Cyclitol analogs of biological interest. Regioselective nucleophilic substitutions of 1,4-cyclohexadiene bisepoxide and bisepisulfide

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Reaction of *cis*-1,4-cyclohexadienebisepoxide with aluminium azide afforded the all-equatorial 1,3-diazido-4,6-cyclohexanediol (**2**) through a metal-template mechanism. Hydrogenation of the product gave 2,5-dideoxystreptamine. Synthon **2** underwent normal coupling with 6-deoxy-6-azido-2,3,4-tris(*O*-benzyl)-α-glucosyl chloride and the resulting product gave the expected glucoside, a precursor of 5-deoxyneamine analogs. The *cis*- and *trans*-1,4-cyclohexadienebisepoxides were converted in good yields to the corresponding bisepisulfides and monoepoxide monoepisulfides. Regioselective opening of the *cis*-bisepisulfide with acetyl chloride and mercuric acetate by a metal-template mechanism led to stereochemically defined dithio analogs of cyclitols.

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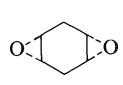
La réaction du *cis*-cyclohexadiène-1,4 bis-époxyde avec l'azoture d'aluminium conduit au diazido-1,3 cyclohexanediol-4,6 complètement équatorial (**2**) par l'intermédiaire d'un mécanisme métal-gabarit. L'hydrogénation du produit conduit à la didéoxy-2,5 streptamine. Le synthon **2** subit le couplage normal avec la chlorure de déoxy-6 azido-6 tris(*O*-benzyl-2,3,4)α-glucosyle et le produit qui en résulte conduit au glucoside attendu, un précurseur des analogues déoxy-5 néamine. Les *cis*- et *trans*-cyclohexadiène-1,4 bis-époxydes peuvent être transformés avec de bons rendements en bis-épisulfures correspondants et en mono-époxyde-mono-épisulfures. L'ouverture régiosélective du *cis*-bis-épisulfure avec le chlorure d'acétyle et l'acétate mercurique par un mécanisme de métal-gabarit conduit à des analogues dithio de cyclitols d'une stéréochimie particulière.

[Traduit par le journal]

We have recently described the synthesis of 2,5-dideoxystreptamine (1) and derivatives from *cis*-1,4-cyclohexadienebisepoxide (**1**) the preparation of which by an improved process has also been described by us (2). This streptamine analog served as starting material for the total synthesis of the biologically effective 5-deoxykanamycine A analog of the kanamycin class of antibiotics (3). Synthetic endeavors of this kind necessitate the cumbersome and uneconomical protection and deprotection of the substrate amino groups. The best way to circumvent these complications would be to use the 2,5-diazido analog **2** of 2,5-dideoxystreptamine as starting material for glycoside synthesis. Reduction at the last stage would quantitatively transform the azido groups to amine functions. Unfortunately, reaction of the azide anion with bisepoxide **1** gives only the expected 1,4-diazido-3,4-diol **4**.[2] We have now found that the use of aluminium azide in THF leads to the desired 1,3-diazido isomer **2** in low yield. No attempt was made to improve the yield. It appears that the major side reaction involved epoxide degradation by tenacious residual aluminium chloride salts. By analogy with the observations of others (4, 9), formation of the 1,3-diazido isomer is attributable to a template effect brought about by the oxophilic aluminium cation as depicted in **5**. The suitability of this diazidodiol in glycoside synthesis was briefly explored using 6-deoxy-6-azido-2,3,4-tris(*O*-benzyl)-α-glucosyl chloride (5) as the reagent. The expected glycosides were formed and one of the diastereomers isolated in crystalline form (**6**). We have not established which of the diastereomers **6***a* or **6***b* actually crystallized. This glucoside is a precursor of 5-deoxyneamine and kanamycin analogs. The practical potential of synthon **2** is thus established.



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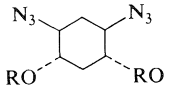

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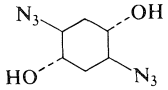

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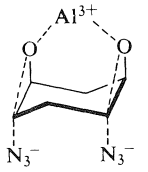

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Another class of cyclitol analogs of potential interest as precursors of biologically active molecules consists in thiol relatives of defined geometry. The bisepisulfide analogs **7** and **9** and monoepisulfides

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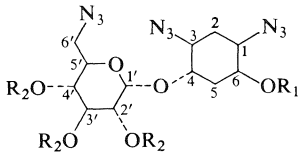
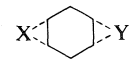
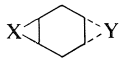


6*a* R_1 = Ac, R_2 = Benzyl
6*b* R_1 and glycosyl are interchanged

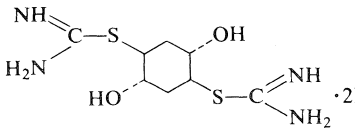


7 X = Y = S
8 X = S, Y = O



9 X = Y = S
10 X = S, Y = O

8 and **10** of the corresponding bisepoxides appeared attractive as starting materials and accordingly their synthesis from *cis*- and *trans*-1,4-cyclohexadienebisepoxides was investigated. In general, epoxides can be converted to episulfides by reaction with thiocyanate, thioamides, thiourea, thiotriphenylphosphine and related reagents (ref. 6 and references therein). In our hands, the thiourea method proved to be the most effective and reliable. Thus, treatment of the *cis*-bisepoxide **1** with a twofold excess of thiourea in the presence of 2 equiv. of sulfuric acid followed by mild base treatment of the intermediate bisisothiouronium salt **11** gave the crystalline *cis*-bisepisulfide **7** in high yield. On standing, it gradually decomposed and underwent rapid polymerization in protic solvents. When the *cis*- or *trans*-bisepoxides (1) were treated with thiourea in the presence of only 1 equiv. of acid followed by base treatment, the corresponding *cis*- and *trans*-monoepisulfide monoepoxide **8** and **10** could be obtained. The configurational assignments are based on the well-known stereochemical course of epoxide–episulfide conversions (6–8) and were confirmed by ^1H and ^{13}C nmr spectroscopy (Table 1). Under the conditions which allowed the *cis*-bisepoxide to react cleanly in the expected manner with hydrazine (1), the bisepisulfide **7** polymerized instantly. However, it reacted readily with acetyl chloride to give the 1,4-dichlorodiacetyl product **12** (the ^{13}C nmr spectrum showing only one signal at 36.156 ppm for the two methylenes). This result parallels Craig's observations with the corresponding *cis*-bisepoxide (9). Reduction of **7** with lithium aluminium hydride (LAH) gave *cis*-1,4-cyclohexane dithiol which was characterized as the diacetyl derivative **13** (the ^{13}C nmr spectrum showed only one signal for the methylenes at 30.401 ppm). The *cis*-bisepisulfide undergoes 1,4-diaxial attack by LAH whereas the *cis*-bisepoxide is reduced to *cis*-1,3-cyclohexane diol (9). This contrasting behavior can be explained on the basis that a template effect by the aluminium ion (as in the formation of **2**) controls the course of reduction with the bisepoxide



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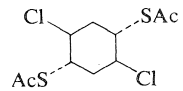

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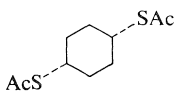

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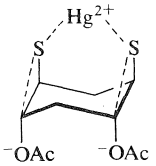

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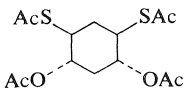

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(9) but not in the case of the bisepisulfide because of the poor affinity of aluminium for sulfur. However, with a strongly thiophilic salt such as mercuric acetate, a template-directed 1,3-diaxial opening of the bisepisulfide by acetate (as in **14**) now occurred. The product was purified as the tetraacetate **15** and in agreement with the assigned structure, the ^{13}C nmr spectrum of the compound showed two signals for the methylenes at 33.02 and 30.64 ppm. The use of these geometrically defined thiocyclitols in the synthesis of potentially bioactive molecules will be reported later.

TABLE 1. Spectral characteristics of 1,4-cyclohexadiene bisepoxide, bisepisulfides, and mixed monoepoxides monoepisulfides

Compound	Mass *m/e*	^1H nmr ($CDCl_3$), δ (ppm)	^{13}C nmr ($CDCl_3$), δ (ppm)
1	112	2.50 (4H, broad q) 3.09 (4H, broad s)	49.20 (CO) 23.60 (CH_2)
7	144	2.28–3.16 (4H, m) 3.10 (4H, s)	33.60 (CS) 29.60 (CH_2)
8	128	2.25–2.75 (4H, m) 3.10 (4H, m)	48.28 (CO) 30.27(CS) 22.17 (CH_2)
9	144	2.65 (4H, m) 2.95 (4H, m)	31.83 (CS) 29.78 (CH_2)
10	128	2.60 (4H, m) 3.18 (4H, m)	48.00 (CO) 33.80 (CS) 27.20 (CH_2)

Experimental

Melting points were evaluated with a Thomas-Hoover capillary apparatus and are uncorrected. The ^1H nmr spectra were obtained with a Varian T-60 spectrometer using tetramethylsilane as the internal standard. The ^{13}C nmr spectra were obtained with a Brucker HX-90 spectrometer and mass spectra with a Varian Mat-CH-5 single focusing spectrom-

eter. Elemental analyses were performed by Sprang Microanalytical Laboratory.

trans-trans-*1,5/2,4-1,5-Diazido-2,4-cyclohexanediol Diacetate (3)*

A solution of anhydrous $AlCl_3$ (5.985 g) in dry THF (90 ml) was added to a suspension of sodium azide (9.65 g) in dry THF (90 ml). The mixture was heated under reflux for 90 min under nitrogen and a solution of the bisepoxide **1** (1) (2 g) in 115 ml THF added dropwise over a 2 h period. Heating under reflux was continued for an additional 2.5 h, the mixture cooled to 0°C, and concentrated HCl (22.5 ml) carefully added followed by a 1:1 mixture of ether–THF (150 ml). The organic phase was separated, washed with aqueous NaCl, dried, and evaporated. The oily residue was treated with excess acetic anhydride in pyridine (room temperature, 17 h), the solution worked up in the usual manner, and the residue purified on thick silica gel plates ($CHCl_3$ as the solvent). The major band yielded an oil which crystallized from hexane–$CHCl_3$ to give 650 mg of crystals, mp 78°C; ir (KBr) 2100, 1740 cm^{-1}; ^1H nmr (CD_3Cl_3) δ: 4.83 (2H, m), 3.55 (2H, m), 2.75–1.20 (4H, m), 2.10 ppm (6H, s); ^{13}C nmr ($CDCl_3$) δ: 169.25 (C—O), 71.46 (C—O), 59.97 (C—N_3), 33.21 and 31.86 (CH_2), 20.43 ppm (CH_3); M^+ 282. *Anal.* calcd. for $C_{10}H_{14}N_6O_4$: C42.55, H5.00, N29.78; found: C42.60, H4.89, N29.78.

trans-trans-*1,5,2/4-1,5-Diazido-2,4-cyclohexanediol (2)*

The preceding diacetate (0.5 g) in methanol (150 ml) was heated under reflux in the presence of the resin Rexyn 101 (2 g) for 3–4 h, the resin removed by filtration, and the filtrate evaporated *in vacuo* to give **2** (323 mg) which after recrystallization from EtOAc–hexane had mp 80–81°C; ir (KBr): 3500–2700, 2080 cm^{-1}. *Anal.* calcd. for $C_6H_{10}N_6O_2$: C36.36, H5.09, N42.41; found: C36.43, H5.12, N42.26.

2,5-Dideoxystreptamine Dihydrochloride

A solution of the preceding diazido diol **2** (0.20 g) in ethanol (10 ml) was shaken under a pressure of 48 psi of hydrogen over Raney Ni at room temperature. After 2 h, the mixture was worked up in the usual manner, the residue treated with ethanolic HCl to give in quantitative yield, the title compound, mp 290–293°C (lit. (4) mp 290–295°C) identical in every respect with an authentic specimen (1).

A solution of the diazido diol **2** (1.265 g) in dry DMF (11.3 ml) was mixed under nitrogen at room temperature with $CaSO_4$ (4.13 g) (preheated to 240°C for 4 h) and after stirring for 10 min, the temperature was raised to 80°C and a solution of 6-deoxy-6-azido-2,3,4-tris(*O*-benzyl)-α-D-glucopyranosyl chloride (3.158 g) (5) in DMF (11.3 ml) added dropwise (30 min) followed by the addition of $Hg(CN)_2$ (4.735 g). The mixture was stirred at 80°C for 23 h, 2.35 g of $Hg(CN)_2$ added, and heating to 87°C maintained for another 7 h. After standing overnight at room temperature, CH_2Cl_2 was added and the precipitate filtered off and the solids washed repeatedly with CH_2Cl_2. The combined filtrate and washings were washed with water, dried and evaporated to yield a dark syrup heterogeneous by tlc. Chromatography on silica ($CHCl_3$–hexane 1:1 as the eluent) gave a crude fraction (3.61 g) R_f 0.14 ($CHCl_3$) which was rechromatographed on thick plates of silica ($CHCl_3$–hexane 1:1). The major band was treated with acetic anhydride in pyridine in the usual manner and after work-up, the product chromatographed on thick plates of silica ($CHCl_3$–hexane 1:1). The band with R_f 0.5–0.6 appeared to consist of the two diastereomers **6***a* and **6***b* as judged by nmr spectroscopy. On standing in ethanol one of the isomers crystallized (151 mg), mp 96–97°C; ir (KBr): 2100, 1710 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.25 (15H, m, 3 C_6H_5); 5.10–4.25 (8H, m, 3 benzylic-CH_2, H, and 6H), 4.25–2.90 (9H, m, at 2′,3′,4′,5′,6′ and 1,3,4), 2.06 (3H, s, CH_3CO) and 2.90–1.18 (4H, m, at 2,5); $[\alpha]_D^{25}$ 50° (*c* 1, $CHCl_3$). *Anal.* calcd. for $C_{35}H_{39}N_9O_7$: C60.24, H5.63, N18.07; found: C60.30, H5.70, N17.84. It was not possible to obtain the other isomer in crystalline form from the mother liquors.

cis-*4,8-Dithiatricyclo[5.1.0.0^{3,5}]octane (7)* (cis-*1,4-Cyclohexadiene bisepisulfide*)

The bisepoxide **1** (1.12 g) was added at 0°C to a stirred suspension of thiourea (2.064 g) in 2 *N* H_2SO_4 (10 ml) under nitrogen. The icebath was removed and stirring continued for 1 h during which time the product dissolved gradually to be replaced by a white precipitate of the bisisothiouronium salt **11**. Aqueous Na_2CO_3 was added to bring the pH to 8.5 and the mixture immediately extracted with benzene. The combined extracts were dried and evaporated to give the bisepisulfide **7** (1.2 g; 83%), mp 64–65°C (hexane–$CHCl_3$). The spectral characteristics are given in Table 1. *Anal.* calcd. for $C_6H_8S_2$: C49.95, H5.59, S44.45; found: C50.07, H5.58, S44.47.

trans-*4,8-Dithiatricyclo[5.1.0.0^{3,5}]octane (9)* (trans-*1,4-Cyclohexadiene bisepisulfide*)

The preceding procedure was followed using 0.336 g of *trans*-1,4-cyclohexadiene bisepoxide (1) and 0.456 g of thiourea in 3 ml of 2 *N* H_2SO_4. After work-up, **9** was obtained (0.28 g; 64.8%) as an oil which upon sublimation *in vacuo* gave crystals, mp 47–48°C. See Table 1 for spectral data. *Anal.* calcd. for $C_6H_8S_2$: C49.95, H5.59, S44.45; found: C49.97, H5.72, S44.51.

cis-*4-Oxa-8-thiatricyclo[5.1.0.0^{3,5}]octane (8)*

To a suspension of *trans*-1,4-cyclohexadienebisepoxide (1) (0.336 g) and thiourea (0.228 g) in water (9 ml) was added at 5°C under nitrogen 1.5 ml of 2 *N* H_2SO_4. The icebath was removed and after 20 min a white precipitate had separated. Stirring was continued for 20 min, the pH brought to 8.5 with aqueous $NaHCO_3$, and the mixture extracted with benzene. The combined extracts were combined, dried and evaporated to give a semisolid mass which was purified on thick plates of silica ($CHCl_3$–hexane 4:1). The major band yielded 0.158 g (36.5% yield) of the *trans*-bisepisulfide **9** (identical to the above product) and the minor band yielded a 0.047 g (12.3% yield) of **8** as an unstable colorless oil, bp 40°C/0.1 Torr. The spectral characteristics are given in Table 1. Reliable microanalyses could not be obtained because of its instability. Unchanged starting material was recovered in 44.6% yield.

trans-*4-Oxa-8-thiatricyclo[5.1.0.0^{3,5}]octane (10)*

Application of the preceding procedure to 0.896 g of **1** and 0.729 g of thiourea in 4 ml of 2 *N* H_2SO_4, led after work-up and chromatography on thick plates of silica ($CHCl_3$–CH_3OH 96:4) to 0.230 g (20% yield) of **10** which after sublimation had mp 62–63°C. See Table 1 for spectral data. *Anal.* calcd. for C_6H_8OS: C56.24, H6.29, S25.02; found: C56.10, H6.23, S24.53.

trans-trans-*1,4/2,5-2,5-Dichloro-1,4-cyclohexanedithiol Diacetate (12)*

A solution of the bisepisulfide **7** (0.65 g) in acetyl chloride was stirred under nitrogen at room temperature for 17 h after which time the mixture was evaporated *in vacuo*, the residue taken up in CH_2Cl_2, the solution washed with aqueous NaCl, dried, and evaporated. From hexane, crystals mp 89–90°C, were obtained (0.587 g or 43.5% yield); ir (KBr): 1680 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 4.03 (4H, m), 2.70–2.40 (4H, m), 2.40 ppm (6H, s); ^{13}C nmr ($CDCl_3$) δ: 192.55 (C—O), 57.68 (C—Cl), 45.00 (C—S), 36.16 (CH_2), 30.38 ppm (CH_3); M^+ 300. *Anal.* calcd. for $C_{10}H_{14}Cl_2O_2S_2$: C40.05, H4.67, S21.22; found: C40.01, H4.72, S21.21.

cis-*1,4-Cyclohexanedithiol Diacetate (**13**)*

A solution of **7** (1.12 g) in dry THF (30 ml) was added dropwise to a refluxing suspension of LAH (0.5 g) in dry ether (30 ml) under nitrogen and heating continued for 2 h after which time a mixture of aqueous HCl–THF was carefully added while cooling in ice. The organic layer was separated, dried and evaporated to give a colorless oil which was taken up in pyridine–acetic anhydride. After standing at room temperature overnight, the mixture was worked up in the usual manner to yield a semisolid consisting of **13** (0.542 g or 30% yield). Sublimation gave white crystals mp 63–65°C; ir (KBr): 1685 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 3.60 (2H, m), 2.30 (6H, s), 1.80 ppm (8H, m); ^{13}C nmr ($CDCl_3$) δ: 30.401 (CH_2 groups), 30.759 (CH_3), 40.92 (C—S), 195.065 ppm (C=O); M^+ 232. *Anal.* calcd. for $C_{10}H_{16}O_2S_2$: C51.69, H6.94, S27.60; found: C51.60, H6.87, S27.63.

trans-trans-*1,5/2,4-2,4-Dithiol-1,5-cyclohexanediol Tetraacetate (**15**)*

A solution of **7** (0.458 g) in dry THF (80 ml) was heated under reflux for 17 h in the presence of $Hg(OAc)_2$ (2.02 g) under nitrogen. Water (5 ml) was added and a stream of H_2S passed through the mixture until precipitation of HgS was complete. Ethyl acetate (100 ml) was added, the mixture filtered, the filtrate washed with aqueous NaCl, dried and evaporated to give an oil which was taken up in pyridine–acetic anhydride. After 16 h, the solution was worked up in the usual manner and the resulting oil purified on thick plates of silica ($CHCl_3$). The major band yielded 0.24 g (21.7% yield) of **15** which crystallized from hexane–$CHCl_3$; mp 121°C; ir (KBr): 1730, 1690 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 4.93 (2H, m), 3.90 (2H, m), 3.00–1.80 (4H, m), 2.40 ppm (6H, s); ^{13}C nmr ($CDCl_3$) δ: 193.13 (S—CO), 169.61 (O—CO), 70.13 (C—O—), 41.65 (C—S), 33.02 and 30.64 (CH_2), 20.93 ppm (CH_3); *m/e* 289 (M^+ – AcO). *Anal.* calcd. for $C_{14}H_{20}O_6S_2$: C48.27, H5.79, S18.41; found: C48.38, H5.70, S18.47.

Acknowledgements

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