ACTA CHEMICA SCANDINAVICA 25 (1971) 1860–1870

Anchimerically Assisted Sulfoxide Reactions

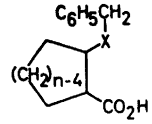
VI. 4-, 5- and 6-Membered 2-Benzylsulfinylcycloalkanecarboxylic Acid Ring Systems. Correlation Between Structure and Reactivity

STIG ALLENMARK and HÅKAN JOHNSSON

Institute of Chemistry, University of Uppsala, Box 531, S-751 21 Uppsala 1, Sweden

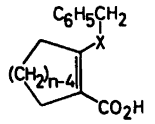
Base-catalyzed nucleophilic addition of phenylmethanethiol to 4-, 5- and 6-membered cycloalkene-1-carboxylic acids has been used for the preparation of *cis-trans*-isomeric 2-benzylthiocycloalkanecarboxylic acids, which, in turn, were oxidized to sulfoxides and sulfones. The determination of configurations is based upon NMR-spectra and rate studies of the hydriodic acid reduction of the sulfoxides.

In a preliminary communication [1] we reported briefly the synthesis of the substituted cyclopentanes IIa–c and the assignment of configurations to the various compounds obtained, with the exception of the two isomers of *trans*-IIb, where the question of *syn*- and *anti*-configuration still remains open.



I (n=4) } a (X=S)
II (n=5) } b (X=SO)
III (n=6) } c (X=SO$_2$)

As we had previously observed in the corresponding unsaturated systems (IVb and Vb), that ring size has a great influence upon the rate of anchimerically assisted reduction [2] of these compounds, we extended our investigations to the cycloalkane series I–III.



IV (n=5) } a (X=S)
V (n=6) } b (X=SO)
c (X=SO$_2$)

Attempts to reduce the double bond in IVa or Va proved unsuccessful because of C–S bond hydrogenolysis. Instead, the compounds I–IIIa were

prepared by nucleophilic thiol-addition to the cycloalkene-1-carboxylic acid. This reaction yielded, in all cases, a mixture of the two possible geometric isomers, which were separated by fractional crystallization and characterized by the melting points and elemental analyses given in Table 1, and by IR- and NMR-spectra. Similarly, we were able to separate the *syn*- and *anti*-forms of the sulfoxides obtained upon oxidation of each sulfide isomer. The corresponding data for these compounds, as well as for the sulfones I – IIIc, are also represented in Table 1. The synthetic routes leading to the various compounds used in this investigation are summarized in Scheme 1.

Reaction of the thiol with cyclobutene-1-carboxylic acid in the presence of pyridine was found to proceed satisfactorily at room temperature, giving a high yield (between 75 and 90 %) of Ia with an approximate 4:1 ratio between the low-melting (IaL) and high-melting (IaH) isomer, respectively.

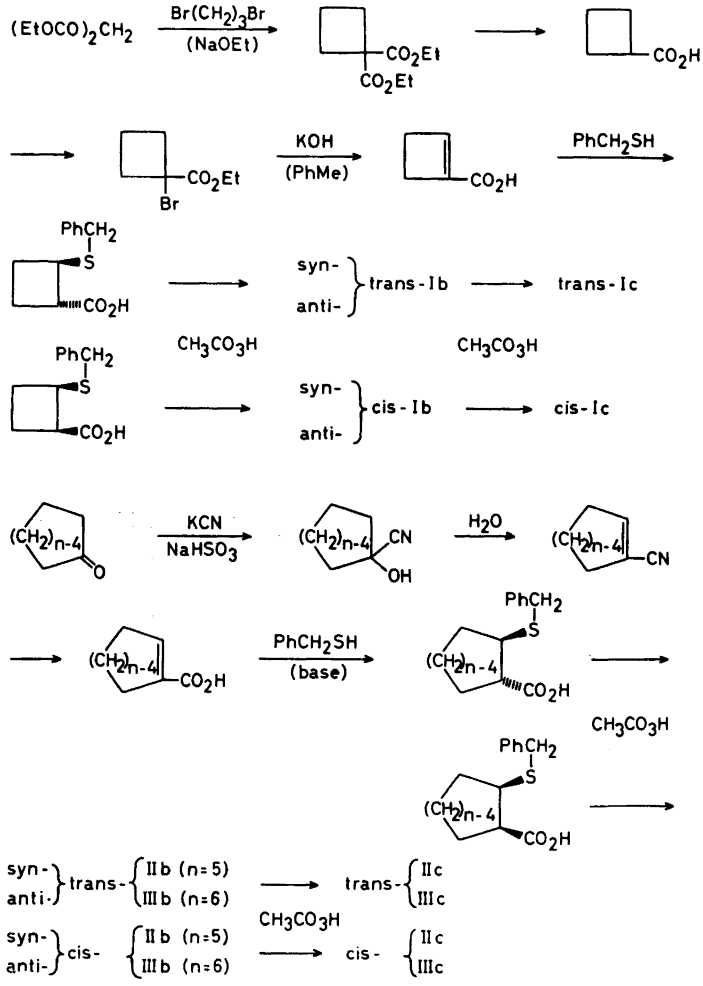
Table 1. Characteristics of compounds I – IIIa – c.

Compound No.	Isomer	Parent compound	M.p. °C	Elemental analyses, %					
				Found			Calculated		
				C	H	S	C	H	S
Ia	L	–	34 – 36	64.78	6.36	14.16	64.83	6.35	14.43
	H	–	81	64.63	6.28	14.45			
IIa	L	–	53 – 54	66.20	6.82	13.59	66.07	6.82	13.57
	H	–	101	66.03	6.78	13.57			
IIIa	L	–	69 – 70	66.97	7.33	12.75	67.16	7.25	12.81
	H	–	72 – 72.5	67.14	7.20	12.72			
	1	IaL	145 – 146	–	–	–			
Ib	2	»	108 – 108.5	60.64	5.95	13.23	60.48	5.92	13.46
	3	IaH	161	60.20	5.81	13.42			
	4	»	125.5 – 126	60.74	6.05	13.35			
	1	IIaL	135.5	61.75	6.45	12.68			
IIb	2	»	116 – 116.5	61.86	6.37	12.66	61.88	6.39	12.71
	3	IIaH	156	61.79	6.34	12.49			
	4	»	164 – 164.5	61.68	6.42	12.61			
	1	IIIaL	173	62.94	6.81	12.14			
IIIb	2	»	139 – 140	–	–	–	63.13	6.81	12.04
	3	IIIaH	154 – 154.5	62.98	6.82	12.05			
	4	»	182	63.18	6.85	12.07			
Ic	1	IaL	170	56.59	5.56	12.35	56.68	5.55	12.61
	2	IaH	139	56.36	5.50	12.41			
IIc	1	IIaL	185 – 185.5	58.32	6.08	11.89	58.18	6.01	11.95
	2	IIaH	149	58.25	6.05	11.90			
IIIc	1	IIIaL	126	59.59	6.44	11.32	59.57	6.42	11.33
	2	IIIaH	136	59.60	6.41	11.40			

Cyclopentene-1-carboxylic acid reacted more slowly, as expected. With piperidine and benzyltrimethylammonium hydroxide (Triton B) as catalysts in boiling benzene, a 70 % yield of IIa, containing about 3:1 of IIaL and IIaH, respectively, was obtained. The reaction between the thiol and cyclohexene-1-carboxylic acid was performed at 120°C without solvent and with piperidine and Triton B as catalysts. The yield of IIIa was 80 %; both forms, *i.e.* IIIaL and IIIaH, were isolated, but we were unable to determine the isomer distribution.

Studies of rates of reduction >SO→>S

In all kinetic experiments, the iodide ion concentration has been sufficiently high to create conditions where the reaction can be treated as going essentially



Scheme 1. Routes for the syntheses of compounds I–IIIa–c.

to completion, and where the change in this concentration during the reaction is small enough not to influence the rate.[3]

The perchloric acid concentration used has been in the range 0.025 M – 1.00 M. Because the reaction studied involves a consumption of hydrogen ions, and the rate is dependent upon the hydrogen ion concentration,[3] it can be approximated to pseudo first-order only at high acid concentrations. The rate constants calculated for reactions in 0.025 M perchloric acid are therefore of the second-order (first-order in sulfoxide as well as hydrogen ions).

Good linearity was obtained for the plots of experimental kinetic data, and all rate constants were evaluated by the graphic method.

Kinetic data for the reduction of sulfoxides I – IIIb by hydriodic acid are given in Table 2.

Table 2. Rates of hydriodic acid reduction of compounds I – IIIb in 50 % ethanol at 25°C.

Compound	C_{HClO_4}M	C_{NaI}M	Pseudo first-order k_{obs} min^{-1}	Second-order k_{obs} lit mol^{-1} min^{-1}	Rel. rate in 0.5 M $HClO_4$
Ib1	1.00	0.2	[a]	–	–
Ib2	1.00	0.2	[a]	–	–
Ib3	0.50	0.2	0.0146	–	1.00
Ib4	0.50	0.2	0.0018	–	0.12
IIb1	1.00	0.2	[a]	–	–
IIb2	1.00	0.2	[a]	–	–
IIb3	0.50	0.2	> 0.6	–	~ 50
»	0.025	0.2	–	1.02	–
»	0.025	0.4	–	1.06	–
»	0.025	0.1	–	0.65	–
IIb4	0.50	0.2	0.0267	–	1.8
»	0.50	0.1	0.0184	–	–
»	0.025	0.2	–	0.039	–
IIIb1	1.00	0.2	5.8×10^{-4}	–	< 0.02
IIIb2	1.00	0.2	9.5×10^{-4}	–	0.03
IIIb3	0.50	0.2	0.15	–	10.3
»	0.025	0.2	–	0.17	–
IIIb4	0.50	0.2	0.0066	–	0.45

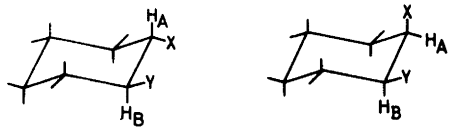
[a] No reaction observed under these conditions.

It is obvious from our results that in the four- and five-membered ring-systems, only the two *cis*-isomers [1] are reduced at a rate fast enough to be observed. In the cyclohexane-system, all four isomers are reduced, one pair however, more slowly than the pair with opposite geometric configuration. The rate constants further show that the anchimerically assisted pathway is favoured in the reduction of both pairs of IIIb, a fact which should be attributed to the flexibility of the cyclohexane ring.

A rough comparison of the rates found for compounds I – IIIb3 – 4 shows the following reactivity order with respect to ring size: cyclopentane > cyclohexane > cyclobutane.

NMR-spectra

NMR-spectra of compounds IIIaL and H were recorded. Making the assumption that the substituents of the *trans*-isomer preferentially occupy a diequatorial position, which has been shown to be the case for 1,2-cyclohexanedicarboxylic acid,[4-6] then its α- and β-protons will be anti-periplanar and display the larger coupling constant of the two isomers.



trans-IIIa cis-IIIa

In each case, both H_A and H_B have three neighbouring protons; therefore three different coupling constants for each nucleus are obtained. In the *trans*-case, however, the eight-line spectrum from H_A will contain two *trans*-couplings and similarly for H_B, but in the *cis*-case, the axial-equatorial positions permit only one *trans*-coupling in the combined spectrum of H_A and H_B.

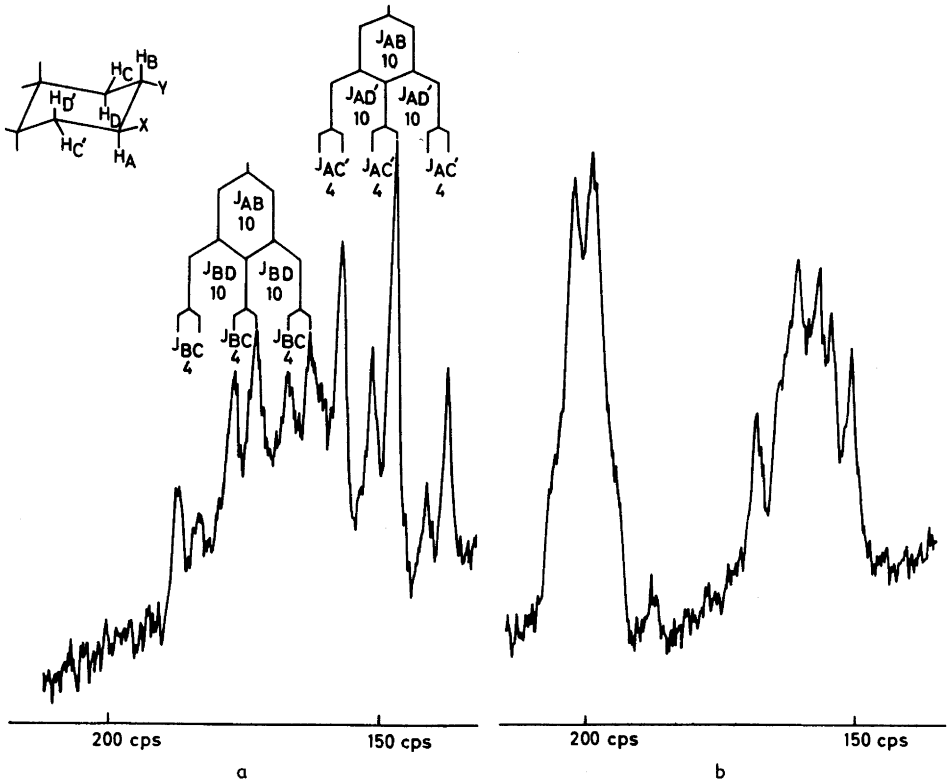


Fig. 1. NMR-spectra (α- and β-protons) of IIIaL (a) and IIIaH (b), respectively, in benzene solution at 60°C.

A complication in the discussion of coupling constants in the spectrum of *cis*-IIIa is the fact that a significant contribution of the other possible chair conformer should not be left out of consideration. In this case, the coupling constants are averaged [7] according to eqn. 1.

$$J_{12} = X_I J_{I-1ax2ax} + X_{II} J_{II-1eq2eq}$$
$$J'_{12} = X_I J_{I-1ax2eq} + X_{II} J_{II-1eq2ax} \quad (1)$$

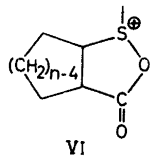
Thus, if X_I/X_{II}, which is the conformer ratio, tends to unity (X_I/X_{II} is arbitrarily chosen to be > 1), the second-term contribution will greatly decrease the value of J_{12} (diaxial coupling). Similarly, diequatorial coupling constants will be increased.

Fig. 1 shows the $H_A - H_B$ part of the NMR-spectra of IIIaL and IIIaH. From the preceding discussion it is quite evident that IIIaL is the *trans*-isomer, and IIIaH the *cis*-isomer, despite the fact that the spectrum of IIIaH has not been fully analyzed.

RESULTS AND DISCUSSION

On the basis of our results there are no ambiguities concerning the *geometric* configurations of all the compounds investigated. Those compounds which are related to the low-melting forms I – IIIaL are the *trans*-isomers (Table 1).

In the case of the four- and five-membered rings Ib and IIb, the geometric configuration is found directly from their rates of reduction, because the *trans*-isomers cannot form the intermediate (VI) necessary for fast reduction.[1,2] For the six-membered rings IIIb, however, an assignment of geometric configuration on the basis of kinetic data alone is not as clear.

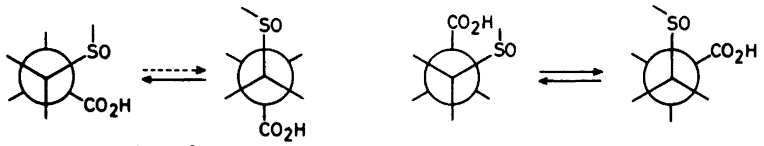


VI

From known values of bond lengths and valency angles one may construct VI from all isomers of IIIb without obtaining too strained a system. It seems probable that the cyclohexane ring will adopt a half chair-like conformation. A comparison of VI with similar systems is illustrative. Anhydrides of cycloalkane-1,2-dicarboxylic acids are only known for the *cis*-isomers of the four- and five-membered rings,[8,9] but for both the isomers of cyclohexane-1,2-dicarboxylic acid.[10,11] In the latter case, however, the *trans*-isomer is known from thermochemical data [12] to be the one of higher energy content. Further, it has been shown that while only *cis*-1,2-cyclopentanediol forms intramolecular hydrogen bonds, this is the case for both the isomers of 1,2-cyclohexanediol.[13,14] Greater energy is required in the *trans*-compound, however, to distort the chair conformation and to bring the two substituents into the close proximity necessary for hydrogen bonding, a fact which was also verified experimentally by IR-technique.[13,14] These things are well understood if one

takes into account that a ring inversion forces the two substituents to pass each other in the *cis*- but not in the *trans*-isomer.

Accordingly, the formation of VI should be expected to be greatly facilitated in the case of *cis*-IIIb. Thus, from reaction kinetic data alone (Table 2), compounds IIIb1 and IIIb2 should be *trans*-, and IIIb3 and IIIb4 *cis*-isomers. This is consistent with the configurations obtained from the NMR-spectra of IIIa (*cf.* Table 1).



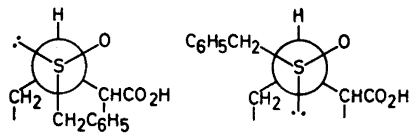
The question of *syn*- or *anti*-configuration is somewhat more complex. Obviously, however, not only geometric configuration but also the configuration around sulfur is of importance for the rate of the assisted reduction of the sulfoxides, as shown by the rate constants in Table 2. Because the formation of VI has been shown to be the rate-determining step in this reaction,[1,3] all factors that favour or disfavour its formation should be reflected in the observed rate. Considering the *cis*-isomers, we think that eclipsing effects constitute a factor of very great importance. It seems reasonable to assume that of the two possible diastereomers of VI, the one which has the more favoured substituent arrangement around the ring carbon-sulfur bond is most rapidly formed. In other words, because nonbonded interactions are necessarily less important in the ground state than in the transition state, they will increase the free energy of activation for the formation of VI.

If we use the *syn*- and *anti*-definition given by Ghersetti *et al.*[15] for analogous bicyclic systems, the two *cis*-isomers of I – IIIb can be represented as below.

The change in rate of reduction due to a change in configuration at sulfur can be expressed as the ratio between the rate constants for the two isomers 3 and 4 (Table 2). The values found are: Ib ~ 8, IIb ~ 28, IIIb ~ 23, *i.e.* the ratio decreases with decreasing reactivity. Even if these figures should not be taken too seriously, they at least indicate that the eclipsing effects mentioned become more important in reactive systems where $\Delta G^{\ddagger}$ is low. Thus, in systems where strain effects appear, such as Ib and *trans*-IIIb (ratio ~ 1.6), these differences in nonbonded interactions are outweighed by the greater free energy of activation required for the reaction.

It seems safe to conclude that the eclipsing effects, arising from nonbonded interactions, are greater in the *syn*-isomers, because in this case

such a bulky substituent as the benzyl group has to be forced against a methylene group in the ring.



syn- *anti-*

Therefore, the *anti*-isomers should be the more reactive species.* For *trans*-IIIb, however, the reactivity difference is too small to allow any safe conclusions. Table 3 summarizes the results regarding the configurations of the compounds.

Table 3. Configurations of compounds I–IIIa–c.

Compound No.	I–IIIaL	I–IIIaH	I–IIIb1	I–IIIb2	I–IIIb3	I–IIIb4
Configuration	*trans*	*cis*	*trans*	*trans*	*cis*	*cis*
	–	–	?	?	*anti*	*syn*

Compound No.	I–IIIc1	I–IIIc2
Configuration	*trans*	*cis*
	–	–

EXPERIMENTAL

Cyclobutanecarboxylic acid was prepared by a malonic ester synthesis according to Cason and Allen.[16]

Cyclobutene-1-carboxylic acid. Ethyl 1-bromocyclobutanecarboxylate, obtained from the previous compound by standard methods,[17] was reacted with potassium hydroxide in boiling toluene, yielding the unsaturated acid[17] after acidification and extraction with ether.

2-Benzylthiocyclobutane-1-carboxylic acid (Ia). To a solution of the previous compound (2.5 g, 0.024 mol) in 50 ml of a mixture of ether, ethanol, and piperidine (8:1:1) was added 7 g (0.056 mol) of phenylmethanethiol at room temperature. After 15 h, the reaction mixture was diluted with water, extracted with ether, acidified, and extracted

* This conclusion is based upon the assumption that the formation of the intermediate VI occurs without substitution at sulfur, leaving its configuration unchanged. Results obtained recently by Landini and Torre (*Boll. Sci. Fac. Chim. Ind. Bologna* **27** (1969) 217) and by Oae *et al.* (*Chem. Ind.* **1971** 576) seem to indicate, however, that this step proceeds with inversion. We hope to obtain a more definite answer regarding the stereochemistry of this reaction and to the question of *syn-* or *anti*-configuration through an X-ray structure determination of one of our compounds.

again. The latter ethereal extracts were combined, dried, and the ether evaporated, yielding 5 g of a crude liquid product. This was diluted with petroleum ether and cooled, which caused the deposition of a crystalline material. The procedure was repeated until no more solid product could be obtained. In this way, 1.4 g of a compound with m.p. 81°C and consisting of pure *cis*-Ia was obtained.

The remaining oil after the isolation of *cis*-Ia, diluted with petroleum ether, was kept at −15°C. After 3 days, another deposit of crystals could be isolated. These had a m.p. of 34 – 36°C and were shown to consist of pure *trans*-Ia.

Cyclopentene-1-carboxylic acid was prepared by dehydration [18] of the cyanohydrin of cyclopentanone, and hydrolysis [19] of the unsaturated nitrile thus obtained.

2-Benzylthiocyclopentane-1-carboxylic acid (IIa). To a solution of 19 g (0.16 mol) of the unsaturated acid in dry benzene, containing 10 ml of piperidine and 4 ml of Triton B, was added 55 g (0.44 mol) of phenylmethanethiol at reflux temperature. The reaction mixture was kept at this temperature for 12 h, and at room temperature for 60 h. After that, the work-up was performed as described for the synthesis of Ia. 28 g (70 %) of a crude product, most of which melting between 32 and 63°C, was obtained. From recrystallizations in petroleum ether, 5.5 g of a product with m.p. 96 – 97°C was obtained. A further recrystallization from water:ethanol (5:1) raised the m.p. to 101°C. This material was shown to be pure *cis*-IIa.

The remaining product, consisting mostly of *trans*-IIa, was purified by recrystallizations from water-ethanol. Pure *trans*-IIa of m.p. 53 – 54°C could be obtained in this way.

Cyclohexene-1-carboxylic acid was prepared by hydrolysis [19] of the unsaturated nitrile [20] with phosphoric acid for 4 h at 140°C.

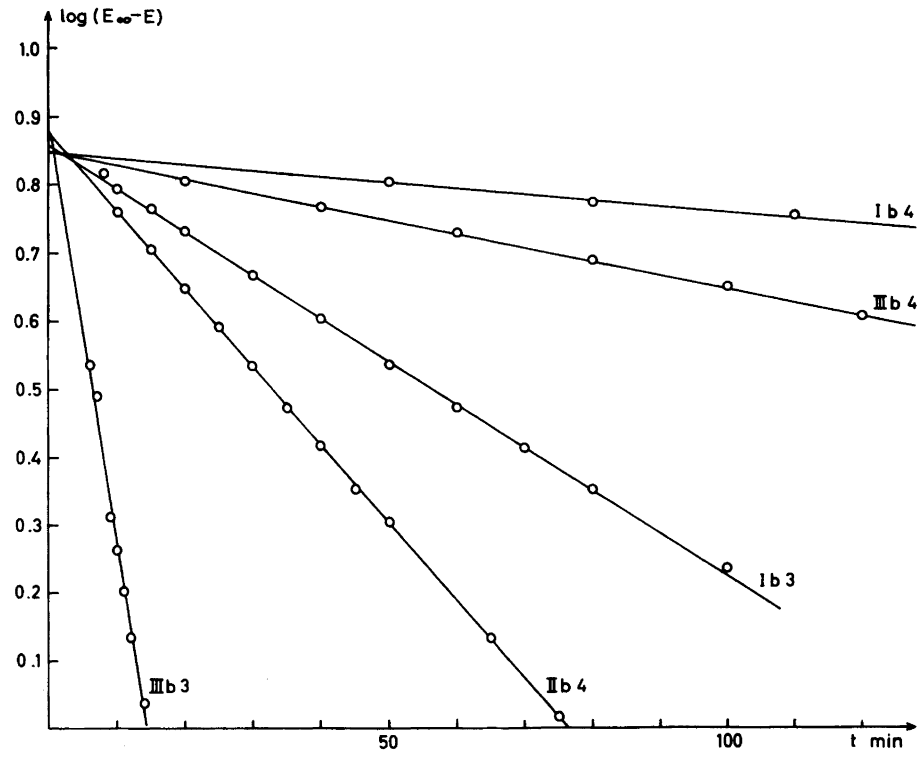


Fig. 2. Illustration of the validity of the integrated pseudo first-order rate law. 0.5 M $HClO_4$ and 0.2 M NaI in 50 % ethanol at 25°C.

2-Benzylthiocyclohexane-1-carboxylic acid (IIIa). A mixture of 30 g (0.24 mol) of cyclohexene-1-carboxylic acid, 66 g (0.53 mol) of phenylmethanethiol, 15 ml of piperidine, and 3 ml of Triton B were kept at 120°C for 48 h. After the usual work-up, an oil remained, which was distilled at reduced pressure. In this way, 48 g (80.5 %) of a viscous oil with $b.p._{0.15} = 202-204$°C was obtained. Several attempts to induce a crystallization of this product failed. However, a solution of it in petroleum ether, kept at −15°C, finally deposited a crystalline material. In this way, repeated recrystallization gave 3 g of the isomer with m.p. 69−70°C (*trans*-IIIa). During this work we were also able to isolate 0.3 g of a compound, melting between 72 and 72.5°C. IR-spectra and a mixed m.p.with the previous compound (42−46°C) showed that the other isomer (*cis*-IIIa) was present.

Preparation of sulfoxides (I−IIIb) and sulfones (I−IIIc). Oxidation with peracetic acid [21] converted the compounds I−IIIa to the corresponding sulfoxides (I−IIIb) and sulfones (I−IIIc). Separation of the *syn*- and *anti*-isomers was achieved by fractional crystallization.

Kinetic experiments. The reduction $>SO \rightarrow >S$ was studied in 50 % ethanol as solvent with an initial sulfoxide concentration of 0.005 M. The concentrations of perchloric acid and sodium iodide are given in Table 2.

The rates of the reaction were obtained spectrophotometrically by following the triiodide ion formation as a function of time. This was performed by measuring the optical density (E) at 525 nm (Fig. 2). The instrument used was a Hitachi Perkin-Elmer Model 139 UV-VIS spectrophotometer. Interference with air oxidation of hydriodic acid was carefully avoided by degassing the solvents with nitrogen, by using quite filled, closed UV-cells, and by compensating for any possible air oxidation with the reference cell. Further, an inspection of the reference cell after each kinetic run gave as a result, that competing oxidation of hydriodic acid by air oxygen was almost negligible.

The temperature was kept constant to within approximately ±0.1°C.

All reagents and solvents used were of analytical grade purity.

The NMR-spectra were recorded with a Varian A-60 A spectrometer with TMS as internal reference.

Acknowledgements. We greatly appreciate the financial support given by the *Swedish Natural Science Research Council.*

REFERENCES

1. Allenmark, S. and Johnsson, H. *Acta Chem. Scand.* **23** (1969) 2902.
2. Allenmark, S. and Johnsson, H. *Acta Chem. Scand.* **21** (1967) 1672.
3. Allenmark, S. *Acta Chem. Scand.* **19** (1965) 1.
4. Sicher, J., Šipoš, F. and Jonáš, J. *Collection Czech. Chem. Commun.* **26** (1961) 262.
5. Sommer, P. F., Pascual, C., Arya, V. P. and Simon, W. *Helv. Chim. Acta* **46** (1963) 1734.
6. Montaudo, G. and Overberger, C. G. *J. Am. Chem. Soc.* **81** (1959) 753.
7. Bovey, F. A. *Nuclear Magnetic Resonance Spectroscopy*, Academic, New York and London 1969, p. 139.
8. Buchman, E. R., Reims, A. D., Skei, T. and Schlatter, M. J. *J. Am. Chem. Soc.* **64** (1942) 2696.
9. Fuson, R. C. and Cole, W. *J. Am. Chem. Soc.* **60** (1938) 1237.
10. Diels, O. and Alder, K. *Ann.* **460** (1928) 114.
11. Windaus, A., Hückel, W. and Reverey, G. *Ber.* **56** (1923) 92.
12. Roth, W. A. and Müller, F. In Landholt-Börnstein, *Physikalisch-Chemische Tabellen*, 5. Auflage, E 1, 875, Springer, Berlin 1927.
13. Kuhn, L. P. *J. Am. Chem. Soc.* **74** (1952) 2492.
14. Kuhn, L. P. *J. Am. Chem. Soc.* **76** (1954) 4323.
15. Ghersetti, S., Hogeveen, H., Maccagnani, G., Montanari, F. and Taddei, F. *J. Chem. Soc.* **1963** 3718.
16. Cason, J. and Allen, C. F. *J. Org. Chem.* **14** (1949) 1036.
17. Campbell, A. and Rydon, H. N. *J. Chem. Soc.* **1953** 3002.

18. Cook, A. H. and Linstead, R. P. *J. Chem. Soc.* **1934** 959.
19. Wheeler, O. H. and Lerner, I. *J. Am. Chem. Soc.* **78** (1956) 63.
20. House, H. O., Paragamian, V., Ro., R. S. and Wluka, D. J. *J. Am. Chem. Soc.* **82** (1960) 1461.
21. Criegee, R. In Houben-Weyl, *Methoden der organischen Chemie*, Thieme, Stuttgart 1952, Vol. VIII, p. 41.

Received October 21, 1970.