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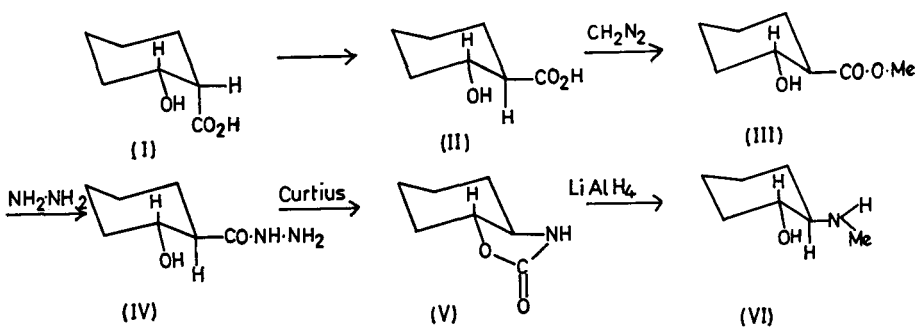
LETTERS TO THE EDITOR

The absolute configuration of *trans*-2-dimethylaminocyclohexyl acetate methiodide: chemical verification

In a recent paper in this series (Kay & Robinson, 1969), the absolute configuration of (−)-*cis*-2-methylaminocyclohexanol, (−)-*cis*-2-dimethylaminocyclohexyl acetate methiodide and (−)-*cis*-2-dimethylaminocyclohexyl benzoate methiodide was established as (1*R*,2*S*) by unambiguous synthesis from (1*S*,2*R*)-(−)-*cis*-2-hydroxycyclohexanecarboxylic acid. The fact that both (−)-*trans*- and (−)-*cis*-2-dimethylaminocyclohexyl benzoate methiodide displayed plain negative optical rotatory dispersion curves in the region 600–280 nm led us to suggest that these compounds have the same absolute configuration at C-1. Thus, (−)-*trans*-2-dimethylaminocyclohexyl benzoate methiodide [and from the synthetic routes employed (−)-*trans*-2-dimethylaminocyclohexyl acetate methiodide] has the (1*R*,2*R*)-configuration. However, the absence of an established "octant rule" relating the ord spectrum of a compound containing an aromatic chromaphore to its absolute configuration (for reviews see Crabbé, 1967; Crabbé & Klyne, 1967), together with the fact that one is dealing here with a non-rigid compound (see Martin-Smith, Smail & Stenlake, 1967), requires the use of chemical methods to unambiguously establish the absolute configuration of the enantiomers of the *trans*-series. The present paper thus reports the conversion of (1*S*,2*R*)-(−)-*cis*-2-hydroxycyclohexanecarboxylic acid (I) to (−)-*trans*-2-methylaminocyclohexanol (VI) by the route shown.



A sample of partially resolved (−)-*cis*-2-hydroxycyclohexanecarboxylic acid (I) (optical purity 38%) was converted to (−)-*trans*-2-hydroxycyclohexanecarboxylic acid (II) by a previously reported method (Febrer, Gomis & Pascual, 1964). The product was separated from unreacted (−)-*cis*-isomer by column chromatography of the methyl esters on alumina (Peter Spence, Type H, 100–200 mesh); initially light petroleum (b.p. 30–40°) was used followed by light petroleum (b.p. 30–40°) containing increasing amounts of solvent ether as eluent. Evaporation of each fraction and examination of the residue by infrared* spectroscopy and gas-liquid chromatography† showed that the initial fractions contained a mixture of (−)-*cis*- and (−)-*trans*-isomers, whereas the later fractions contained only methyl (−)-*trans*-2-hydroxycyclohexanecarboxylate (III), $b.p._{10}$ = 107–108° (optical purity 38%) (Faixat, Febrer & Pascual, 1961).

The methods employed for the conversion of methyl (−)-*trans*-2-hydroxycyclohexanecarboxylate (III) via the (−)-hydrazide (IV) and cyclic urethane (V) to (−)-*trans*-2-methylaminocyclohexanol (VI) (optical purity 20%) were as reported for analogous reactions on the *cis*-enantiomers (Kay & Robinson, 1969).

The final product (−)-*trans*-2-methylaminocyclohexanol (VI) had a infrared spectrum identical to that of an authentic sample of the racemate prepared by the addition of methylamine to cyclohexene oxide (Kay & Robinson, 1969). Thus, (−)-*trans*-2-methylaminocyclohexanol has the (1*R*,2*R*)-configuration (this result is not invalidated by the use of only partially resolved materials, as none of the reagents or solvents used was asymmetric), and as the conversion of this compound to (−)-*trans*-2-dimethylaminocyclohexyl benzoate methiodide and (−)-*trans*-2-dimethylaminocyclohexyl acetate methiodide has been previously reported, it follows that these compounds also have the (1*R*,2*R*)-configuration. These results agree with the earlier assignment made from the comparison of the ord spectrum of (1*R*,2*S*)-(−)-*cis*-2-dimethylaminocyclohexyl benzoate methiodide with that of (−)-*trans*-2-dimethylaminocyclohexyl benzoate methiodide (Kay & Robinson, 1969).

It has previously been suggested that both (±)-*cis*- and (±)-*trans*-2-dimethylaminocyclohexyl acetate methiodide are good substrates for the enzyme acetylcholinesterase (Baldridge, McCarville & Friess, 1955). It now becomes possible to discuss the activity of each enantiomer when acting as a substrate for the enzyme or as a muscarinic agent in relation to the known stereospecificity patterns exhibited by the active site of the enzyme and the tissue receptor (Kay, Robinson & others, 1970).

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* Characteristic absorptions were shown in the region 800–1000 cm^{-1} (liquid film). Methyl (—)-*cis*-2-hydroxycyclohexanecarboxylate: ν_{max} 830, 850, 875 (sh), 895, 925, 975, 988 cm^{-1}; methyl (—)-*trans*-2-hydroxycyclohexanecarboxylate: ν_{max} 845, 860, 870, 895 (sh), 905, 952, 960 and 985 cm^{-1}.

† 6 feet × ¼ inch stainless steel column containing Silicone gum rubber E301 (2·5%) on Chromasorb G AW-DMCS (97·5%), N_2 carrier gas at 19 lb/$inch^2$, column temperature 110°, injector temperature 275°, detector temperature 80°. Retention time, *cis*-isomer 7·4 min, *trans*-isomer 8·4 min.

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