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Note

Conversion of L-rhamnose and D-mannitol into the enantiomeric acetyl-α- and -β-methylcholines

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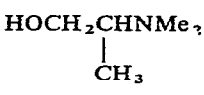
Derivatives of 2-dimethylaminopropan-1-ol (**1**) and 1-dimethylaminopropan-2-ol (**2**) have been used for studies of drug–receptor interactions in the central and peripheral nervous systems. For example, benzylic esters of **1** and **2** antagonise the action of acetylcholine, whereas acetyl-α-methylcholine [**3**; (2-acetoxy-1-methylethyl)-trimethylammonium iodide, from **1**] and acetyl-β-methylcholine [**4**; (2-acetoxypropyl)-trimethylammonium iodide, from **2**] act similarly to acetylcholine in the central and peripheral nervous system[1]. However, pharmacological and biochemical studies of such derivatives are of reduced value unless optically pure enantiomers of **1** and **2** are available. Previously, enantiomeric derivatives of **1** were obtained from D- and L-alanine[2,3], and those of **2** were obtained by resolution of (±)-1-dimethylamino-propan-2-ol[3,4] or from resolved D- and L-lactic acids[2,5]. To avoid resolution procedures and to assess the optical purity of previously described products, we have prepared the enantiomers of **1** and **2** from L-rhamnose and D-mannitol by a series of stereospecific reactions and converted them into acetylcholine analogues.

(S)-(+)-*Acetyl-β-methylcholine.* — 5-*O*-Benzyl-L-rhamnitol (**5**, m.p. 141–143°, from ethanol) was prepared in 40% overall yield from L-rhamnose by application in sequence of borohydride reduction[6], acetonation[6], benzylation[7], and acidic hydrolysis. Periodate oxidation of **5** in aqueous ethanol, followed by reduction with lithium aluminium hydride and toluene-*p*-sulphonylation, afforded **6** which, after chromatographic purification over silica gel, was smoothly hydrogenolysed to yield **7** (m.p. 35–36°) in 67% yield from **5**. Compound **7** reacted with dimethylamine in ethanol at 100° to give (*S*)-1-dimethylaminopropan-2-ol which, with methyl iodide, afforded a crystalline methiodide **8**, m.p. 178° (from ethanol), $[\alpha]_D^{20}$ +27.7° [lit., +27.5° (ref. 2), +24.7° (ref. 4), +24.1° (ref. 5)]. Acetylation of **8** afforded (*S*)-(+)-acetyl-β-methylcholine (**9**), m.p. 177° (from ethanol), $[\alpha]_D^{20}$ +25.6° [lit., +27° (ref. 2), +27° (ref. 3), +25.2° (ref. 5)].

An alternative route from **6** to the methiodide **8** was unsuccessful. Reaction of **6** with dimethylamine gave (*S*)-2-benzyloxy-1-dimethylaminopropane which gave a crystalline methiodide, m.p. 178°. Both 2-benzyloxy derivatives were resistant to catalytic hydrogenolysis, even at elevated temperature and pressure.

(R)-(−)-*Acetyl-β-methylcholine.* — 1,2:3,4-Di-*O*-isopropylidene-D-mannitol[8]



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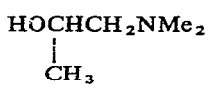

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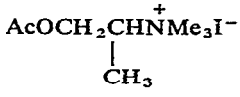

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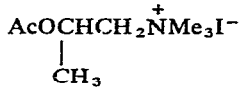

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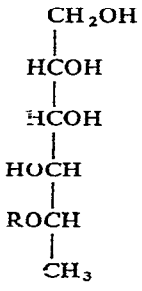

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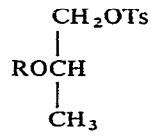

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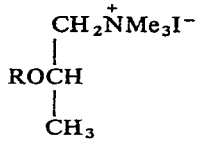
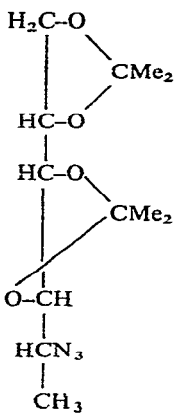
7 R = H



8 R = H
9 R = Ac



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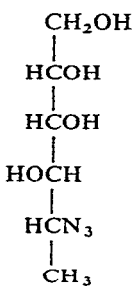

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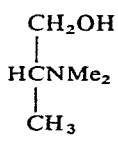

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prepared from D-mannitol was converted into 1,2:3,4-di-*O*-isopropylidene-D-rhamnitol by successive toluene-*p*-sulphonylation and reduction with lithium aluminium hydride. (*R*)-1-dimethylaminopropan-2-ol was prepared from the D-rhamnitol derivative in analogous fashion to that described for the (*S*)-isomer and converted into a crystalline methiodide, $[\alpha]_D^{20}$ −25.4° [lit., −29° (ref. 2), −24.7° (ref. 4), −26.8° (ref. 5)]. (*R*)-(−)-Acetyl-*β*-methylcholine had m.p. 160–165°, $[\alpha]_D$ −27.2° [lit., −27.4° (ref. 2), −26.8° (ref. 3), −23.7° (ref. 5)].

It will be noticed that acetylation of (*S*)-(+)-*β*-methylcholine caused a rotational change from +27.7 → +25.6°, whereas acetylation of (*R*)-(−)-*β*-methylcholine caused a rotational change from −25.4 → −27.2°. These differences are not significant but probably result from slight chemical, rather than optical, contamination. It has been observed previously that 10–12 recrystallisations of these methiodides are required to obtain maximal rotations[9].

(R)-(+)-*Acetyl-α-methylcholine.* — 1,2:5,6-Di-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-L-rhamnitol was converted into the corresponding 5-azido-6-deoxy-D-gulitol derivative **10**, m.p. 45–50° (from ethanol), by reaction with sodium azide in hot *N*,*N*-dimethylformamide. This reaction proceeds with preponderant substitution, unlike similar displacements with dimethylamine where extensive elimination occurs[10]. Acidic hydrolysis of **10** afforded 5-azido-5,6-dideoxy-D-gulitol (**11**), m.p. 138–140° (from ethanol). Application, in sequence, to **11** of periodate oxidation, reduction with lithium aluminium hydride, and methylation gave (*R*)-(+)-2-dimethylaminopropan-1-ol (**12**) which was converted into a crystalline methiodide, m.p. 200–250° (decomp.), $[\alpha]_D$ +4.0° (lit.[2] +4.1°), and into (*R*)-(+)-acetyl-α-methylcholine, m.p. 107–108°, $[\alpha]_D$ +8.8° [lit., +8.6° (ref. 2), +6.5° (ref. 3)].

(S)-(−)-*Acetyl-α-methylcholine.* — (*S*)-(−)-2-Dimethylaminopropan-1-ol was prepared from 1,2:3,4-di-*O*-isopropylidene-D-rhamnitol by procedures similar to those described for the corresponding (*R*)-isomer from the L-rhamnitol series. (*S*)-(−)-2-Dimethylaminopropan-1-ol afforded a crystalline methiodide, m.p. 297–299°, $[\alpha]_D^{20}$ −3.9° (lit.[2] −4.1°) and (*S*)-(−)-acetyl-α-methylcholine, m.p. 107–108°, $[\alpha]_D^{20}$ −8.9° [lit., −9.1° (ref. 2), −6.3° (ref. 3)].

The above stereospecific preparations of enantiomeric methylcholines illustrate the utility of carbohydrates in the synthesis of non-carbohydrate compounds of biological significance and confirm that previous preparations[2–5] have given products which are essentially optically pure. The individual reactions in the synthesis of the (*R*)- and (*S*)-1-dimethylaminopropan-2-ol derivatives all gave better than 80% yields, and so the method may be of some practical significance. Unfortunately, the yields obtained in the synthesis of the 2-dimethylaminopropan-1-ol derivatives were much less satisfactory. The (*R*)- and (*S*)-isomers of **1** and **2** have been esterified with (*R*)- and (*S*)-2-cyclohexyl-2-hydroxy-2-phenylacetic acids[11] which were also obtained from carbohydrate precursors, and the pharmacological comparisons of these compounds will be reported elsewhere.

EXPERIMENTAL

All products and intermediates had n.m.r. and i.r. spectra consistent with the assigned structure. Optical rotations were measured with a Perkin–Elmer 141 polarimeter at concentrations of 1–2% in 9:1 (v/v) ethanol–water.

Toluene-*p*-sulphonylations were carried out with toluene-*p*-sulphonyl chloride in pyridine at room temperature overnight, and acetylations were with acetic anhydride at 120° for 30 min. Acidic hydrolyses of isopropylidene derivatives were effected with toluene-*p*-sulphonic acid in aqueous methanol, and the hydrolysis products were isolated after neutralisation with Amberlite IRA-400 (OH^-) resin. Reductions with lithium aluminium hydride were carried out in dry ether.

The 5-azido-5,6-dideoxy-D- and -L-gulitols were converted into the corresponding (*R*)- and (*S*)-2-dimethylaminopropan-1-ols by the following procedure. For example, a solution of 5-azido-5,6-dideoxy-L-gulitol (6 g) and sodium periodate (20 g) in water

was stored at room temperature for 30 min and then extracted with ether. The ether solution was dried ($MgSO_4$) and added dropwise to a suspension of lithium aluminium hydride (1.5 g) in ether. Excess of lithium aluminium hydride and alkoxides were decomposed in the usual way, and the mixture was dried ($MgSO_4$) and concentrated to 20 ml. This solution, to which formaldehyde (3 ml) and formic acid (4 ml) were added, was heated at 95° for 9 h. The solution was concentrated, dissolved in ethanol, and passed over Amberlite IRA-400 (OH^-) resin. The eluate was concentrated to afford crude 2-dimethylaminopropan-1-ol which was treated with methyl iodide in ether to afford (*S*)-(−)-2-dimethylaminopropan-1-ol methiodide (0.5 g, 50%), m.p. 297–298°.

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