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A SIMPLE, STEREOSPECIFIC SYNTHESIS OF DL-MUSCARINE AND DL-ALLOMUSCARINE

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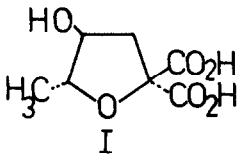
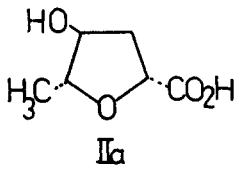
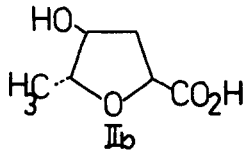
In the previous papers[1)2)] concerning the synthesis of muscarines, we reported a partially stereospecific synthesis in which the hydroxyl group of a diacid (I) was introduced selectively in trans manner to the methyl group. Decarboxylation of I, however, proceeded non-stereoselectively giving a mixture of two stereoisomeric monocarboxylic acids, IIa and IIb in a ratio of 1:1. The two acids (IIa, IIb) were converted to dl-muscarine (III) and dl-allomuscarine (IV) respectively.



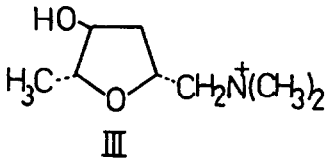
I



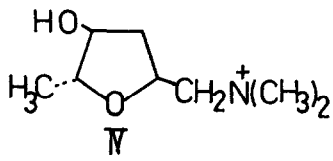
IIa



IIb



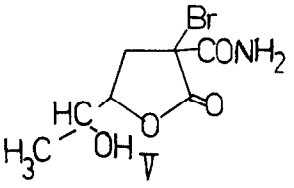
III



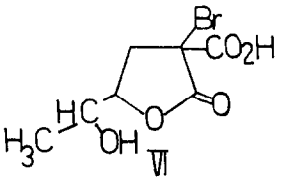
IV

Present communication describes a simple, fully stereospecific synthesis of muscarines starting from the bromolactone amide (V) obtained earlier[1)2)] as

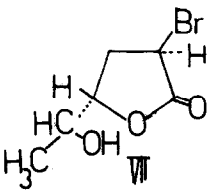
an intermediate for the synthesis of muscarines.



V

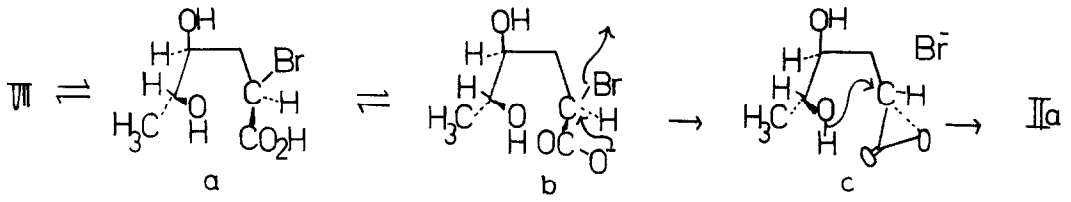


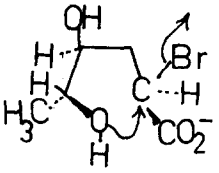
VI



VII

Hydrolysis of V with 3N-hydrochloric acid gave a bromolactonecarboxylic acid (VI), m.p. 126-128°; ν_{max}^{nujol} 3400 (OH), 1780 (lactone C=O), 1732 (CO_2H) in 83% yield. Decarboxylation of VI by heating in a sealed tube at 150-160° for 1 hr. afforded, besides a small amount of a neutral product VII, b.p. 107-115°/1mmHg, m/e, 272 (M-HBr, base peak), ν_{max}^{film} 3420 (OH), 1780 (lactone C=O), τ[3] 8.79 (3H, doublet J=7cps, $\overset{|}{C}H-CH_3$), 7.07-7.83 (2H, multiplet, CH_2), 5.18-6.07 (3H, multiplet),[3] an acidic compound, m.p. 142-143° in 66% yield. The acid was identified as IIa by mixed melting point determination and comparison of the infrared spectrum with that of the previously obtained sample IIa[1]. Since the conversion of IIa to dl-muscarine has already been known,[1] direct, specific formation of IIa means a simple, fully stereospecific synthesis of dl-muscarine. On the other hand, decarboxylation of VI in anhydrous dioxane gave the bromolactone (VII), which was also converted to IIa by hydrolyzing at 150-160° in water for 1 hr., though hydrolysis of VII with a solution of sodium hydroxide (4%) yielded a mixture of IIa and IIb. Therefore, it is quite probable that the bromolactone (VII) is the intermediate in the conversion of VI to IIa. It is well known that hydrolysis of α-bromopropionate in weakly alkaline condition yields lactate with retention of configuration at the α-carbon.[4] If the trans configuration is assumed for the bromolactone, the formation of IIa from VII would be explained by a similar mechanism.

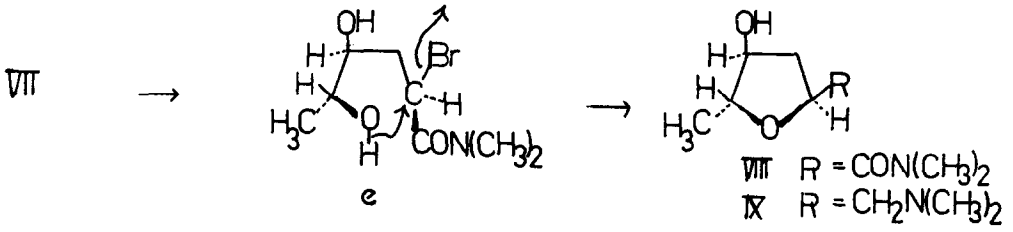




d

A hydrolyzed species a of VII in dilute alkaline medium may be equilibrated with a carboxylate b, in which participation of carboxylate anion would be possible and facilitate cyclization to the acid (IIa) with retention of configuration. On the other hand, in strongly alkaline solution, the reaction proceeds through species b and d to give IIa and IIb.

Supporting evidence for the trans configuration of Br/CH_3-$\underset{OH}{CH}$ in the bromolactone (VII) was obtained by cyclising VII to a tetrahydrofuran derivative (VIII) through a S_n-2 reaction (e) without carboxyl group participation.



e

VIII R = $CON(CH_3)_2$
IX R = $CH_2N(CH_3)_2$

Treatment of VII with dimethylamine in benzene (30 vol.%) gave VIII as an oil in 84% yield. The infrared spectrum of VIII was superimposable on that of the previously obtained dimethylamide VIII.[1] Further confirmation was made with dimethylamino compound (IX), obtained by reduction of VIII with lithium aluminium hydride. The dimethylamino compound (IX) and the tetraphenylboronate of IX were identical in all respects with those of allonormuscarine which is convertible to dl-allomuscarine.[1] The sequence of reactions on the bromolactone (VII) thus provides evidence for its trans configuration as well as a new, stereospecific route to muscarine and allomuscarine.

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2) T. Matsumoto and A. Ichihara, Biochem. Z. 331, 589 (1959).

3) N.m.r. spectra were measured on a Varian A-60 spectrometer in deuterated chloroform.

4) W. A. Cowdrey, F. D. Hughes and C. K. Ingold, J. Chem. Soc.,1208 (1937).