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Synthesis of Cyclohexane-1,3/2-triol

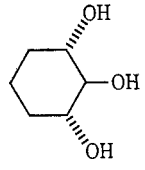
Peter M. Fredericks[A] *and R. D. (Gus) Guthrie*[A,B]

[A] School of Science, Griffith University, Nathan, Qld. 4111.
[B] To whom correspondence should be addressed.

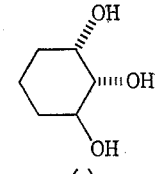
Abstract

Repetition of a published method for the alleged synthesis of cyclohexane-1,3/2-triol showed that the product was in fact the 1,2/3 isomer. A new synthesis of the 1,3/2 compound is described.

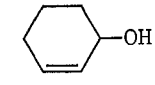
For part of a program on research into synthetic analogues of aminoglycoside antibiotics, a supply of cyclohexane-1,3/2-triol (1) was required. Several syntheses have been described in the literature.[1–6] Recently Russian workers[6] claimed a facile route, in which cyclohex-2-enol (3) was treated with monoperoxysuccinic acid.



(1)



(2)



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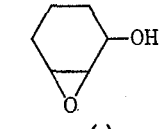
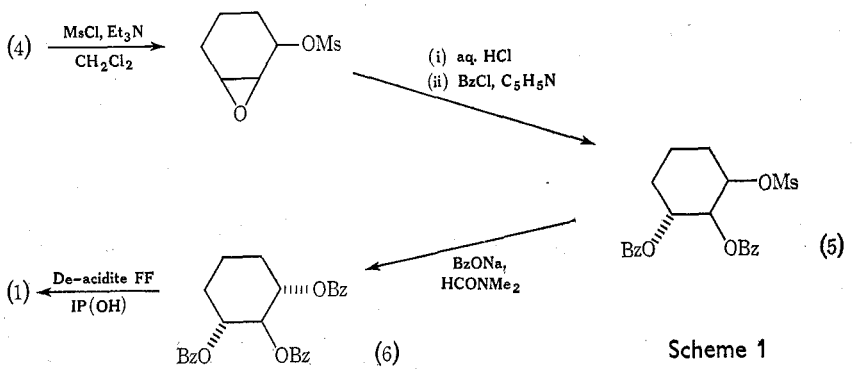


(4)

We decided to use this route because of its simplicity. The accepted m.p. of the 1,3/2 isomer (1)[1,4,5] is 107–108° and that of its tribenzoate[1,3–5] 125°, whilst the 1,2/3 compound (2) has[1,3–5] m.p. 124–125°, and its tribenzoate a m.p. variously recorded[1,3–5] between 181° and 184°. The product from the Russian workers' synthesis[6] had m.p. 108°. Repetition of their sequence gave a product melting at 120–121°, that on benzoylation gave a product of m.p. 182–183°. This evidence, together with a complex ^{1}H n.m.r. spectrum and a ^{13}C n.m.r. spectrum of the tribenzoate with six distinct resonances for the cyclohexane carbons, showed that the Russian synthesis yielded the 1,2/3 isomer and not the 1,3/2 one. In fact it provides a useful route to the former compound. The Russian paper[6] has no record of any spectral data, nor was the tribenzoate of their product prepared; their product was obviously an impure sample of the 1,2/3 compound.

[1] Brunel, L., *C. R. Acad. Sci.*, 1910, **150**, 986.
[2] Kotz, A., and Richter, K., *J. Prakt. Chem.*, 1925, **111**, 387.
[3] Gogek, C. J., Moir, R. Y., McRae, J. A., and Purves, C. B., *Can. J. Chem.*, 1951, **29**, 938.
[4] Lindemann, H., and Lange, A. de, *Justus Liebigs Ann. Chem.*, 1930, **483**, 31.
[5] McRae, J. A., Moir, R. Y., Haynes, J. W., and Ripley, L. G., *J. Org. Chem.*, 1952, **17**, 1621.
[6] Emel'yanov, N. P., and Lopatik, D. V., *Dokl. Akad. Nauk Beloruss. SSR*, 1968, **12**, 718; *Org. Katal.*, 1970, 15.

Further consideration of the Russian synthesis shows that the 1,3/2 isomer is not the product one would expect from the sequence used. If cyclohexen-2-ol (2) is attacked by monoperoxysuccinic acid in the same manner as it is by perbenzoic acid[7] it would yield the *cis*-epoxide (4). Reaction of (4) with lithium aluminium hydride yielded[7] *cis*-cyclohexane-1,2-diol, from attack of the nucleophile in Fürst–Plattner fashion on the epoxide in the OH-*eq* conformation. Reaction under the Russian workers' conditions would by analogy yield the 1,2/3 triol and not the 1,3/2 isomer.



Scheme 1

Still needing a route to the 1,3/2-triol we developed that shown in Scheme 1, starting from the readily available epoxy alcohol (4). The 1,3/2 stereochemistry of the triol tribenzoate was established by comparison of m.p. data and from the symmetry shown in its p.m.r. and c.m.r. spectra (the latter showed only four lines for the cyclohexane ring carbons).

Experimental

Thin-layer chromatography was carried out on Merck silica gel GF_{254}, with chloroform as solvent, unless otherwise stated. Components were located by charring with 50% methanolic sulphuric acid, by u.v. irradiation or by exposure to iodine vapour. P.m.r. spectra were run in deuterochloroform, unless otherwise stated.

Cyclohex-2-enol (3)

This compound was prepared from cyclohexene by standard methods.[8,9] The clear, colourless liquid (35%) had b.p. 60–80°/15 mm (lit.[9] 62–65°/12 mm).

Reaction of Cyclohex-2-enol with Monoperoxysuccinic Acid[6]

Monoperoxysuccinic acid (5·1 g, 0·0218 mol) and water (17·5 ml) were placed in a flask equipped with a magnetic stirrer and a reflux condenser. The mixture was heated at 50° on a water bath for about 20 min until a clear solution was obtained. The solution was cooled to 40° and cyclohex-2-enol (2·0 g, 0·0204 mol) was added dropwise over 5 min, with efficient stirring, which was continued for a further 2 h at 40°. The mixture was kept at 5° overnight and the precipitated succinic acid removed by filtration. The filtrate was neutralized with sodium bicarbonate solution and the solvents evaporated. The solid residue was extracted with ethanol/acetone (1 : 1) at room temperature. Solvents were removed to give a semi-solid (1·94 g). Crystallization and recrystallization from ethyl acetate afforded colourless crystals of cyclohexane-1,2/3-triol (2) (1·10 g, 41%), m.p. 120–121°, ^{1}H n.m.r. (δ C_5D_5N containing small amount of D_2O) 4·40, m, 2H, H1,3; 3·9,

[7] Henbest, H. B., and Wilson, R. A. L., *J. Chem. Soc.*, 1957, 1958.
[8] Monson, R. S., 'Advanced Organic Synthesis. Methods and Techniques' p. 48 (Academic Press: New York 1971).
[9] Otzet, L., Pascual, J., and Sistare, J., *An. Real. Soc. Espan. Fis. Quim., Ser. B.*, 1966, **62**, 965.

dd, $J_{1,2}$ 7·5, $J_{2,3}$ 3·0 Hz, 1H, H2; 1·3–2·3, envelope, 6H, remaining ring protons. ^{13}C n.m.r. δ ($CDCl_3$) 18·7, C5; 28·3, 29·2, C4, C6; 71·2, 71·3, C1, C3; 73·2, C2.

Compound (2) (200 mg) was dissolved in dry pyridine (2 ml) and benzoyl chloride (850 mg) was added. The mixture was left at room temperature for 15 h and poured into ice water. After the usual workup a white solid (760 mg) was obtained. This was recrystallized from ethanol to give tri-*O*-benzoylcyclohexane-1,2/3-triol as a white solid (560 mg, 83%), m.p. 182–183°.

2,3-Epoxycyclohexanol (4)

Cyclohex-2-enol was epoxidized by the method of Henbest and Nicholls,[10] except that *m*-chloroperoxybenzoic acid was used in place of peroxybenzoic acid, to give the title compound as a clear, colourless liquid (90%), n_D^{22} 1·4865 (lit.[7] n_D^{18} 1·4867).

2,3-Di-O-Benzoyl-1-O-mesylcyclohexane-1,2/3-triol (5)

The epoxy alcohol (4) (1·03 g) was dissolved in dichloromethane (10 ml) containing triethylamine (1·33 g), and the solution cooled to 0°. Methanesulphonyl chloride (1·1 g) was added, with stirring, and the mixture stirred at 0° for 30 min. The reaction mixture washed successively with ice-water, 1N aqueous hydrochloric acid solution, saturated aqueous sodium bicarbonate solution and finally more ice-water. The organic phase was dried and the solvents were removed to give a pale yellow liquid (1·62 g). The crude liquid was refluxed with water (10 ml) containing one drop of 2N hydrochloric acid solution for 2 h and allowed to cool. Ion exchange resin, De-acidite FF-1P (OH form), (about 0·5 g) was added and the mixture stirred for 5 min and filtered. The solvent was removed from the filtrate to give a yellow syrup (1·54 g) which was dried in a vacuum over phosphorus pentoxide. The dry syrup was dissolved in dry pyridine (15 ml), benzoyl chloride (2·17 g) was added and the mixture left at room temperature for 15 h, and worked up in the usual way to yield a white solid. Recrystallization from ethanol afforded the *title compound* (5) [2·24 g, 60% from compound (4)], m.p. 108–109° (Found: C, 60·0; H, 5·3. $C_{21}H_{22}O_7S$ requires C, 60·3; H, 5·3%). ^{1}H n.m.r. δ [100 MHz, $(CD_3)_2CO$] 7·35–8·05, m, 10H, aromatic; 5·45, m, 2H, H2,3; 5·28, m, 1H, H1; 3·07, s, 3H, mesyl; 1·50–2·40, envelope, 6H, remaining ring protons.

Tri-O-benzoylcyclohexane-1,3/2-triol (6)

Sodium benzoate (0·516 g) was added to a solution of compound (5) (0·50 g) in dry dimethylformamide (10 ml) and the mixture refluxed with stirring for 6 h. On cooling, chloroform was added and the mixture washed with water (4 × 20 ml). The organic phase was dried and the solvents removed to give a pale yellow syrup (0·53 g), which was crystallized and recrystallized from ethanol to give the *title compound* as colourless crystals (0·47 g, 89%), m.p. 140–141° (Found: C, 72·5; H, 5·6. $C_{27}H_{24}O_6$ requires C, 73·0; H, 5·4%). ^{1}H n.m.r. δ 7·10–8·10, m, 15H, aromatic; 5·70, t, $J_{1,2} = J_{2,3}$ 9·2 Hz, 1H, H2; 5·28, m, 2H, H1,3; 1·40–2·20, envelope, 6H, remaining ring protons. ^{13}C n.m.r. δ ($CDCl_3$) 19·7, C5; 29·9, C4,6; 73·4, C1,3; 75·1, C2.

Cyclohexane-1,3/2-triol (1)

The tribenzoate (6) (110 mg) was dissolved in dry methanol (4 ml) and in ion-exchange resin De-acidite FF-IP (OH form) (about 0·5 g) was added. The mixture was stirred at room temperature for 15 h and filtered through Celite; the solvent was removed. The syrup was partitioned between water (3 ml) and chloroform (10 ml), and the water layer was washed with more chloroform (3 × 10 ml). The water was evaporated to give a white solid (31 mg, 95%), m.p. 106·5–107° (lit.[1] 108°).

Acknowledgments

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[10] Henbest, H. B., and Nicholls, B., *J. Chem. Soc.*, 1957, 4608.