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FREE-RADICAL REACTIONS OF CYCLIC ETHERS AND SULFIDES WITH BROMOTRICHLOROMETHANE[1]

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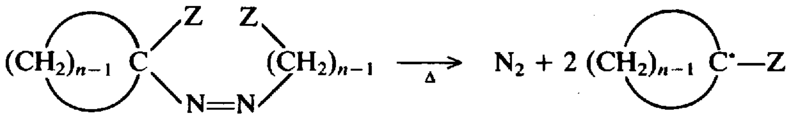
ABSTRACT

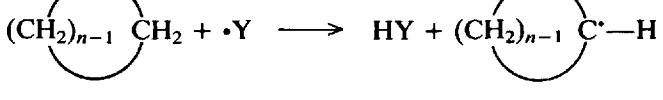
The relative rates of hydrogen atom abstraction from a series of twelve saturated cyclic ethers and sulfides were determined at 70 °C. The abstracting radical could be generated from bromotrichloromethane both photolytically or by the thermal decomposition of AIBN. The reaction rates did not show a dependence upon method of radical generation. Reaction occurred only at the position adjacent to the heteroatom. The reactivity of the cyclic ethers was in the order $C_4H_8O > C_6H_{12}O > C_3H_6O > C_5H_{10}O$. This trend would indicate appreciable influence by ring strain, however, the slightly greater reactivity of tetrahydrofuran relative to oxepane suggests a contribution by stereoelectronic factors as well. The reactivity of the cyclic sulfides, which reacted faster than the corresponding ethers, was in the order $C_4H_8S > C_5H_{10}S > C_6H_{12}S$. This would imply little influence of ring strain. The major structural effect would be that of variable electron donating ability of the sulfur atom. The rate of reaction of thietane was also determined. It was found to preferentially undergo S_H2 attack at the sulfur atom followed by ring opening rather than hydrogen abstraction. The reactivities of both series of compounds were decreased by the inductive effect of a second heteroatom beta to the reaction site.

The effect of ring size on the ease of generation of cycloalkyl radicals has been frequently investigated. The means most often employed have been the thermal decomposition of 1-substituted-azocycloalkanes,[2] equation (1), and hydrogen atom abstraction from the parent



(1)

cycloalkanes by both electrophilic[3] and nucleophilic[4] radicals, equation (2). Despite the inherent differences between these two reaction types and the variation of substituents or



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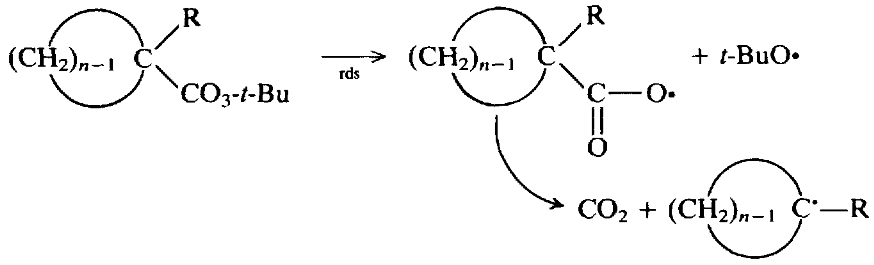
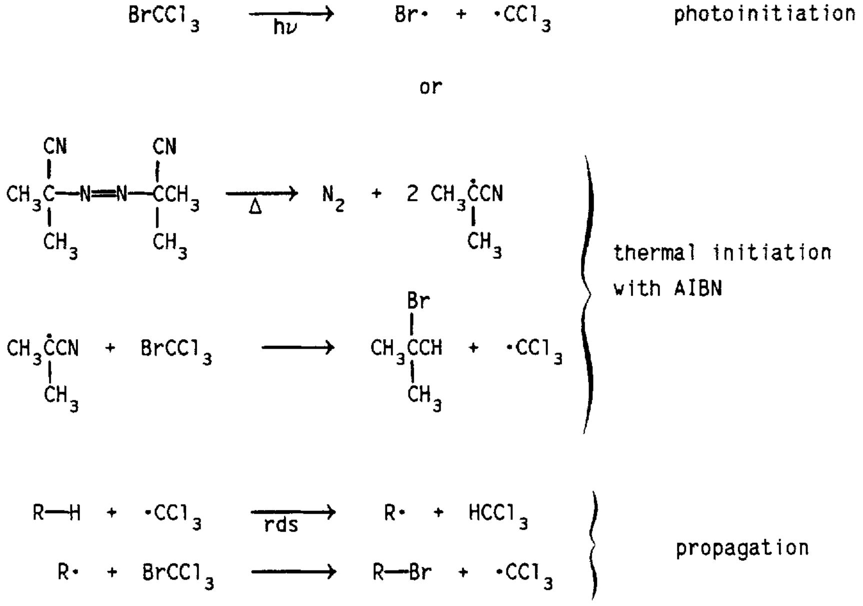
abstracting agents, there exists a common dependence on ring size which may be defined as 'typical'. This trend, expressed in terms of units present in the ring is $7 > 5 > 6 \gg 4$. The same order has been observed for reactions which generate the corresponding carbocations.[5] The similarity in the ease of forming either of these reactive intermediates is expected in terms of Brown's I-strain effect[6] since both carbocation and radical are trigonal, planar species. The generation of cycloalkyl carbanions, which are presumably pyramidal, does not show the 'typical' dependence on ring size.[7] Free-radical reactions of cyclic species in which the formation of the cycloalkyl radical occurs after the rate determining step will also not exhibit this trend. A well-studied example of this is the thermal decomposition of various *t*-butyl 1-substituted-cycloalkanepercarboxylates,[8] equation (3).



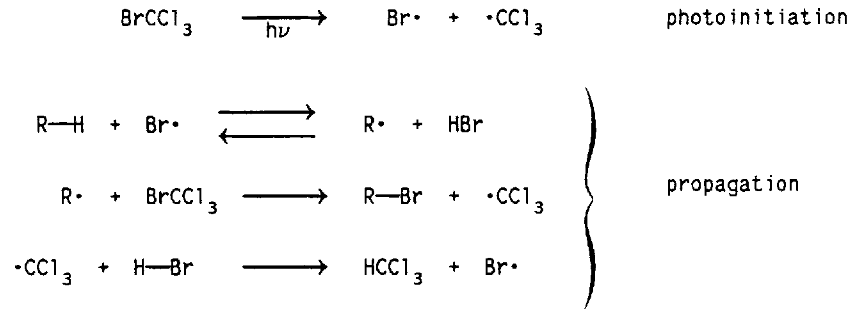
(3)

It has long been known that radicals are readily generated on carbon atoms adjacent to heteroatoms. The presence of alpha oxygen or sulfur atoms markedly accelerates the decomposition of azoalkanes.[9] Phenyl radicals show a pronounced preference to abstract hydrogen atoms from carbons adjacent to such heteroatoms in both acyclic and cyclic systems.[10] An extensive literature on hydrogen atom abstraction by *t*-butoxyl radical from the carbinol position of ethers exists.[11-14] Many of the more recent investigations have directed attention to the fact that the facilitation of radical formation by adjacent oxygen is of a stereoelectronic, rather than an electronic nature.[12,13] That is to say, specific anomeric interactions between electron pairs on oxygen and the developing radical are dependent upon geometry. A preferred dihedral angle of *ca.* 30° between the orbitals on oxygen and the carbon—hydrogen bond being broken leads to observed optimal rate acceleration.[14] When unsubstituted cyclic ethers were allowed to react with *t*-butoxyl radical, the relative reactivities did not show the 'typical' dependence on ring size previously discussed. Walling and Mintz reported a reactivity order of $4 > 5 > 6$[11] while Malatesta and Scaiano observed $5 > 7 > 4 > 6$.[14] Somewhat surprisingly, the latter group has expressed the opinion that the differences in observed reactivity relative to that reported by the earlier workers is small and may reflect cumulative errors. This, may indeed, be the case when one takes into account the rather small range of reactivities which are being considered (*ca.* 2–3). It must also be pointed out that the data of Malatesta and Scaiano describe total reactivity. Hydrogen atom abstraction from positions other than the carbinol site should add to these values. This should be particularly important for tetrahydropyran.[14] This modest dependence on ring size, as well as the specific rate enhancement found for the four membered system (oxetane), represents a marked deviation from the results obtained for the aforementioned cycloalkanes. It seems probable that the reactive *t*-butoxyl radical uses an early transition state in hydrogen atom abstraction from the present series of substrates. As a result, ground state considerations, such as stereoelectronic effects, are more important than the steric requirements of the more fully formed radical although the latter need not be completely absent. It is of interest to note that the reactivity observed by Walling and Mintz parallels the basicity of these ethers and may, in part, reflect an inherent ability of the electron pair to become involved in the anomeric interaction.[15]

If the dichotomy of behavior developed above is valid, it would be of interest to investigate the reaction of cyclic ethers with a radical less reactive than *t*-butoxyl. The potential for greater selectivity might lead to a situation wherein the 'typical' dependence on ring size is encountered. Despite a current controversy as to the identity of the chain carrying (hydrogen atom abstracting) species, we have chosen to use bromotrichloromethane as the radical source in such an investigation. Traditionally the trichloromethyl radical has been considered to be the chain carrying species in this system.[16] Tanner and co-workers have suggested, however, that the bromine atom is the hydrogen atom abstracting agent in photolytically initiated reactions of bromotrichloromethane.[17] These mechanisms are presented respectively in Schemes 1 and 2. Irrespective of the identity of the chain carrying species, the hydrogen atom



Scheme 1. Traditional mechanism for radical bromination using bromotrichloromethane



Scheme 2. Tanner mechanism for photobromination using bromotrichloromethane

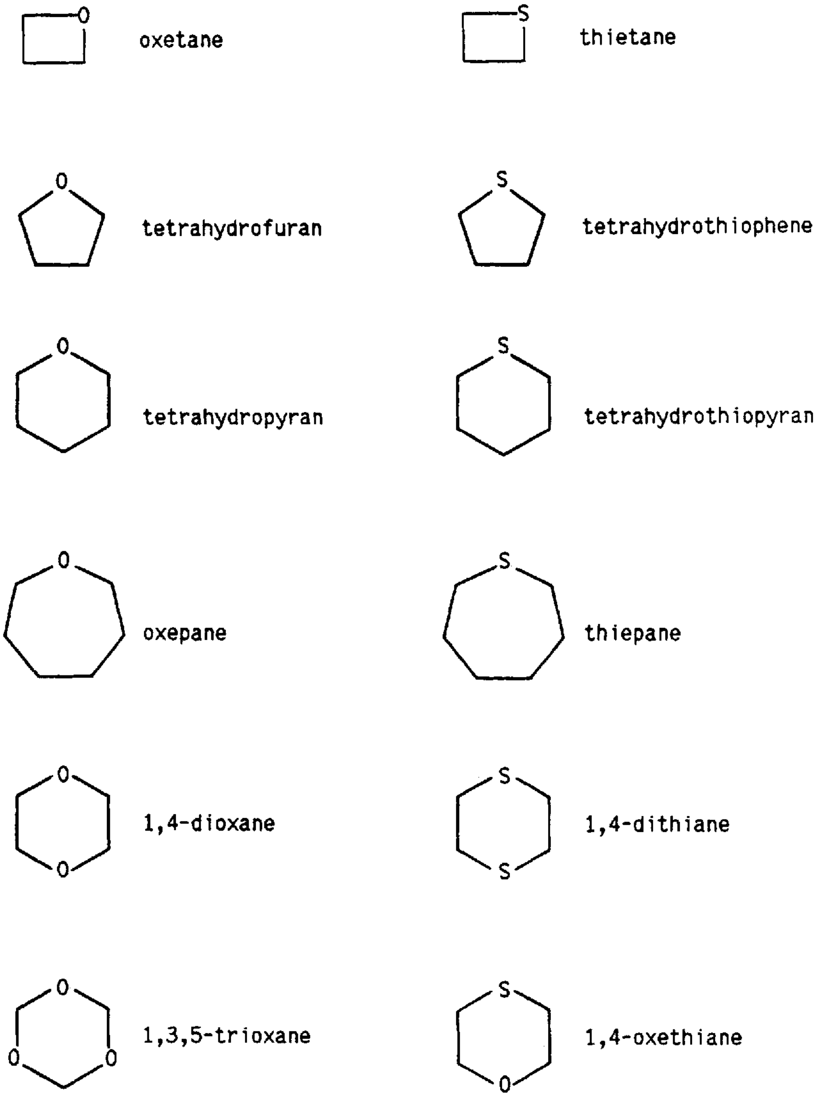


Figure 1. Cyclic ethers and sulfides investigated in the present study

abstraction reactions of bromotrichloromethane exhibit greater selectivity than those using *t*-butoxyl radical.[10] One of the results discussed below suggests that a high concentration of trichloromethyl radical is present. This investigation, however, was not undertaken to differentiate between the two mechanisms and we hope that the intended purpose of this study will not be forgotten.

The reactivities of six cyclic ethers relative to *p*-xylene toward bromotrichloromethane at 70° were obtained. The systems studied are shown in Figure 1. All studies were carried out in replicate under an inert nitrogen atmosphere. Those substrates containing a single oxygen atom were examined under conditions of both photochemical and thermal (AIBN) initiation.

Because of the known lability of the alpha brominated ethers formed in the reaction, no attempt to isolate products was made. Proton NMR spectra of reaction mixtures showed characteristic absorption at *ca.* 6·5 ppm which would be expected for such products. Relative reactivities were determined using gas chromatography to monitor the loss of cyclic ether and *p*-xylene relative to an inert internal standard (chlorobenzene or bromobenzene). Chloroform should be produced in amounts equivalent to the two substrates consumed. This was experimentally verified; however, in several cases small excesses (no more than thirteen percent) of chloroform were found. This is due to a modest amount of hydrogen atom abstraction from the initially formed products. In blank runs, conducted in the absence of initiator, or in vessels protected from light, no disappearance of substrates was observed. The rate data is found in Table 1. For purposes of comparison, relative reactivities of the same substrates toward *t*-butoxyl radical are also presented in this table.

Table 1. Relative rates of hydrogen atom abstraction from cyclic ethers by the radical generated from bromotrichloromethane at 70 °C

Cyclic ether	Number of runs	Relative rate rate relative to *p*-xylene	Reactivity per labile hydrogen	Relative rate for hydrogen atom abstraction by *t*-butoxyl	
				Ref. 11	Ref. 14[a]
Oxetane					
(photolytic)	6	2·10 ± 0·07	18·1	3·10	1·45
(thermal)	6	1·90 ± 0·08	—		
Tetrahydrofuran					
(photolytic)	6	4·50 ± 0·14	38·8	2·13	3·00
(thermal)	4	4·39 ± 0·25	—		
Tetrahydropyran					
(photolytic)	14	0·116 ± 0·008	(1)	(1)	(1)
(thermal)	4	0·130 ± 0·012	—		
Oxepane					
(photolytic)	7	2·64 ± 0·18	22·8	—	1·64
(thermal)	4	2·42 ± 0·10	—		
1,4-Dioxane					
(photolytic)	5	0·062 ± 0·007	0·267	0·31	0·27
1,3,5-Trioxane					
(photolytic)	6	0·326 ± 0·049	1·87	—	0·48

[a] The total values of hydrogen atom abstractions for these systems may include variable contributions from abstraction at positions other than those adjacent to the oxygen atom.

Certain definite conclusions may be reached. The similarity in rate data for systems studied by both photolytic and thermal initiation strongly suggests that the same radical is functioning as the hydrogen atom abstracting agent in the two instances. The mono-ethers show relative reactivities in the order tetrahydrofuran > oxepane > oxetane > tetrahydropyran (5 > 7 > 4 > 6). This is the same order as observed by Malatesta and Scaiano; however, the total reactivity range is nearly twenty-fold greater! Inclusion of temperature effects further magnifies the overall dependence on ring size since the present findings were obtained under conditions nearly 45° higher in temperature.

The cyclic polyethers 1,4-dioxane and 1,3,5-trioxane also yield interesting results. The former is appreciably less reactive than tetrahydropyran, though both compounds have comparable steric demands. The second oxygen atom in this molecule is confined to a beta position and cannot favor radical formation by either stereoelectronic or direct mesomeric interactions. It has recently been suggested that a stabilizing interaction can occur between a radical center and the LUMO of a beta carbon—oxygen bond.[18] In the present case, however, it would appear that polar affects are more important and that the second, beta oxygen atom disfavors hydrogen atom abstraction by any electrophilic radical.

Quite a different situation should be found for the 1,3,5-trioxane. Each potentially liable hydrogen atom should experience the favorable effect of two adjacent oxygen atoms. In the present, photolytically initiated, reaction with bromotrichloromethane, 1,3,5-trioxane is *ca.* 1·9 times as reactive as tetrahydropyran per labile hydrogen atom. Literature results for the reaction of these substrates with *t*-butoxyl radical do not yield a consistent picture. Malatesta and Scaiano report a relative rate value of *ca.* 0·49 which is somewhat surprising.[14] The earlier work of Malatesta and Ingold offers a corresponding value of nearly eleven.[12] This appears to us to be a more reasonable value.

It is felt that the present results are in keeping with a late transition state for the hydrogen atom abstraction process which is mostly dependent on steric (ring size) factors. Electronic factors are not absent as can be seen from the enhanced and decreased reactivity of 1,3,5-trioxane and 1,4-dioxane relative to tetrahydropyran respectively. The very large rate enhancement of oxetane may be also due to stereoelectronic factors as may also be the reversal of the relative reactivities of five and seven membered rings from that found in the corresponding cycloalkane systems.

Although certain recent calculations suggest that an adjacent oxygen atom is slightly more effective in stabilizing a carbon radical than is an adjacent sulfur atom,[19] experimental results on the decomposition of substituted azoalkanes[9] and hydrogen atom abstractions[10] support the opposite view. The results of ESR measurements show that a sulfur atom adjacent to a radical center can more effectively delocalize the unpaired electron than can a corresponding oxygen atom.[20] Figure 1 shows some cyclic sulfides, analogous to the previously described ethers, whose reactions with bromotrichloromethane at 70 °C were investigated. Because of the photolability of the alpha brominated sulfides formed in these reactions, it was impossible to study to photoinitiated reaction. After short irradiation periods the solutions became extremely opaque and all further reaction ceased. Therefore, only the thermally initiated (AIBN) process will be discussed. As expected, the sulfides were more reactive than the corresponding ethers. This necessitated the use of a more reactive reference compound than *p*-xylene and durene was used in most instances. Other reactions conditions were identical to those employed for the corresponding ethers. Relative rates of disappearance of the cyclic sulfides and reactivity per alpha hydrogen atom are given in Table 2.

In addition to showing greater inherent reactivity than the cyclic ethers, the majority of the cyclic sulfides exhibited a greater propensity to undergo secondary reaction. Large excesses of chloroform (up to seventy percent) were observed in the reactions of these substrates. The singular exception to this was thietane. This compound reacted rapidly yet produced approximately only fifteen percent of the expected chloroform. In the absence of initiator, thietane was completely unreactive. It would thus appear that eighty-five percent of this four membered cyclic sulfide is consumed by a competing radical process.

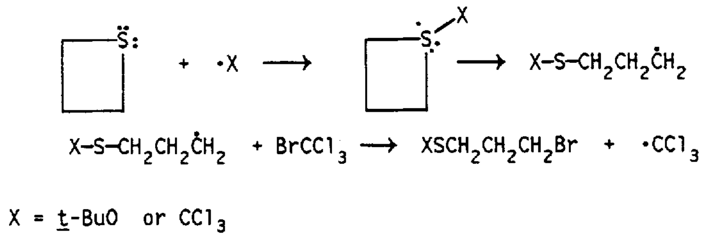
The interaction of most cyclic sulfides with *t*-butoxyl radical is a very clean reaction which

Table 2. Relative rates of disappearance of and hydrogen atom abstraction from cyclic sulfides by the radical generated thermally (AIBN) from bromotrichloromethane at 70 °C

Cyclic sulfide	Number of runs	Disappearance relative to durene	Relative rate of labile hydrogen atom abstraction per hydrogen atom
Thietane	7	10·0 ± 1·2	—
Tetrahydrothiophene	4	3·54 ± 0·05	2·83
Tetrahydrothiopyran	7	1·25 ± 0·06	(1)
Thiepane	7	1·13 ± 0·01	0·904
1,4-Dithiane	6	0·239 ± 0·031[a]	0·096
1,4-Oxethiane	6	0·301 ± 0·015[a]	0·241

[a] Disappearance measured relative to *p*-xylene and then corrected.

leads exclusively to alpha hydrogen atom abstraction.[21,22] In a fashion analogous to the present findings, thietane is an exception. In this case ring opened products are formed.[23] This finding is explicable in terms of the ability of sulfur to act as a site for S_H2 reactions by the ready expansion of its outer octet of electrons.[24] This is shown in Scheme 3. Although a primary alkyl radical is formed in subsequent ring opening, this process relieves nearly 20 kcal/mol of strain energy.[25]



Scheme 3. Radical ring opening reactions of thietane

We have observed appreciable yields of trichloromethyl 3-bromopropyl sulfide **1** in our reaction mixtures. The mode of formation is shown in Scheme 3.

$$Cl_3C—S—CH_2CH_2CH_2Br$$

1

It should be pointed out, that while this result cannot be used to assess the identity of the hydrogen abstracting species formed from bromotrichloromethane, it requires the presence of a high trichloromethyl radical concentration. Characterization of **1** was based on mass spectrometric and nuclear magnetic resonance data. Details are given in the experimental section.

The rates of hydrogen atom abstraction from the remaining cyclic mono-sulfides are in the order of 5 > 6 > 7 based on ring size. A total reactivity range of only *ca.* three is found for these compounds. Both the smaller dependence on ring size and the specific ordering of individual compounds support the proposition that an earlier transition state is found in hydrogen atom abstraction from sulfides than from ethers. The ordering in the former case is consistent with stereoelectronic control in terms of probable availability of the electron pair on the heteroatom.

Two six-membered systems containing two heteroatoms were also studied. Like 1,4-dioxane, 1,4-dithiane shows a marked decrease in reactivity per active alpha hydrogen atom. The electron withdrawing, deactivating effect of the second heteroatom may again be blamed. Alone among the compounds examined in this study, 1,4-oxethiane has non-equivalent potential reaction sites. It has been found, however, that, in reaction with *t*-butoxyl radical, hydrogen atom abstraction occurs only from the position adjacent to sulfur.[21] Here again the second heteroatom produces a decelerating effect on the hydrogen atom abstraction process.

EXPERIMENTAL

Materials

All compounds except thiepane were obtained by purchase. Thiepane was prepared by a standard literature method.[26] All materials were purified before use and showed no detectable impurities on gc analysis.

Procedure for kinetic runs

Solutions of the cyclic ether or sulfide, reference (*p*-xylene or durene), and internal standard (bromobenzene or chlorobenzene) were prepared in bromotrichloromethane solvent in approximate molar ratio of 1:1:1:10. For kinetic runs using thermal initiation, AIBN was added in an approximate molar ratio of 0·2. The solution was divided among several ampoules and then frozen in an acetone–dry-ice slurry. The ampoules were evacuated at 0·5–1·0 mm and flushed with nitrogen during three intermediate thawings. They were then sealed under partial vacuum. One ampoule was reserved for analysis to determine starting materials concentration. The remaining ampoules were placed horizontally just below the surface of an oil bath maintained at 70·0 ± 0·5 °C. Kinetic runs initiated photochemically were then irradiated with a GE 275-W sunlamp placed 20 cm from the surface of the oil. Reaction times varied from two to twenty four hours which corresponds to between four and ninty nine percent reaction of the starting materials. After completion of the reaction, the ampoules were cooled and opened. The concentration of the cyclic ether or sulfide and reference compound were measured relative to the nonreactive internal standard via gas chromatography. The amount of chloroform produced was determined against the internal standard using previously obtained calibration curves. Relative rates were evaluated from the above data by standard relationships.[27]

Identification of trichloromethyl 3-bromopropyl sulfide

A Finnigan 4023 instrument equipped with a quadrupole mass analyzer was used to record the positive ion chemical ionization mass spectrum of compound **1**. Methane was the reagent gas used. The parent ion was observed as MH_2^+ at m/z 275 rather than at 273. The fragmentation patterns are consistent with the proposed structure.

$$m/z\ 275[MH_2\ 26\%],\quad 193[(M-Br)^+\ 11\%],\quad 157[(M-CCl_3)^+\ 100\%],$$

$$121[(M-HSCCl_3)^+\ 46\%],\quad 81[Br^+\ 8\%]$$

The proposed structure of **1** was also confirmed by NMR spectroscopy. A Bruker AM-400 spectrometer was used to obtain spectra of solutions of **1** in $CDCl_3$ which also contained TMS as an internal standard. The proton spectrum of **1** showed two triplets and a pentet of approximately equal intensity centered at δ3·53, δ3·32, and δ2·33 respectively. Decoupling of the signal at δ2·33 led to the collapse of the two triplets into singlets. Unambiguous assignment of the carbons bearing heteroatoms was accomplished through two dimensional NMR techniques (proton–carbon correlated spectra.).

^{1}H-NMR ($CDCl_3$) δ 2·33(p, J = 6·7 Hz, 2H, 2′-CH_2), δ 3·32 (t, J = 7·1 Hz, 2H, 3′-CH_2), δ 3·53 (t, J = 6·0 Hz, 2H, 1′-CH_2).

^{13}C-NMR ($CDCl_3$) δ 30·20 (2′-C), δ 31·53 (3′-C), δ 35·23 (1′-C), δ 97·65.

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