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A SIMPLE, STEREOSPECIFIC SYNTHESIS OF DL-MUSCARINE AND DL-ALLOMUSCARINE[1]

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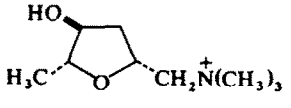
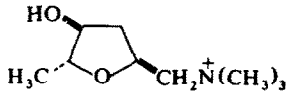
Abstract—A bromolactone (VII) was stereospecifically converted to a tetrahydrofuran (IVa, Me/CO_2H *cis*) and a dimethylamide (VIII, Me/$CONMe_2$ *trans*). Possible mechanisms for these reactions are discussed. Since IVa and VIII have been transformed to DL-muscarine (I) and DL-allomuscarine (II) respectively, stereospecific formation of IVa and VIII provides a stereospecific synthesis of these muscarines.

SINCE structural determination of muscarine,[2] the syntheses of muscarine and its stereoisomers have been studied by several groups.

A synthesis of L-muscarine starting from L-chitaric acid unequivocally established its absolute configuration,[3] and further excellent work by Eugster *et al.*[4] has made possible the synthesis of DL-muscarine itself and all other stereoisomers. However, only the synthesis starting from the naturally occurring chitaric acid is stereospecific. In a previous report on muscarine,[5] a partial stereospecific synthesis of DL-muscarine (I) and DL-allomuscarine[5a] (II) was described. In this synthesis the OH group of a



I

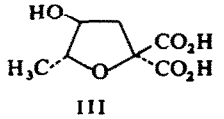


II

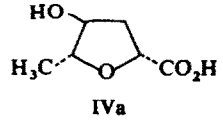
diacid (III) was introduced stereospecifically in a *trans* manner to the Me group, but subsequent decarboxylation of the diacid (III) did not proceed in a stereospecific way and gave two stereoisomers IVa and IVb in a ratio of 1:1.

The present paper describes a simple, fully stereospecific synthesis of IVa and VIII starting from a bromolactone amid (V) obtained earlier[5a, b] as an intermediate for our previous synthesis. Since the acids IVa and VIII have been converted to DL-muscarine and DL-allomuscarine respectively,[5a] stereospecific formation of IVa and IVb or their derivatives implies a stereospecific synthesis of DL-muscarine and DL-allomuscarine.

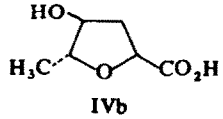
Hydrolysis of the amide (V) with 3N HCl at 65–70° for 30 min gave a bromolactone carboxylic acid (VI), m.p. 120–128°, ν max 3400 (OH), 1780 (lactone C=O), 1732 cm^{-1}



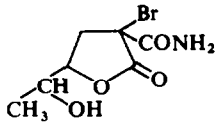
III



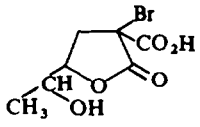
IVa



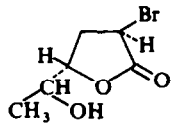
IVb



V



VI

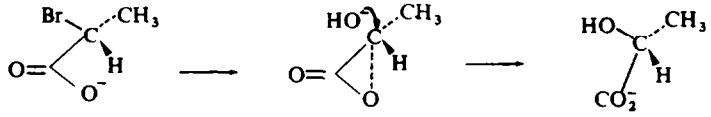


VII

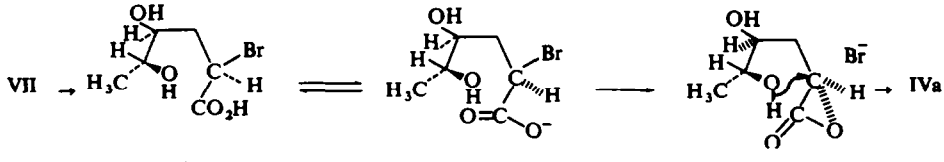
(CO_2H). Decarboxylation of VI by heating in a sealed tube at 150–160° for 1 hr afforded a mixture, from which two compounds were isolated. The minor product, b.p. 107–115°/1 mmHg, a neutral compound was shown to have the structure VII by the IR spectrum (a γ-lactone band at 1780 cm^{-1}).

The major product, m.p. 142–143°, obtained in 66% yield was an acidic compound which was identified as IVa by mixed m.p. and comparison of the IR spectrum with that of the previously obtained IVa. Decarboxylation of VI in anhydrous dioxan gave the bromolactone (VII) in 69% yield. Since VII was also converted to the acid (IVa) by hydrolysing at 150–160° in water for 1 hr, VII is most probably the intermediate in the formation of IVa from VI. On the other hand, hydrolysis of the bromolactone (VII) in a dilute solution of sodium hydroxide (4%) afforded a mixture of IVa and IVb.

A mechanistic interpretation of the results mentioned is given as follows. It is well known that hydrolysis of α-bromopropionate in weak alkali yields a lactate with retention of configuration at the α-carbon[6] while under stronger basic conditions the reaction proceeds with partial inversion. If we assume a *trans* configuration for the

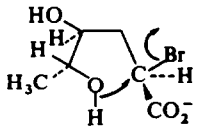


bromolactone (VII), formation of IVa from VII could be explained by a similar mechanism. A hydrolysed species (A) of VII in water may be equilibrated with a carboxylate anion (B) in which participation of carboxylate group would be possible and facilitate cyclization of C to the acid (IVa) with retention of configuration.



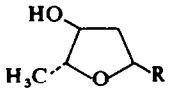
A B C

On the other hand, in alkaline solution, the reaction proceeds through C and D to give a mixture of IVa and IVb.

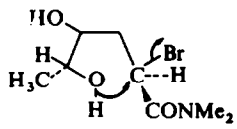


D

Since further treatment of IVa with an alkaline solution only recovered starting material, epimerization of IVa to IVb did not occur. Further supporting evidence for the *trans* configuration of VII was that the bromolactone (VII) was stereospecifically cyclized with dimethylamine to a tetrahydrofuran amide (VIII) through an SN-2 reaction as shown in E. In the transition state approximated by E, the carboxylate participation is clearly impossible.



VIII: R = $CONMe_2$
IX: R = CH_2NMe_2



E

Thus, reaction of VII with dimethylamine in benzene at 100° for 3 hr gave VIII as an oil in 84% yield. The IR spectrum of the amide (VIII) was superimposable on that of the previously obtained VIII. Further identification was carried out with the amine (IX), obtained by reduction of VIII with LAH. The reduced compound (IX) and its derivatives were identical with the authentic norallomuscarine (IX) and the corresponding derivatives in all respects. Thus, the stereochemical structure proposed for the bromolactone (VI) not only accounts for the transformation of the bromolactone (VII) to the bromolactone amide (VIII) as discussed, but also permits the rational interpretation of the formation of the tetrahydrofuran carboxylic acid (IVa) from the bromolactone (VII).

EXPERIMENTAL

All m.ps were determined in open capillary tubes and are uncorrected. NMR spectra were measured on a Varian A-60 instrument, using TMS as internal standard. IR spectra were recorded on a Jasco Model IR-S instrument.

2-Bromo-2-carbamoyl-3,4-dihydroxypentanoic acid lactone (1 → 4) (V). The amide was prepared according to the same procedure described in the previous synthesis of DL-muscarine.[5a]

2-Bromo-2-carboxy-3,4-dihydroxypentanoic acid lactone (1 → 4) (VI). A soln of 12 g of V in 60 ml 3N HCl was heated at 65–70° for 30 min. The mixture was concentrated at 50° under reduced press and the residue was extracted 3 times with EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated *in vacuo* to give 10·0 g of VI, m.p. 126–128°, ν_{max}^{mull} 3400 (OH), 1780 (lactone C=O), 1732 cm^{-1} (CO_2H), τ 8·78 (3H, doublet J = 7 c/s CH_3—CH(OH)).

Decarboxylation of the acid VI

(a) *In aqueous solution.* A soln of 5 g of VI in 100 ml water was heated at 150–160° for 1 hr in a sealed tube. The mixture was concentrated *in vacuo* and the concentrate extracted with $CHCl_3$ to give 1·1 g of VII, b.p. 107–115°/1 mm Hg, m/e 272 (M^+—HBr); ν_{max}^{neat} 3420 (OH), 1780 (lactone C=O), 1193 (C—O) cm^{-1}; τ 8·79 (3H, d, J = 7 Hz, CH—CH_3), 7·70–7·83 (2H, m, CH_2), 5·18–6·07 (3H, m, —CH—O— and —CH—Br).

The aqueous layer was concentrated *in vacuo* to a residue which crystallized after keeping overnight. Recrystallization from dichloroethane gave a compound, 1·9 g, m.p. 142–143°, whose IR spectrum and mixed m.p. showed that the acid was identical with an authentic sample of IVa.

(b) *In dioxan solution.* A soln of 10 g of VI in 100 ml anhyd dioxan was heated at 150–160° for 30 min in a sealed tube. The mixture was concentrated *in vacuo* and the residue distilled under reduced press to give 5·7 g of a distillate, b.p. 107–115°/1 mm Hg, which was identical with VII in the IR spectrum.

Hydrolysis of the bromolactone in water. A soln of 0·6 g bromoactone in 20 ml water was heated at 150–160° for 1 hr. The mixture was extracted with $CHCl_3$ to give 0·3 g recovered bromolactone. The aqueous layer was evaporated repeatedly with benzene to give a crystalline material (0·1 g). Recrystallization from dichloroethane gave the acid which was identical with IVa.

Hydrolysis of the bromolactone in alkaline solution. A soln of 155 mg VII and 65 mg (2 mole equivs) NaOH in 8 ml water was allowed to stand for 5 hr at 65°. After cooling, the mixture was neutralized with AcOH and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and evaporated *in vacuo* to give an amorphous solid (ca. 100 mg). Recrystallization of the solid from dichloroethane gave 30 mg of *trans* IVa, m.p. 143·5–145°. Concentration of the mother liquor gave a crystalline material, which was recrystallized from the same solvent to give 25 mg of the *cis* IVb, m.p. 109–111°.

Alkaline treatment of the trans *acid* (IVa). A soln of 73 mg of IVa and 41 mg NaOH in 2 ml water was heated at 65° for 3 hr. The mixture was eluted through a column of ion exchange resin (IR-120). The eluate was concentrated *in vacuo* to give 63 mg of the recovered IVa, m.p. 141–140°.

Conversion of the bromolactone (VII) *to the dimethylamide* (VIII). A soln. of 0·4 g bromolactone in 20 ml benzene soln containing 30% (by vol) Me_2NH was heated at 100° for 3 hr in a sealed tube. The mixture was concentrated *in vacuo* and the concentrate washed with water and then dried over anhyd Na_2SO_4. The soln was next evaporated *in vacuo* to give 0·27 g of an oil whose IR spectrum was identical with that of the previously obtained VIII.

Reduction of the amide (VIII) *with* LAH. Reduction of VIII was carried out according to the procedure previously described.[5a] The IR spectrum of the product (IX) was identical with that of norallomuscarine.[5a] The reinecke salt of IX melted at 161–162° (lit.[5a] 164–165°).

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