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SYNTHESIS AND EPOXIDATION OF TRANS-5,6-DIACETOXY-1-BENZOYLOXYMETHYL-1,3-CYCLOHEXADIENE

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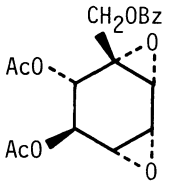
Epoxidation of a newly prepared trans-5,6-diacetoxy-1-benzoyloxymethyl-1,3-cyclohexadiene by m-chloroperbenzoic acid in dichloroethane gave several isomeric compounds of the biologically important highly oxygenated cyclohexane derivatives.

Crotepoxide (1)[1] and senepoxide (2)[2] belong to a family of highly oxygenated cyclohexane derivatives which exhibit tumor-inhibitory, antiluekemic, or antibiotic activity. Pipoxide,[3] the structure of which has recently been revised to 3,[4] is also a member of these biologically important substances. As we have been studying the structure-activity relationship of mono- and diepoxycyclohexanes,[5] we report herein the synthesis of several isomeric compounds of this class by epoxidation of suitably functionalized 1,3-cyclohexadiene.

trans-5,6-Diacetoxy-1-benzoyloxymethyl-1,3-cyclohexadiene (5) was chosen as a starting material, from which four monoepoxides (2, 4, 11, and 12) and four diepoxides (1, 13, 14, and 15) were expected to be obtainable by epoxidation with peracid. Three monoepoxides 4, 11, and 12, and one diepoxide 15 were practically isolated from the mixtures of products, and their structures were assigned on the basis of ^{1}H NMR spectroscopy.



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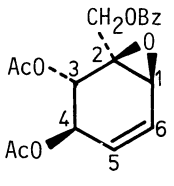

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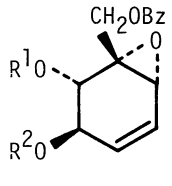
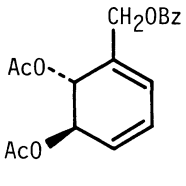


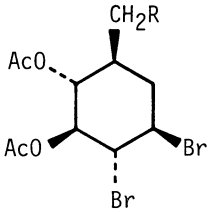
3 : R^1 = H, R^2 = Bz

4 : R^1 = R^2 = Ac

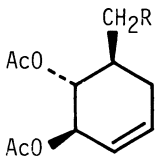


5

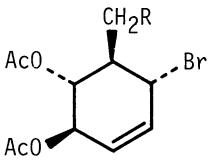
Firstly, the diene 5 was prepared in the following sequence. Treatment of the readily accessible di-O-acetyl-(1,3/2,4,6)-3,4-dibromo-6-bromomethyl-1,2-cyclohexanediol (6a)[6,7] with zinc dust in acetic acid (70°C, 10 min.) gave the olefin (7a), mp 83–84°C, in 92% yield. Bromination of 7a with 1.5 molar equiv. of N-bromosuccinimide (NBS) in carbon tetrachloride in the presence of α,α'-azobisisobutyronitrile



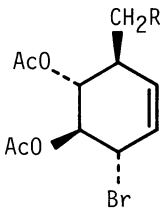
6a,b



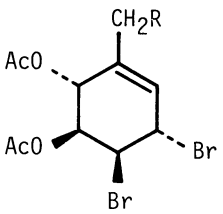
7a,b



8a,b

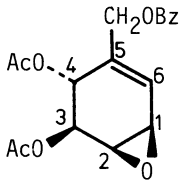


9a,b



10a,b

a : R = Br, b : R = OBz



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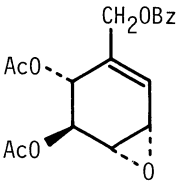

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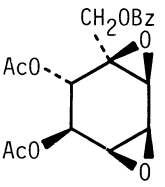

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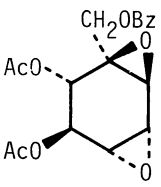

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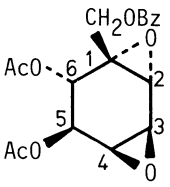

15

(reflux, 20 min.) gave a mixture of bromides, which was fractionated by chromatography on silica gel to give two monobromides (8a) (mp 103–105°C) and (9a) (mp 126–128°C), and a dibromide (10a) (syrup), in 23, 7, and 9% isolated yields, respectively.[8] When 2.5 molar equiv. of NBS was used, 10a was obtained in a quantitative yield.[9] Preferential substitution of the C-7 bromine atom by a benzoate ion was achieved by treatment with a slight excess of sodium benzoate in 90% aqueous N,N-dimethylformamide (room temperature, 6.5 h) to give the corresponding 7-benzoyloxy derivative (10b), mp 133–134°C, in 47% yield. Alternatively, 6a was first converted into the corresponding benzoate (6b), mp 154–155°C, in the analogous way in 66% yield, and then it was debrominated with zinc dust to give the olefin (7b), mp 75–76.5°C, in 81% yield. Similar bromination of 7b (1.5 molar equiv. of NBS, reflux, 2h) gave two monobromides (8b) (20%, syrup) and (9b) (10%, mp 90–92°C), along with 10b (18%) identical with the dibromide derived from 10a. Debromination of 10b was effected by treatment with zinc dust in ethanol (70°C, 30 min.) giving rise to 5 as a syrup in 69% yield. The structure of 5 was established by its ^{1}H NMR spectrum, which showed coupled one-proton doublet of doublets (H-5, J = 5 and 4 Hz) and one-proton doublet (H-6, J = 5 Hz) at δ 5.25 and 5.35, respectively. The signal due to three olefinic protons appeared as a three-proton broad multiplet (δ 5.6–6.2). These spectral data were in line with those of the corresponding 1-benzyloxymethyl derivative.[10] Compound 5 suffered aromatization upon standing at room temperature.

Epoxidation of 5 was carried out using m-chloroperbenzoic acid (mCPBA) in dichloroethane. When an equimolar amount of mCPBA was used at room temperature (2 days), three monoepoxides were predominantly formed. Separation on a silica gel column with 2-butanone–toluene (1 : 2, v/v) as an eluent gave di-O-acetyl-1,2-anhydro-2-C-benzoyloxymethyl-5-cyclohexene-1,2,3/4-tetrol (4) (mp 112–113°C), and di-O-acetyl-1,2-anhydro-5-benzoyloxymethyl-5-cyclohexene-1,2,3/4- (11) (syrup) and

1,2,4/3-tetrol (12) (mp 116–117.5°C), in 14, 8.4, and 13% yields, respectively.

The structure of 4 was proposed by comparison of the ^{1}H NMR spectrum with those of 2[2] and 3.[4] Thus, the spectrum contained the signals due to two olefinic protons [δ 5.73 (J = 10, 2, and 1.5 Hz) and 6.05 (J = 10, 4, and 2 Hz)] and one epoxide proton [δ 3.53 (J = 4 and 2 Hz)], showing that 4 was an isomer of 2. The signals due to H-3 and H-4 appeared as a two-proton narrow multiplet at δ 5.50 relative to those of 2 [H-3 (δ 5.57) and H-4 (δ 5.17)], which indicated that the C-4 proton was deshielded by the proximate 1,2-epoxide group in the half-chair (sofa) conformation with two acetoxyl groups being diequatorially situated. The above spectral data suggested the structural similarity of 3 and 4.

The ^{1}H NMR spectra of 11 and 12 revealed two epoxide and one olefinic protons, respectively, supporting that they were an epimeric pair of the 3,4-epoxide of 5. In the spectrum of 11, signals due to H-3 and H-4 appeared as a doublet (J = 9 Hz) at δ 5.31 and 5.85, respectively, being consistent with the proposed structure where two acetoxyl groups were oriented diequatorially and the C-4 proton was deshielded by the 1,2-epoxide group. Whereas, in the spectrum of 12, two narrow triplets (J = 2 Hz) appeared at δ 5.29 and 5.41, which could be attributed to H-3 and H-4, respectively, in the preferred conformation with two acetoxyl groups in diaxial positions. The above spectral data tend to suggest that the conformational preference of these compounds might be due to the configurational relationship between trans-vicinal substituents and epoxide group independent of the steric and polar effects of benzoyloxymethyl group.[11]

When the same reaction was carried out under forcing conditions[12] (90°C, 1 h, 2,6-di-t-butyl-p-cresol), a single crystalline diepoxide (15), mp 128–129°C, was isolated, after separation on a silica gel column, in 20% yield, along with monoepoxides 4 (3.5%), 11 (1.3%), and 12 (2.6%). The ^{1}H NMR spectrum of 15 showed two coupled sharp doublets (J = 8.5 Hz) at δ 5.30 and 5.70, attributable to H-5 and H-6, respectively. The observed coupling constants and chemical shifts were in accordance with the proposed structure where the C-5 and C-6 protons adopted the diaxial conformation and the former was deshielded by the proximate 1,2-epoxide group. The structure was further confirmed by epoxidation of the monoepoxides obtained. Epoxidation of 11 occurred smoothly to give 15 selectively. While, 4 did not react with mCPBA at room temperature, however, under forcing conditions, formation of 15 was detected by TLC analysis. On the other hand, although 12 was expected to give 1 and/or 14, it was not epoxidized, but underwent decomposition on prolonged reaction time.

Accordingly, it was noted that the 1,2-double bond of 5 was deactivated by the inductive effect of the C-1 benzoyloxymethyl group, comparing with that of the corresponding diene with benzyloxymethyl group.[10] Stereospecificity of the epoxidation of trans-5,6-diacetoxy-1,3-cyclohexadienyl system seems to depend rather on an interaction of the neighboring group than on the special steric effects,[13] e.g. a conformational requirement of the molecule in the transition state of epoxidation, leading predominantly to the epoxide with two acetoxyl groups in equatorial orientations. Formation of 2 from 5 might possibly be retarded by the eclipsing of the C-6 acetate and C-1 benzoyloxymethyl functions in the transition state.[11]

References and Notes

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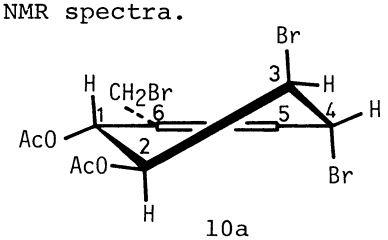
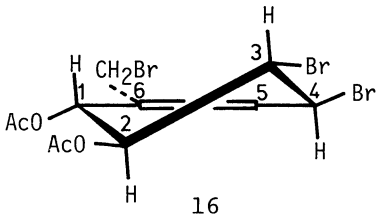
5) S. Ogawa, S. Oki, and T. Suami, Bull. Chem. Soc. Jpn., 52, 1095 (1979).
6) S. Ogawa, I. Kasahara, and T. Suami, Bull. Chem. Soc. Jpn., 52, 118 (1979).
7) All the compounds reported in this paper are racemic. The formulas depict only one of the respective racemates. Unless otherwise stated, ^{1}H NMR spectra were measured at 60 MHz on a Varian A-60D spectrometer in $CDCl_3$ with reference to tetramethylsilane as an internal standard. The new compounds except 5 gave satisfactory analytical data. The isolated yields of the pure epoxides were based on 10b used. The epoxidation reactions were not always conducted under optimum conditions.
8) The structure of 10a, named as di-O-acetyl-t-3,c-4-dibromo-6-bromomethyl-5-cyclohexene-r-1,t-2-diol, was confirmed by the ^{1}H NMR spectrum (100 MHz, $CDCl_3$) δ 2.10 (6H, s, 2OAc), 3.85 (1H, d) and 4.01 (1H, d) (J = 11 Hz, CH_2Br), 4.63 (1H, broad t, $J_{2,3}$ = 3 Hz, $J_{3,4}$ = ca. 4 Hz, H-3), 4.96 (1H, broad t, $J_{4,5}$ = ca. 4 Hz, H-4), 5.51 (1H, dd, $J_{1,2}$ = 7 Hz, H-2), 6.04 (1H, d, H-1), 6.16 (1H, broad d, H-5). The structures of the other bromides were also proposed by their ^{1}H NMR spectra.



10a



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9) The syrupy 10a was deduced by ^{1}H NMR spectrum to contain a small amount of its isomer (16) with all trans configuration: ^{1}H NMR (100 MHz, $CDCl_3$) δ 4.39 (1H, dd, $J_{2,3}$ = 10 Hz, $J_{3,4}$ = 7.5 Hz, H-3), 5.31 (1H, dd, $J_{1,2}$ = 7 Hz, H-2), 5.84 (1H, broad d, H-1).
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