spectrum: ν_{max}^{Nujol} 3345, 1103, 1072, 992, 953, 918 cm^{-1}. (Ref. 7 reported an m. p. of 119.5—120°C.)

Found: C, 33.63; H, 6.24; N, 4.70. Calcd. for $C_8H_{18}O_2NI$: C, 33.47; H, 6.32; N, 4.88%,

The reineckate of *trans*-demethylmuscarine was recrystallized from water-enthanol; m. p. 175.5—177°C (decomp.).

Found: N, 20.32. Calcd. for $C_{12}H_{24}O_2N_7S_4Cr$: N, 20.49%.

***cis*-Demethylmuscarine (Xb).** — The same treatment of IXb as that of the trans-isomer Xa gave a crude product which was recrystallized from water-ethanol to yield *cis*-demethylmuscarine (Xb), m. p. 117—118°C; infrared spectrum: ν_{max}^{Nujol} 3395, 1103, 1067, 1015, 995, 968, 962, 940 cm^{-1}. (Ref. 7 reported an m. p. of 119.5—120.5°C)

Found: C, 33.33; H, 6.36; N, 4.71. Calcd. for $C_8H_{18}O_2NI$: C, 33.47; H, 6.32; N, 4.88%.

The reineckate of *cis*-demethylmuscarine showed an m. p. of 169—171°C (decomp.) after recrystallization from water-ethanol.

Found: N, 20.04. Calcd. for $C_{12}H_{24}O_2N_7S_4Cr$: N, 20.49%.

Summary

Two stereoisomeric *dl*-demethylmuscarines have been prepared by the procedure described for the synthesis of *dl*-muscarine, starting from ethyl allylmalonate.

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