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COUPLING OF EPOXIDES WITH 2-BENZOTHIAZOLYLALKYLLITHIUMS.

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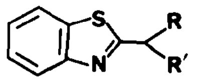
Summary: 2-Benzothiazolylalkyllithiums 1a-e react with epoxides 2a-d furnishing γ-hydroxyalkylbenzothiazoles 3 and 4, 5 and 6, 7 and 8, 9. The reaction of 1b with 2a and 2b proceeds with a pronounced syn-diastereoselection giving 3 and 4 (3/4 ratio > 95/5) and 5 and 6 (5/6 ratio : 86/14) respectively. Such a syn diastereoselection is rationalized in terms of transition state energy. A poor regio- and diastereoselection is observed in the reaction of 1b with 2c wich leads to 7 and 8. The reaction of 1d with 2a is complicated by the selfcondensation of 1d giving a mixture of 10 and 11.

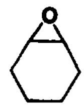
Diasteroselective aldol reactions are of a significant value in synthetic organic chemistry.[1] Similar selective enolate/epoxide chemistry has not been pursued. Neverthless, development of such a chemistry would provide a valuable method of carbon-carbon bond forming reaction leading to a great variety of γ-hydroxycarbonylcompounds.

Enolates of ketones and esters have been reported not to react with epoxides; only E-aluminum enolates of t-butyl propionates have been recently reported to react in a stereoselective manner with unsymmetrical epoxides.[2] Nitrogen containing enolates (e.g. of amides,[3] enamines[4] and ketimines[5]) do open epoxides. However, the stereoselection of such a coupling process has not been studied. Amide enolates do open epoxides stereoselectively, but highly hindered amide enolates are required to achieve high diastereoselectivity.[3a] To our knowledge, the reaction of aza-enolates in which the aza group belongs to a heterocyclic ring with epoxides has never been studied sofar. As a part of our continuing interest in the coupling reaction of heteroaryl alkyl metals with electrophiles[6] we report here the reaction of 2-benzothiazolylalkyllithiums with some epoxides.

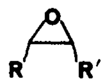
Treatment of 2-benzothiazolylbenzyllithium 1b, promptly available by lithiation (LDA, THF, -78°C) of 2-benzylbenzothiazole 1a with the epoxide 2a led to the cyclohexanols 3 and 4, which could be easily separated by chromatography and characterised by IR and NMR spectroscopy. The reaction turned out to be almost completely syn-diastereoselective.[7] Configurations to 3 and 4 were assigned on the basis of the coupling constants between Ha and Hb protons (J 3.8 Hz for the syn isomer and J 5.8 Hz for the anti isomer).



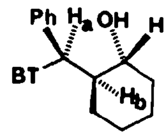
1a : R= Ph ; R'= H
1b : R= Ph ; R'= Li
1c : R= Ph ; R'= MgBr
1d : R= Me ; R'= Li
1e : R= Me ; R'= H



2a



2b : R= R'= Me (trans)
2c : R= Ph ; R'= H
2d : R= Ph ; R'= pClPh (trans)



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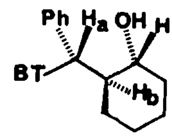

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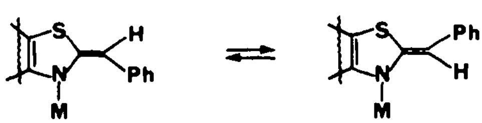
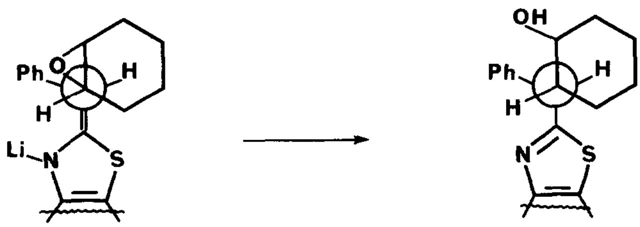
Determination of the configuration at the OH bearing carbon atom of 3 (or 4) was not trivial and could be accomplished only by X-Ray crystallography. Figure 1 clearly shows that the configuration of the OH bearing carbon atom of the cyclohexane ring of 3 was opposite to that of the adjacent carbon involved in the coupling reaction. This indicates that the epoxide ring opening reaction has proceeded with inversion of configuration. This result is in accordance with the literature observation that organometallics cause ring opening of epoxides with complete inversion of configuration.[8] It might be that the preliminary coordination of the organolithium 1b on the epoxide oxygen of 2a activates the C-O bond cleavage. Indeed, we have found that 1c, achievable by transmetallation of 1b with $MgBr_2$, does not react with 2a, presumably because of the weaker coordinating ability of magnesium with respect to lithium. Indeed Mg-O pair is known to be less tightly bound than the Li-O counterpart.[9]

Considering that benzothiazolylbenzyllithium 1b exists as an equilibrium of the two aza-enolate forms (A) and (B), with a preference for the geometrical form (A), with the phenyl group cis to the nitrogen atom,[10] the syn-diastereoselection observed in the coupling between 1b and 2a

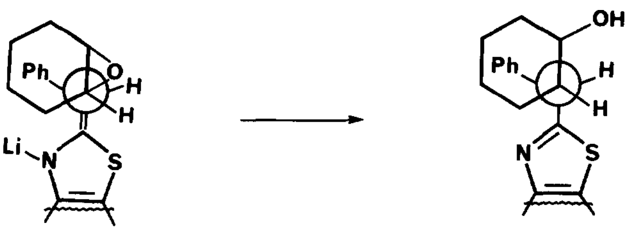


(A) (B)

might tentatively be explained in terms of transition state energy. Transition state ST_1 leading to the syn-diasteomer 3 and arising from a re-si[12] face matching is thermodinamically favored over transition state ST_2 leading to the anti diastereomer 4 and arising from a re-re face matching which experiences a larger steric compression.

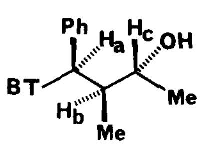


ST_1 (re-si face matching) 3 syn



ST_2 (re-re face matching) 4 anti

The ring opening reaction of the trans-butene oxide 2b with 1b proceeded too in a syn-diastereoselective manner relatively to the newly formed C-C bond to give the alcohols 5 and 6 (5/6 ratio: 86/14).



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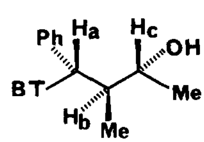

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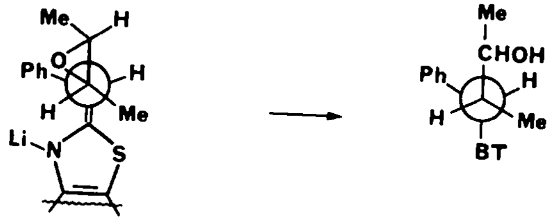
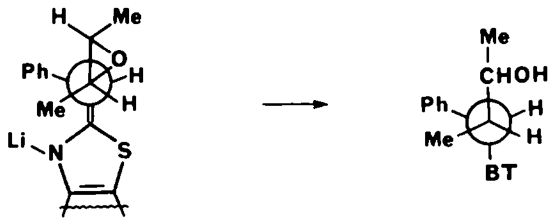
Configuration of 5 and 6 were assigned by measuring the coupling constant between Ha and Hb and between Hb and Hc.

The observed syn-diastereselection here again might be accounted for in terms of transition state energy: transition state ST_3 is energetically favored over transition state ST_4 for steric reasons.

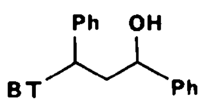


ST$_3$ 5 syn



ST$_4$ 6 syn

The reaction of 1b with a monosubstituted epoxide such as styrene oxide 2c posed problems of regiochemistry other than stereochemistry. Indeed, treatment of 1b with 2c provided a mixture of the regioisomeric alcohols 7 (diastereomeric mixture) and 8 (diastereomeric mixture), compound 8 being the more abundant one.



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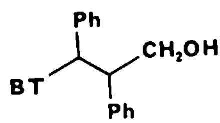

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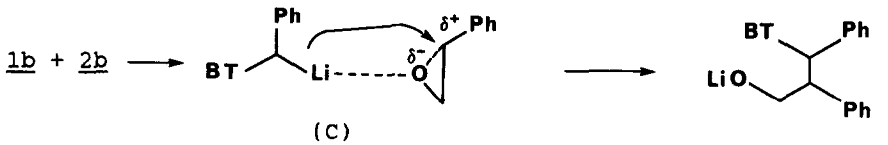
The preferred formation of 8 with respect to 7 (8/7 ratio: 64/36) sounded surprise in view of the long standing generalisation that nucleophilic attack in monosubstituted, geminally disubstituted and trisubstituted non protonated epoxides occurs at the least substituted ring carbon.[11] The benzylic acceleration could be invoked although aryl substituted epoxides have been reported to be less reactive than the alkyl counterparts towards anionic nucleophiles.[12] The benzylic acceleration in our case is supported by the fact that styrene oxide has been found to be much more reactive than the cyclohexene oxide towards 1b in a competitive experiment. Moreover, the preferential formation of 8 in the reaction of 1b with 2c migth be accounted for by assuming a preliminary coordination of the organolithium 1b on the epoxide oxygen of 2c to give the complex C with a higher positive charge density on the phenyl bearing carbon atom that would cause preferential attack of 1b at the α carbon from both sides.



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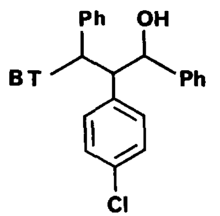
The reaction of 1b with the disubstituted epoxide 2d (trans) afforded exclusively the benzylic alcohol 9 (diastereomers) likely stemming from the attack of 1b at the more electrophilic carbon atom of the epoxide ring that is the one bearing the p-chlorophenyl substituent.



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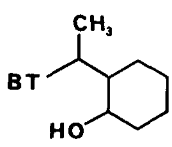
The reaction of other benzothiazolylalkyllithiums with epoxides was complicated by the known tendency of 2-alkylbenzothiazoles to undergo self-condensation in basic conditions.[13] Indeed, the reaction of 2-benzothiazolylethyllithium 1d with cyclohexene oxide 2a furnished an almost equimolecular mixture of the cyclohexanol 10 (diastereomeric mixture) and the ketone 11



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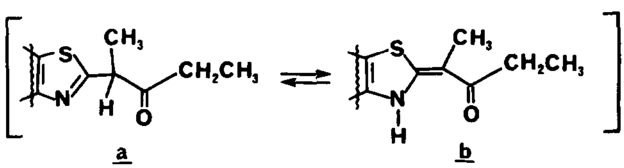
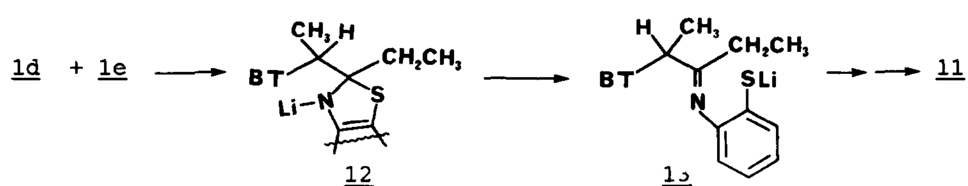


11

The formation of compound 11 might be accounted for by considering that the self-condensed intermediate 12 might undergo ring cleavage to give the imine 13, which then converts to the ketone 11 upon hydrolysis.



EXPERIMENTAL

Melting points were measured on a Electrothermal apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 598 spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-360 A or a Varian XL-200 spectrometers and chemical shifts are reported in parts per million (δ) from internal Me_4Si. Column chromatography was carried out by using Merck 70-230 mesh silica gel.

Materials: Tetrahydrofuran (THF) and diethyl ether (Et_2O) from commercial sources (RS, Carlo Erba) were purified by distillation (twice) from sodium wire in a N_2 atmosphere. Petroleum ether (RS, C.E.) refers to the 40-60°C boiling fraction. 2-benzyl-[13] 1a and 2-ethyl-benzothiazole[13] 1e were prepared as reported. Cyclohexene oxide 2a, 2-butene oxide 2b, styrene oxide 2c and p-chlorostylbene oxide 2d were commercial grade and were used without further purification. n-BuLi (hexane solution, from Fluka) was titrated prior to use.

Lithiation of 2-Benzylbenzothiazole 1a and reaction with cyclohexene oxide 2a

To a stirred solution of lithium diisopropylamide (LDA), prepared by adding an hexane solution of 2.3 N n-BuLi (2.3 ml, 5.3 mmol) to a THF (8 ml) solution of diisopropylamine (0.54 g, 5.3 mmol), was added, dropwise, at -78°, under N_2, a THF (3 ml) solution of 1a (1.0 g, 4.4 mmol). After 5h at -78°C, the reaction mixture was allowed to warm to room temperature and kept there for about 20 h. Quenching with a saturated aqueous solution of NH_4Cl, extraction with diethyl ether (3x25 ml), drying over Na_2SO_4 and solvent removal under reduced pressure, left an oil residue that, after column chromatography on silica gel using Et_2O-petroleum ether (1:9) as eluent, gave mainly syn-2-(2-benzothiazolyl)phenylmethylciclohexanol 3 (0.80 g, 56% yield) m.p. 98-100°C ($EtOH-Et_2O$). IR (nujol) 3600-3120 cm-1 (OH). ^{1}H-NMR ($CDCl_3$-D_2O): δ 0.9-2.7 (m, 8 H), 3.15-3.75 (m, 2 H), 4.73 (d, 1 H, J = 3.8 Hz), 7.3-8.3 (m, 9 H).
When the reaction was carried out under different experimental conditions (30 min at -78°C, 25h at room temperature) usual work up led to an oil residue that, after column chromatography on silica gel using Et_2O-petroleum ether (1:9) as eluent, gave 3 (50% yield) and anti-2-(2-benzothiazolyl)phenylmethyl cyclohexanol 4 (11% yield), m.p. 134-136°C ($EtOH-Et_2O$). IR (nujol) 3600-3200 cm-1 (OH); ^{1}H-NMR ($CDCl_3$-D_2O): δ 0.7-2.85 (m, 8 H); 3.1-3.75 (m, 2 H); 4.92 (d, 1 H, J = 5.8 Hz); 7.26-8.2 (m, 9 H).
A poorer diastereoselection was observed in the reaction of 1b with 2a when n-BuLi was used as lithiating agent (3/4 ratio: 61/39).

Reaction of 2-benzothiazolylphenylmethyllithium 1b with trans-butene oxide 2b

To a stirred solution of 1b (2.66 mmol) prepared as above, a THF (3 ml) solution of 2b (0.23 g, 3.2 mmol), was added dropwise at - 78°C. After 30 min the reaction mixture was allowed to warm to room temperature and kept there for 24 h. Usual work up afforded a mixture of three main compounds that were separated by column chromatography using Et_2O-petroleum ether (1:9) as eluent. The first eluted compound was the starting material 1a, the second was (syn)-4-(2-benzothiazolyl)-4-phenyl-3-methyl-2-butanol 5 (0.177 g, 22%), m.p. 82-84 °C (Et_2O-petroleum ether). IR (nujol) 3550-3100 cm^{-1} (OH). ^{1}H-NMR (200 MHz, $CDCl_3$-D_2O): δ 0.96 (d, 3 H, J = 6.9 Hz), 1.20 (d, 3H, J = 6.4 Hz), 2.47 (m, 1 H), 3.90 (m, 1 H), 4.54 (d, 1 H, J = 9.9 Hz), 7.25-7.45 (m, 7 H), 7.73-7.76 (m, 1 H), 7.97-8.01 (m, 1 H). The third eluted compound was (anti)-4-(2-benzothiazolyl)-4-phenyl-3-methyl-2-butanol 6 (0.028 g , 3%), m.p. 121-123 °C (Et_2O-petroleum ether). IR (nujol) 3400_{broad} cm^{-1} (OH). ^{1}H-NMR (200 MHz, $CDCl_3$-D_2O): δ 1.04 (d, 1 H, J = 6.4

Hz), 1.18 (d, 3 H, J = 10 Hz), 2.6 (m, 1 H), 3.78 (m, 1 H), 4.47 (d, 1 H, J = 10 Hz), 7.2-7.6 (m, 7 H),7.78-7.80 (m, 1 H), 7.99-8.04 (m, 1 H).

Reaction of 2-benzothiazolylphenylmethyllithium 1b with styrene oxide 2c.

To a stirred solution of 1b (2.66 mmol) prepared as above, a THF (3 ml) solution of 2c (0.38 g, 3.19 mmol) was added dropwise at -78°C. After 30 min at -78°C the reaction mixture was allowed to warm to room temperature and kept there for 24h. Quenching with aqueous NH_4Cl and usual work up left a residue (0,97 g) that was column chromatographied on silica gel using Et_2O-petroleum ether (1:9) as eluent to give two main products. The first eluted compound was 3-(2-benzothiazolyl)-1,3- diphenyl-1-propanol 7. Oil (0.283 g, 32%). IR (neat) 3700-3120 cm^{-1} (OH). ^1H-NMR (200 MHz, $CDCl_3$-D_2O) 2.50-2.55 (m, 1 H), 2.79-2.93 (m, 1 H),4.7 (dd, 1 H, J = 5.2 , J = 9.5 Hz), 4.8 (dd, 1 H, J = 4.25, J = 8.57 Hz), 7.24-7.48(m, 12 H), 7.7-7.8 (m, 1 H), 7.90-8.0 (m, 1 H). The second eluted product was a diasteromeric mixture of 3-(2-benzothiazolyl)-2,3-diphenyl-1-propanol 8 (0.416 g, 45%). The diastereomers were then separated by a further column chromatography (CH_2Cl_2 as eluent) and characterized. Syn isomer: oil. IR (neat) 3140-3700 cm^{-1} (OH). ^1H-NMR (200 MHz, $CDCl_3$-D_2O): δ 3.85- 3.91 (m, 3 H), 4.92 (d, 1 H, J = 10.4 Hz), 7.1-7.5 (m, 12H), 7.77-7.81 (m, 1H), 8.01-8.05 (m, 1 H). Anti isomer : m p. 132-134°C (Et_2O-petroleum ether). IR (nujol) 3300-3600 cm^{-1} (OH).^1H-NMR (200 MHz, $CDCl_3$-D_2O): δ 3.69-3.73 (m, 2 H), 3.89-4.0 (m, 1 H), 4.9 (d, 1 H, J = 10.4 Hz), 7.0-7.55 (m, 12 Hz), 7.66-7,70 (m, 1 H), 7.88-7.90 (m, 1 H).

Reaction of 2-benzothiazolylphenylmethyllithium 1b with trans-4-chlorostylbenoxide 2d.

To a stirred solution of 1b prepared by addition of 1a (0.6 g, 2.66 mmol) in 3 ml of THF to a solution of LDA [diisopropylamine (0.32 g, 3.2 mmol), 2,3 N n-BuLi (1.4 ml, 3.2 mmol)], a THF (3 ml) solution of 2d (0.74 g, 3.2 mmol) was added dropwise at -78° C. After 30 min at -78°C the reaction mixture was allowed to warm to room temperature and kept there for 24h. Quenching with aqueous NH_4Cl and usual work up left a residue (1.06 g) that was column chromatographied on silica gel using Et_2O-petroleum ether (1:9) as eluent to give two main products. The first eluted compound was the starting material 1a, the second eluted product was a diastereomeric mixture of 3-(2-benzothiazolyl)-1,3-diphenyl-2- -(4-chlorophenyl)-1-propanol 9 (0,64 g, 53%). ^1H-NMR (200 MHz, $CDCl_3$) : δ 3.3 (broad s, 1H, exchange with D_2O), 3.9-4.0 (m, 1H), 5.09-5.13 (m, 1H), 5.28-5.36 (m, 1H), 6.86-7.52 (m, 16H), 7.82 (d, 1H, J=7.8 Hz), 8.06 (d, 1H, J=7.8 Hz).

Reaction of 1-(2-benzothiazolyl)ethyllithium 1d with cyclohexene oxide 2a.

To stirred solution of 1d, prepared by addition of 1e (3.67 mmol) in THF (3 ml) to a solution of LDA [diisopropylamine (4.05 mmol), 2,3 N n-BuLi (4.05 mmol)], a THF (3 ml) solution of 2a(4.04 mmol) was added dropwise at -78 °C. After 30 min the reaction mixture was allowed to warm to room temperature and kept there for 24 h. Usual workup afforded a mixture of starting material 1e and two main compounds that were separated by column chromatography using Et_2O-petroleum ether (2:8) as eluent. The first eluted compound was 2-(2-benzothiazolyl)-3-pentanone 11. Oil (0,105 g, 13%). IR (neat) (11a + 11b) 3430_{broad} (NH), 1710 cm^{-1} (C=O). ^1H-NMR ($CDCl_3$, 200 MHz) (almost exclusively 11b): δ 1.04 (dd, 3H, J=7.2, J=7.1 Hz), 1.93 (s, 3H), 2.80 (dq, 1H, J=7.1, J=18.8 Hz), 3.02 (dq, 1H, J=7.2, J=18.8 Hz), 5.27 (sharp singlet, 1H, exchange with D_2O), 7.3-7.5 (m, 2H), 7.83-7.88 (m, 1H), 7.99-8.03 (m, 1H). The second eluted compound was 2-[1-(2-benzothiazolyl)ethyl]cyclohexanol 10 (0.173 g, 20%), m.p. 79-80 °C (Et_2O-petroleum ether). IR (nujol) 3500-3100 cm^{-1} (OH). ^1H-NMR ($CDCl_3$-D_2O, 200 MHz): δ 1.16-1.43 (m, 5H), 1.58-1.70 (m, 2H), 2.03-2.11 (m, 3H), 2.63 (ddd, 1H, J=3.9, J=9.8, J=11.7 Hz), 3.27 (dq, 1H, J=4.8, J=10.0 Hz), 6.66-6.76 (m, 2H), 7.01-7.18 (m, 1H), 7.36-7.41 (m, 1H).

X-ray crystallographic data of 3:

Crystal data: $C_{20}H_{21}NOS$, $\underline{M}$ = 323.5, monoclinic, space group $P2_1$, a = 11.571 (2), b = 25.249 (3), c = 5.932 (1) Å, β = 104.09 (2)°, $\underline{U}$ = 1680.9 (5) $Å^3$, Z = 4, Dc = 1.28 gcm^{-3}, F(000) = 688.0, Cu-Kα radiation, λ= 1.54056 Å, μ = 16.9 cm^{-1}, crystal size 0.10 x 0.10 x 0.26 mm.
The intensities of 3222 reflections were collected to a 2 θ_{max} = 130°, on a computer controlled Siemens AED by the ω- 2 θ scan technique. The intensity of standard reflection was measured every 50 reflections to check the stability of the crystal and the electronic. No absorption correction was applied.

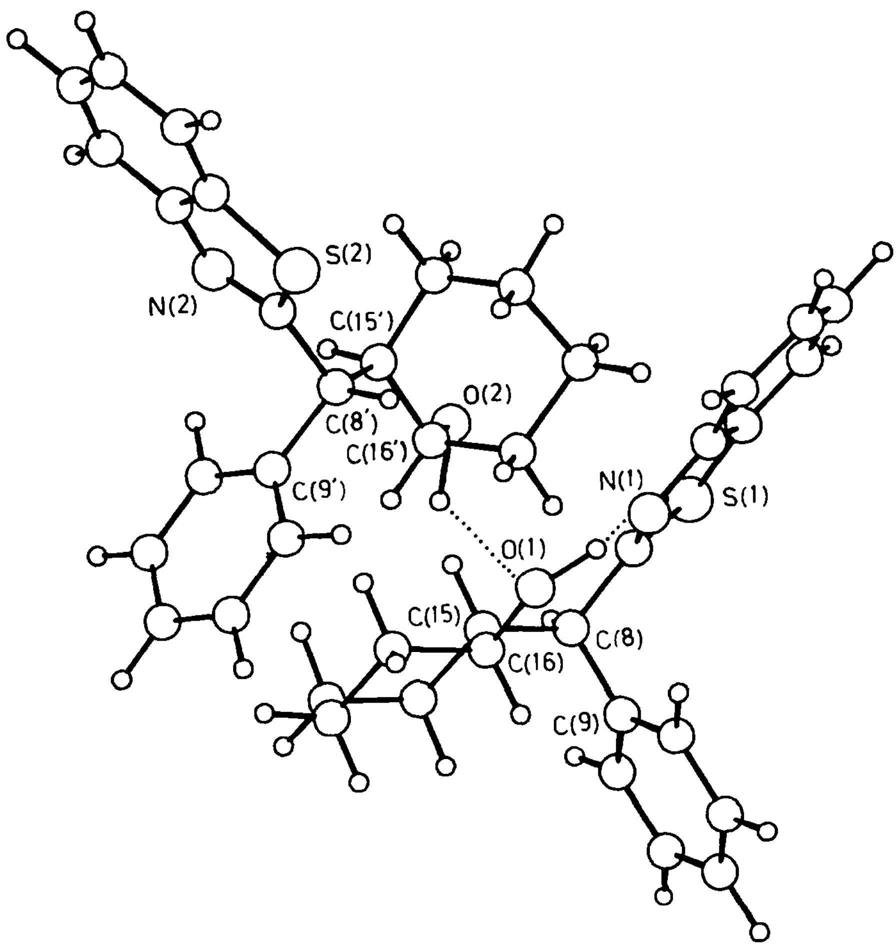


Figure 1. Perspective view of the two independent molecules of 3

The structure was solved by direct methods using the SHELX86 program[14] and refined to a final R value of 10.25%, wR 10.39% for 994 reflections with I>3 σ (I). [w = 1.0158| σ^2 (Fo) + 0.01182 $(Fo)^2]^{-1}$. H atoms were placed in calculated position "riding" on their C atoms exept HO1 and HO2 which were located from a Fourier difference synthesis. In order to maintain a reasonably high parameters- to-data ratio, all carbon atoms were refined isotropically. The value of wR for the alternative enantiomeric distribution was 10.41%, which indicate that the enantiomeric structure cannot be reyected because the accuracy of the analysis is not enough to remove the ambiguity. The standard deviation are appreciably high, because of the low number of reflection available, so a detailed discussion of bond distances and angles is not possible. Scattering factors for C, H, O, N, S was taken from Ref.15, and both the real and imaginary components of anomalous dispersion were included.

The molecular structure consists of two independent molecules with the same absolute configuration but different orientation of the cyclohexanol group relatively to benzothiazole moiety. The rotation of the cyclohexane ring must be due to a favorable situation for a intermolecular hydrogen bond [O2-HO2-•-•O1(1-x,y-1/2,3-z) = 2.93 (2) Å] between oxygen atoms of the two independent molecules. O2 is in axial position [C20'-C15'-C16'-O2 = -67 (3)°] while O1, of the other molecule, is equatorial [C20-C15-C16-O1 = -171 (2)°] and forms an intramolecular hydrogen bond with the nitrogen atom N1 [O1-HO1-•-•N1 = 2.58 (3)Å]. Both cyclohexane rings are in the chair conformation [the puckering parameters are respectively : q_2 = 0.05 (3), 0,09 (3) Å; θ_2 = 5 (2), 171 (2)°]. The arrangement of the hydrogen atoms with respect to C8-C15, C15-C16, C8'-C15', C15'-C16' bonds is defined by the torsional angles: H8-C8-C15-H15 = -65 (2)°; H15-C15-C16-H16 = 179 (2)°; H8'-C8'-C15'-H15' = 179 (2)°; H15'-C15'-C16'-H16' = 84 (2)°.
The packing of the two independent molecules, linked each other by hydrogen bond, is entirely due to Van der Waals forces.

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