$PhCH_2SH$, 100-53-8; Ph_3GeCl, 1626-24-0; Ph_3PbOAc, 1162-06-7; CsF, 13400-13-0; $PhCH_2SSnPh_3$, 2034-10-8; $PhCOCH_2Br$, 70-11-1; $PhCH_2Br$, 100-39-0; $CH_3COCH(Br)CH_3$, 814-75-5; $CH_3(CH_2)_5Br$, 111-25-1; $(PhCOCH_2)_2S$, 2461-80-5; $(PhCH_2)_2S$, 538-74-9; $(CH_3COCH(CH_3))_2S$, 113334-17-1; $(C_6H_{13})_2S$, 6294-31-1; $Br(CH_2)_5Br$, 111-24-0; KF, 7789-23-3; CH_3COCH_2Cl, 78-95-5; $EtCH(Me)CH_2Br$, 10422-35-2; $(ClCH_2)_2CO$, 534-07-6; $(CH_3COCH_2)_2S$, 63578-76-7; $(EtCH(Me)CH_2)_2S$, 96034-00-3; cyclo-$(SCH_2COCH_2)_2$, 16631-05-3; $PhCH_2S(CH_2)_5CH_3$, 34005-03-3; $(C_6H_{13}S)_2$, 10496-15-8; thiane, 1613-51-0.

Effective Molarities and Ionic Chain Mechanism in the Reaction of a Bifunctional Nucleophile with Substituted Bicyclobutane[1]

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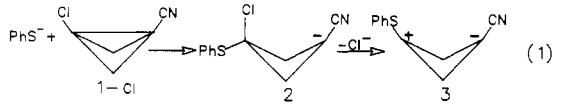
Received July 27, 1989

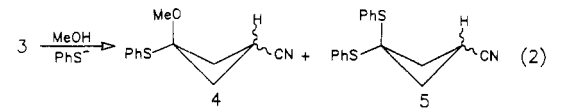
The reactions of ethylenethioglycolate with 3-chlorobicyclobutanecarbonitrile in MeOH and dimethoxyethane (DME) were studied. The reaction in MeOH involves nucleophilic attack followed by solvolysis of the α-chloro thioether moiety to give the ionic bicyclobutane. The latter undergoes mainly internal trapping of the carbenium ion to give the spiro derivative **8** along with addition products of MeOH (**9**) and a second nucleophile molecule (**10**). Addition of $HOCH_2CH_2SH$ to the reaction mixture inhibits the formation of the spiro derivative indicating that the reaction of O^- and not OH is involved in the cyclization process. The effective molarity of O^- in the cyclization reaction is estimated to be 66. In DME, the reactions were heterogenous. Substitution of Cl by $HOCH_2CH_2S$ in a nucleophilic addition–elimination mechanism gave the corresponding bicyclobutane derivative. This reacted further to give the spiro compound by an ionic chain mechanism.

In the course of the reaction of the cyano-activated halobicyclobutane **1** with nucleophiles such as MeO^- and PhS^- in MeOH, the ionic bicyclobutane **3** was obtained as a short lived intermediate.[2,3] The reaction sequence (given for PhS^- in eq 1) involves a nucleophilic attack followed



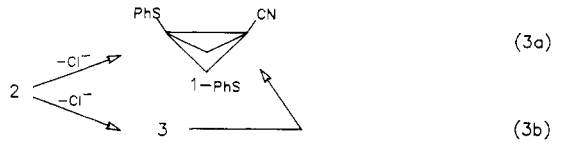
(1)

by solvolysis of the α-halo thioether moiety in **2**. Under the reaction conditions, **3** yields mainly addition products as shown in eq 2.[3] On the other hand, when the reaction



(2)

is conducted in dimethoxyethane (DME) rather than in MeOH, the bicyclic product **1**-PhS is obtained as the major product. This can be derived from **2** by either of two ways: 1,3-elimination (eq 3a) or solvolysis to **3** followed by a collapse of the zwitterion to form the covalent bond (eq 3b).



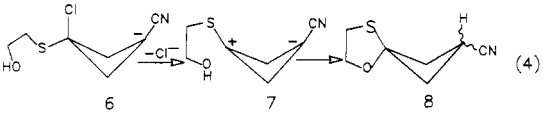
(3a)
(3b)

In order to explore the possibility of the collapse pathway, an experiment in which increasing quantities of MeOH were added to the DME solution was performed.[3] Quantum mechanical and strain barriers reduce the collapse rate of the zwitterion to much below that of a molecular vibration.[2] The added MeOH, depending on its concentration, could therfore trap the carbenium ion, if formed, before the collapse would occur. This should give rise to the trapped product **4** at the expense of **1**-PhS. It was found[3] that in up to 2.5 M of MeOH, **4** is not formed at all, indicating that in DME **2** undergoes 1,3-elimination rather than solvolysis. At higher concentrations of MeOH, the medium polarity is sufficiently increased, inflicting a change in the reaction mechanism.

It is concluded therefore that the reaction pathway is medium dependent. At low medium polarity 1,3-elimination (eq 3a) should prevail whereas at high polarity the solvolytic path (eq 3b) should be favored. In order to further quantify the polarity effect on the two reaction channels we had to find a suitable probe for the detection of carbenium ions. Making use of MeOH as the probe, as we have done in DME,[3] suffers from two major deficiencies: (a) at low MeOH concentration the trapping of the carbenium ion is not very effective and (b) at high MeOH concentration, MeOH affects the medium polarity. The present study describes, therefore, an attempt to design an internal probe which is attached to the nucleophile. Since intramolecular cyclizations are in general relatively very fast, the use of such a probe is likely to eliminate the two aforementioned problems.

Results and Discussion

Ethylenethioglycolate (TEG^-) was chosen as the bifunctional nucleophile. The S^- will launch the first nucleophilic attack whereas the OH function will trap the carbenium ion, if formed. Thus, the solvolytic path will be evidenced by the formation of the spiro compound **8** (eq 4). All the reactions were performed at room temperature. The reaction were followed by gas chromatog-



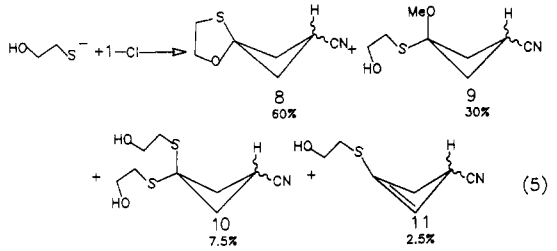
(4)

(1) This is part 16 in the series Cyclobutane–Bicyclobutane System.
(2) Hoz, S.; Aurbach, D. *J. Am. Chem. Soc.* **1983**, *105*, 7685.
(3) Hoz, S.; Aurbach, D. *J. Org. Chem.* **1984**, *49*, 3285.

0022-3263/90/1955-2090$02.50/0

raphy using biphenyl as an internal standard.

Reactions in MeOH. The reactions are relatively very fast, and precipitation of NaCl immediately followed the mixing of the reactants. The concentration of 1-Cl was 0.1 M and that of TEG^-Na^+ was 0.085 M. Products and yields (GC) of the reaction of TEG^- with 1-Cl are presented in eq 5. The spiro compound 8 is most probably obtained



(5)

from an internal trapping of the carbenium ion. The thioketal **9** and the dithioketal **10** are obtained from an intermolecular trapping. The olefin derivative is obtained most probably by deprotonation of the intermediate carbenium as was found for the analogous trifluoroethoxy derivative.[4]

The ratio of internal vs external trapping of the intermediate carbenium (60/30 = 2) indicates a relatively low efficiency of the internal probe. Trapping of the carbenium ion may be effected either by the alcoholic residue of SCH_2CH_2OH (ROH) or by its ionized form ($SCH_2CH_2O^- = RO^-$). In the following discussion we will analyze the two possibilities.

The formation of the dithioketal **10** induces an increase in the basicity of the medium. This is because the second TEG^- moiety which enters the substrate does not come with its own proton, which must therefore come from the solvent. As a result, formation of **8** and **9** may be due in part to reaction of the RO^- and MeO^- and in part due to the reaction of ROH and MeOH (for the internal and external nucleophiles, respectively).

In order to clarify this point, a reaction was performed in the presence of 0.1 M $HOCH_2CH_2SH$ (TEGH). Since TEGH (pK_a = 9.72–9.43)[5a] is more acidic than MeOH (pK_a = 15.5)[5b] it will neutralize the MeO^- and RO^- ions present in the reaction mixture, inhibiting their reactions with the carbenium ion. When TEGH (0.1 M) was added to the reaction mixture, *only* the two ketals **9** and **10** were obtained (52 and 47%, respectively). This result clearly shows that the internal trapping of the carbenium ion is due solely to the interception of the carbenium ion by the ionized function RO^- and not ROH.

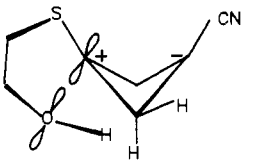
We would like to try and estimate the relative efficiency of the internal vs external trapping for ROH and RO^-. This is usually expressed in terms of effective molarity[6] (EM), which can be defined as the ratio shown in eq 6 (subscripts INTRA and INTER refer to the internal and external trapping, respectively). Assuming that the lower

$$EM = k_{INTRA}/k_{INTER} \quad (6)$$

detection limit for the spiro 8 is 1% then k_{INTRA}/k_{INTER} = 0.019. Correcting k_{INTER} for the concentration of MeOH (24.7 M) one obtains EM ≤ 0.5.

We can also try to estimate the EM for RO^-. For this purpose we will assume that the acidity of MeOH nearly equals that of ROH. This approximation is based on the assumption that the additional CH_2 unit in ROH decreases the acidity whereas the presence of the thiocarbenium ion at the remote δ position counterbalances this effect. From the experiment in the presence of TEGH we conclude that the efficiency of the MeOH in trapping the carbenium ion is similar to that of TEG^- when the concentration of the latter is varied in the course of the reaction from 0.085 to 0.0 M. Thus, the amount of **9** produced in the absence of TEGH due to trapping by MeOH is ≈7.5%. The rest of **9** (22.5%) is therefore due to the reaction of RO^-. Since we assume that the equilibrium constant between RO^- and MeOH is ≈1 (eq 7), implementing it in eq 8 and substituting the result in eq 6 gives an approximate EM value of 66 M for the cyclization of RO^- (it is assumed in the calculations that [ROH] >> [RO^-]).

Chart I



$$K = 1 = [ROH][MeO^-]/[RO^-][MeOH] \quad (7)$$

$$\frac{rate_{INTRA}}{rate_{INTER}} = \frac{k_{INTRA}[RO^-]}{k_{INTER}[ROH][MeO^-]} \quad (8)$$

While the EM of RO^- is not very high, that of ROH is much smaller. Clearly TEG^- cannot be used, therefore, as a nucleophile with an internal probe for our purposes. The difference in the EM of the two moieties ROH and RO^- is very interesting. The origin of this difference is not clear, and at this stage we can merely speculate about it.

One possible reason for the low EM of ROH may stem from the difference in the nature of the two lone pairs on the oxygen atom.[7] An attack by the π lone pair would be much more facile than by the σ lone pair, which is of much lower energy. The π lone pair is perpendicular to the plane defined by the COH array. Thus, an approach geometry which aligns the π lone pair with the empty orbital on the carbenium may increase the energy of the transition state due to steric repulsion between the OH hydrogen and the hydrogen of the cyclobutylmethylene group toward which it is being forced (see Chart I). Yet the MeOH molecule can approach the carbenium center with its π lone pair without being necessarily restricted to this conformation which places two H atoms close to each other. Thus its reactivity may be enthalpically favored over that of ROH. RO^- on the other hand does not suffer from this deficiency of ROH and therefore exhibits a higher EM. In addition, it is possible that the presence of a carbenium ion α to S induces an sp^2 geometry, making the formation of the five-membered ring less favorable. This effect would be felt less with the more reactive RO^-, which according to the Hammond[8] postulate has an earlier transition state and a larger O···C distance.

Reactions in DME. The reactions in DME were heterogeneous. Although the TEG^-Na^+ was added (unless otherwise noted) in a quantity equivalent to a concentration of 0.085 M, solubility studies showed that its actual concentration in the solution does not exceed 4×10^{-4} M. The reactions were performed at room temperature, and reaction times were usually about 4 h. Reaction rates are

(4) Hoz, S.; Aurbach, D. *J. Chem. Soc., Chem. Commun.* **1984**, 364.
(5) (a) Serjeant, E. P.; Dempsy, B. *Ionization Constants of Organic Acids In Aqueous Solutions*; IUPAC chemical data series; Pergamon Press: New York, 1979. (b) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795.
(6) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.
(7) Jorgensen, W. L.; Salem, L. *The Organic Chemist Book Of Orbitals*; Academic Press: New York, 1973; p 42.
(8) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

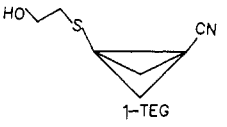
Table I. Reactants Concentrations and Product Distribution in the Reaction of TEG⁻ with 1-Cl in DME[a,b]

no.	reactants (concn, M)			% products 8	10	11	1-TEG
1	1 (0.1)	TEG⁻Na⁺ (0.085)		76	7	17	-
2	1 (0.1)	TEG⁻Na⁺ (0.17)		60	30	10	-
3	1 (0.1)	TEG⁻Na⁺ (0.085)	TEGH (0.1)	0	86	14	-
4[c]	1 (0.1)	TEG⁻Na⁺ (0.085)		50	24	12	14
5[d]	no. 4 + t-BuO⁻Na⁺			64	24	12	-

[a] Performed at room temperature. [b] In experiments 1, 3, and 4, ca. 15% of unreacted starting material were observed. The percentages indicate distribution among the products. [c] Performed without stirring. [d] The t-BuO⁻Na⁺ was added to the NMR tube containing the $CDCl_3$ solution of experiment no. 4.

accelerated by stirring. We have however no indication whether the reaction takes place on the surface or in the solution.[9]

The results of a series of reactions performed under these conditions are given in Table I. In the first experiment the spiro derivative **8** was obtained as the major product. In MeOH, this product was obtained by an internal trapping of the carbenium ion. However, as our studies with PhS^- in DME show, in this apolar medium the carbenium ion is not an intermediate on the reaction path. In the following discussion we will show that the reaction indeed does not involve a solvolytic step and that the precursor of **8** is 1-TEG.

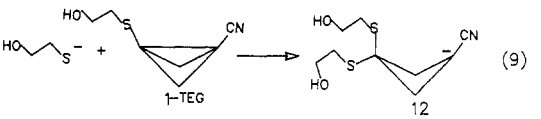


In order to prove the intermediacy of 1-TEG, 1-Cl (0.1 M) was allowed to react in an NMR tube with TEG^-Na^+ (0.043 M) and TEGH (0.05 M) in $CDCl_3$. NMR analyses during the reaction showed that 1-TEG was formed in the course of the reaction, disappearing later on to give mainly **11**. The final product mixture consisted of unreacted starting material (55%), **11** (7%), and **10** (38%). In experiment 2 (Table I), 2 equiv of TEG^-Na^+ rather than one were added. As a result, **10** was obtained in larger amounts at the expanse of **8** and **11**. Since, as we have already shown, 1-TEG is the precursor of **11**, in light of this latter experiment it is reasonable to assume that **11** is also the precursor of **8**. In the sequel we will further justify this conclusion.

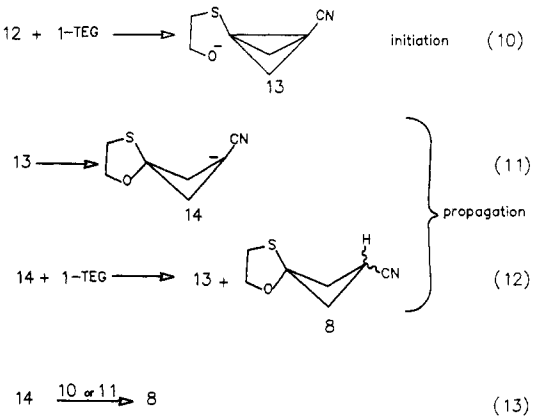
In order to determine whether **8** is obtained by an internal attack of RO^- or ROH, experiment 1 was repeated in the presence of an equimolar concentration of TEGH. The results of this experiment (no. 3, Table I) show that spiro formation was entirely inhibited by the added acid, indicating that **8** is obtained only by the internal attack of RO^-.

Experiment 4 was performed without stirring and after 2 h a sample of the solution was withdrawn and analyzed by NMR. It showed that, under these conditions, 1-TEG was obtained in 11% yield (GC analysis showed 14% yield, see Table I). The NMR sample (in $CDCl_3$) was then treated with t-BuO^- (experiment 5). As can be seen from Table I, the addition of base converted 1-TEG completely to **8** without affecting the concentration of the other products.

Based on these experiments our conclusion is that **8** is indeed obtained by an internal cyclization of 1-TEG after deprotonation of its OH residue. This deprotonation is due to the fact that the medium becomes increasingly basic as **10** is formed (eq 9).



A closer look at the details of this reaction shows it to be one of the rarely encountered cases of an ionic chain reaction. The outline of this mechanism is given in eqs 10–13.



The deprotonation of 1-TEG to give **13** enables the cyclization step (eq 11) which produces carbanion **14**. The latter in turn deprotonates another molecule of 1-TEG in the cycle of propagation. Termination may occur when 1-TEG is consumed or in the presence of a proton source which does not deprotonate substantially 1-TEG. Clearly, the last carbanion formed in each chain absorbs a proton from the ROH residues of **10** or **11** (eq 13).

Assuming that each formation of **10** results in a chain initiation, the average chain length can be calculated from the ratio **8**/**10**. This ratio in experiment 1 gives an average chain length of 11. Increasing the concentration of the initiator is expected to lead to shorter chains (a) because there is a larger number of initiation per a given amount of 1-TEG, and (b) because the higher concentration of **10** produced under these conditions reduces the probability for preferential deprotonation of the ROH moiety in 1-TEG. Indeed, in experiment 2, the average chain length has dropped to 2.

(9) A referee has suggested that since in experiments 1 and 2 in Table I the product composition depends on the amount of TEG^-Na^+ yet its maximum concentration in the solution is 4×10^{-4} M, the reaction must be heterogeneous. We would like to point out, however, that if the rate-limiting step is desolution of the salt, its instantaneous concentration in the solution will be much smaller than 4×10^{-4} M. In this case its solution concentration will depend on the desolution rate which in turn depends on its surface area (i.e. the total amount of the added salt) and thus the reaction may still be homogeneous.

Finally we would like to address the formation of the olefinic product 11 in DME. For the reactions in MeOH, we have suggested that this product is produced by deprotonation of the methylene group α to the carbenium center as in the case of the analogous reactions with alkoxides. In DME, however, carbenium ions are not intermediates and therefore this mechanism cannot be operative. Nevertheless we know (see above) that 1-TEG is converted to 11. Three different mechanisms are conceivable for the bicyclobutane → cyclobutene rearrangement. The first one involves homolytic cleavage of the central bond followed by H shift.[10,11] This mechanism could be discarded in the present case because it would have led most probably to reduction products which were not observed even in the presence of a good H donor such as TEGH. Another possible mechanism involves a heterolytic cleavage of the central bond followed by H^+ shift to the negative center. This mechanism can also be discarded since we have already shown that the ionic bicyclobutane is not obtained as an intermediate under these conditions. We are thus left with the third possibility of a concerted $\sigma_{2s} + \sigma_{2a}$ suggested by Woodward and Hoffmann[12] and Hamon[13] for the isomerization of bicyclobutane. Usually this mechanism necessitates relatively high temperature, whereas the present reactions were performed at room temperature. It is, however, highly likely that the presence of the polar groups at positions 1 and 3 as in this study lower significantly the activation barrier for this concerted reaction.

Experimental Section

General. NMR spectra were recorded on a Bruker AM-300 spectrometer and measured in $CDCl_3$ solution. Mass spectra were taken with a Finnigan 4021 mass spectrometer. For analytical purposes, a Packard Model 878 (FI detector) gas chromatograph was used whereas for preparative separations a Varian 920 gas chromatograph (TC detector) was used. The columns were of 0.5% XE 60 on Chromosorb W, acid washed 60–80 mesh.

Reactants and Solvents. 3-chlorobicyclobutanecarbonitrile (1-Cl) was prepared according to literature procedure.[14] Sodium ethylene thioglycolate (TEG^-Na^+) was prepared in the following way: to a 50-mL solution of 4.2 g (0.05 mol) of ethylene thioglycol (TEGH) in dry ether was added 1.15 g (0.05 mol) of freshly cut sodium. The mixture was stirred overnight, and the white solid was filtered, washed with several portions of ether, and dried under vacuum for 12 h. The solid salt was potentiometrically titrated with a 0.2 M solution of HCl. Only one end point was observed. The molecular weight of the salt calculated from the titration data was 119 ± 5 (compared to 100, the MW of TEG^-Na^+). It is therefore assumed that the salt is obtained as a monohydrate. MeOH (Frutarom, analytical) was treated with Mg and distilled.[15] Dimethoxyethane (DME, Merck) was treated with kOH and distilled from sodium.

Preparation of Products. 8-Oxa-5-thiaspiro[3.4]octane-2-carbonitrile (8). A suspension of 0.1 g of TEG^-Na^+ (0.85 mmol) and 0.114 g of 1-Cl (1 mmol) in 2 mL of DME was stirred for 6 h at room temperature. 8 was obtained in 81% yield (GC). The filtered solution was evaporated, and the product was separated by preparative chromatography to give a mixture of two geometrical isomers in a 3:2 ratio. The ^1H NMR of the mixture of the two isomers was resolved into two sets of partly overlapping peaks, each belonging to a different geometrical isomer. Major isomer: ^1H NMr δ 4.07 (t, J = 6 Hz, 2 H), 3.18 (q, J = 7 Hz, 1 H), 3.13 (t, J = 6 Hz, 2 H), 2.86 (m, 4 H); ^{13}C NMR δ 121.44 (s, CN), 90.58 (s, CS, O), 69.53 (t, CH_2O), 43.22 (t, CH_2), 34.23 (t, CH_2S), 16.43 (d, CHCN). Second isomer: δ 4.01 (t, J = 6 Hz, 2 H), 3.14 (q, J = 7 Hz, 1 H), 3.07 (t, J = 6 Hz, 2 H), 2.86 (m, 4 H). ^{13}C NMR δ 121.35 (s, CN), 89.80 (s, CS, O), 70.28 (t, CH_2O), 43.93, (t, CH_2), 34.80 (t, CH_2S), 14.65 (d, CHCN); MS (CI) 156, 138, 129. Satisfactory C, H, N, S elemental analyses were obtained.

3-((2′-Hydroxyethyl)thio)bicyclobutanecarbonitrile (1-TEG). DME (2 mL) was addded to 0.1 g of TEG^-NA^+ (0.85 mmol) followed by 0.114 g (1 mmol) 1-Cl. The mixture was allowed to react overnight at room temperature without stirring. The mixture was filtered, and the solvent was evaporated. The ^1H NMR spectrum of the mixture showed the typical absorptions of a bicyclobutane system (δ 2.29 and 1.64): ^1H NMR δ 2.29 (t, J = 1 Hz, 2 H), 1.64 (t, J = 1 Hz, 2 H), 3.75 (t, J = 6 Hz, 2 H), 2.97 (t, J = 6 Hz, 2 H), 1.96 (b, H). The product 1-TEG (yield 14% by NMR) is unstable and undergoes decomposition with rearrangement to the olefin 11. Two experiments were performed in order to ascertain its structure. (a) t-BuOK (0.11 g) was added to the $CDCl_3$ solution. In less than 1 min, the peaks due to 1-TEG disappeared and the spiro derivative 8 was quantitatively obtained. (b) The solution was incubated overnight at 30 °C. The ^1H NMR spectrum showed that 1-TEG underwent complete conversion to the olefin 11.

3-Methoxy-3-((2′-hydroxyethyl)thio)cyclobutanecarbonitrile (9). To a 2-mL methanolic solution of 0.1 g of TEG^-Na^+ (0.85 mmol) was added 0.114 g of 1-Cl (1 mmol) at room temperature. An immediate exothermic reaction accompanied by precipitation of NaCl takes place. A mixture of the two geometrical isomers of 9 was obtained (GC yield 55%). We were unable to isolate the individual isomers by a variety of chromatographic methods in a pure form. The best results were obtained by preparative TLC (silica gel, ether–hexane, 3:1, extraction with $CHCl_3$). The isomers which slowly decompose were contaminated mainly with the decomposition products; the disulfide, the corresponding ketone, and traces of the olefin 11 (the NMR spectrum was obtained from that of the mixture). First isomer: ^1H NMR δ 3.73 (t, J= 6 Hz, 2 H), 3.25 (s, 3 H), 3.05 (q, J = 7 Hz, 1 H), 2.70 (t, J = 6 Hz, 2 H), 2.64 (d, J = 10 Hz, 4 H); ^{13}C NMR δ 120.91 (s, CN), 85.05 (s, CO, S), 62.18 (t, CH_2O), 50.08 (t, CH_3O), 40.05 (t, CH_2), 32.45 (t, CH_2S), 14.36 (d, CHCN); MS (CI) 188, 156, 110. Second isomer: ^1H NMR δ 3.76 (t, J = 6 Hz, 2 H), 3.26 (s, 3 H), 3.16 (q, J = 7 Hz, 1 H), 2.72 (t, J = 6 Hz, 2 H), 2.64 (m, 4 H); ^{13}C NMR δ 121.82 (s, CN), 86.07 (s, CO, S), 62.05 (t, CH_2O), 50.23 (s, CH_3O), 39.27 (t, CH_2), 32.27 (t, CH_2S), 15.72 (d, CHCN); MS (CI) 188, 156, 110.

3,3-Bis((2′-hydroxyethyl)thio)cyclobutanecarbonitrile (10). To a 10-mL solution of TEG^-Na^+ (0.15 g, 1.275 mmol) in DME were added 0.078 g TEGH (1 mmol) and 0.114 g 1-Cl (1 mmol). The reaction mixture was stirred at room temperature for 3 h. The filtered solution was evaporated. The product was obtained by preparative TLC (silica gel, ether–hexane 3:1, extraction with $CHCl_3$): ^1H NMR δ 3.82 (t, J = 6 Hz, 2 H), 3.79 (t, J = 6 Hz, 2 H), 3.44 (q, J = 8 Hz, 1 H), 2.85 (t, J = 6 Hz, 2 H), 2.81 (t, J = 6 H, 2 H), 2.77 (m, 4 H); ^{13}C NMR δ 120.86 (s, CN), 60.94 (t, CH_2O), 55.71 (s, CS S), 42.20 (t, CH_2), 34.12, 34.27 (t, CH_2S), 17.92 (d, CHCN); HRMS calculated 233.0556, observed 233.0641.

3-((2′-Hydroxyethyl)thio)cyclobutenecarbonitrile (11). To a stirred suspension of 0.1 g of TEG^-Na^+ (0.85 mmol) in 2 mL of DME was added 0.114 g of 1-Cl (1 mmol) over 1 h. After 3 additional hours at room temperature, the mixture was filtered and the solvent was evaporated. 11 was obtained as a colorless liquid (33% yield, GC): ^1H NMR δ 5.76 (d, J = 1 Hz, 1 H), 3.82 (t, J = 6 Hz, 2 H), 3.62 (ddd, J = 5, 2, 1 Hz, 1 H), 3.06 (dd, J = 14, 4 Hz, 1 H), 2.95 (dd, J = 14, 4 Hz, 1 H), 2.92 (t, J = 6 Hz, 2 H); ^{13}C NMR δ 144.51 (s, CS), 120.73 (d, CH), 119.64 (s, CN), 60.72 (t, CH_2O), 37.71 (t, CH_2), 34.15 (t, CH_2S), 26.61 (d, CHCN); MS (CI) 156. Satisfactory C, H, N, S elemental analyses were obtained.

Reaction Procedures. All the reactions were followed by analytical gas chromatography using biphenyl as an internal standard. Reaction volumes were usually 1 mL, and the substrate was added after the salt and the solvent. In MeOH the reactions

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were homogeneous (except from the precipitation of NaCl) and in DME they were heterogeneous. At the end of the reactions the solids were filtered off, the solvent was evaporated, and the NMR spectrum of the products mixture was taken in $CDCl_3$. The NMR results were in good agreement (±3%) with the GC data.

Registry No. 1-TEG, 125331-78-4; 1-Cl, 23745-75-7; *cis*-**8**, 125331-76-2; *trans*-**8**, 125331-77-3; *cis*-**9**, 125331-80-8; *trans*-**9**, 125331-81-9; **10**, 125331-82-0; **11**, 125331-79-5; TEG^-, 37482-11-4.

Supplementary Material Available: ^{13}C NMR spectrum for compound **10** (1 page). Ordering information is given on any current masthead page.

Transannular Cyclizations of 5-(Hydroxyamino)dibenzo[*a*,*e*]cyclooctatrienes. Regioselective Synthesis of Dibenzohomotropane Analogues

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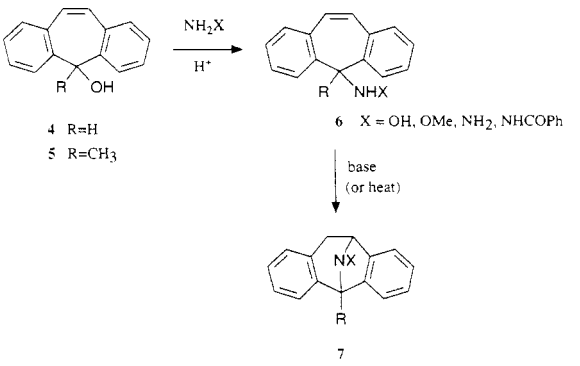
Received August 18, 1989

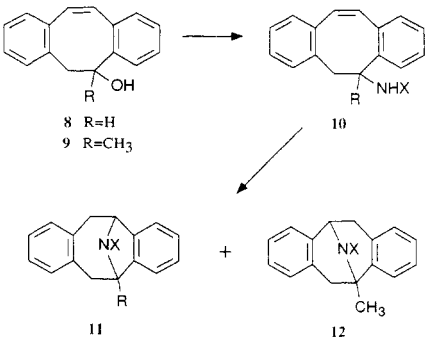
Solvolyses of 5-[(tosyloxy)methyl]dibenzo[*a*,*d*]cycloheptenes **18** provided substituted dibenzo[*a*,*e*]cyclooctatrien-5-ols **19** and **20**, the product distribution implicating the intermediacy of cyclopropyl phenonium ions **22** and **23**. Treatment of 5-methyl-5-hydroxydibenzo[*a*,*e*]cyclooctatrienes (e.g. **9**) with hydroxylamine under acidic conditions led to exclusive formation of N-hydroxy dibenzohomotropanes (e.g. **30**). Cyclizations of substituted derivatives, followed by reductive cleavage of the *N*-hydroxy groups, gave derivatives **2**, **35-42**, and **46**, which are ring homologues of the uncompetitive NMDA antagonist MK-801 (**1**). The more rapid rate of ring closure of 5-(hydroxyamino)dibenzo[*a*,*e*]cyclooctatrienes (e.g. **28**) relative to the corresponding cycloheptenes is rationalized by differences in strain energy in the transition states required for cyclization.

Tetracyclic analogues of the dibenzo[*a*,*d*]cycloheptenimine **1** (MK-801)[1] have potential therapeutic utility as anticonvulsant and neuroprotective agents. The biological effects of **1** are believed to result from specific antagonism of the *N*-methyl-D-aspartate (NMDA) preferring subtype of excitatory amino acid receptor.[2] The NMDA receptor, which is widespread in the mammalian central nervous system, is linked to a membrane-bound ionophore permeable to calcium ions and is believed to play a key role in learning and memory processes.[3] However, excessive stimulation of the receptor by the endogenous transmitter glutamic acid is thought to occur following cerebral ischaemic attacks (e.g. stroke), and the resulting increased cellular calcium influx probably contributes to subsequent cell death.[4] Compound **1** and other NMDA antagonists have been shown to possess neuroprotective activity in animal models of cerebral ischaemia.[5] Electrophysiological[2] and receptor binding[6] studies suggest that **1** acts by entering the open ion channel of the activated NMDA receptor and consequently blocking the cellular entry of calcium ions. MK-801 (**1**) is the most potent of a series of related analogues[1] and other structurally diverse molecules[6] that share this biological activity. As part of a study designed to define the structural and conformational properties necessary for ligand binding to the NMDA receptor, we required access to ring homologated analogues of **1**, including dibenzo[*a*,*e*]cyclooctanimines (**2** and **3**).

Scheme I



Scheme II



Routes developed for the synthesis of the bicyclo[3.2.1] ring system found in **1**[7,8] have made use of transannular

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