The Stereochemistry and Reduction of the 1-Oxa-4-thia-8-*t*-butylspiro[4.5]decanes and -[5.5]undecanes

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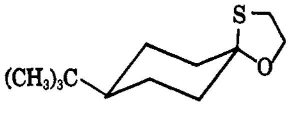
Received August 4, 1964

The configuration of the stereoisomeric 1-oxa-4-thia-8-*t*-butylspiro[4.5]decanes (4-*t*-butylcyclohexanone ethylene monothioketals, I and II) previously assigned on the basis of n.m.r. data has been confirmed through oxidation rate data of the corresponding sulfoxides with perbenzoic acid. The presumed equatorial sulfoxide reacts about twice as fast as the axial. Repetition of the lithium aluminum hydride reduction of the monothioketals gave, along with the previously observed *trans*-2-hydroxyethyl-4-*t*-butylcyclohexyl sulfide (XIII, 78%), some of the *cis* isomer (XIV, 22%). The two stereoisomers XI and XII of the higher homolog 1-oxa-4-thia-8-*t*-butylspiro[5.5]undecane (4-*t*-butylcyclohexanone trimethylene monothioketal) have also been synthesized and their configurations were tentatively assigned through n.m.r. spectra. Definitive assignment by oxidation rate studies failed in this case because the appropriate sulfoxides could not be isolated. Equilibrium of the six-membered ring monothioketals by boron trifluoride etherate gave a nearly 50:50 mixture, similarly as in the case of the five-membered homologs. Results of hydride reduction in the six-membered series were also stereochemically similar to those for the five-membered ring compounds.

In a previous publication[1] we described the preparation of the 4-*t*-butylcyclohexanone ethylene monothioketals (1-oxa-4-thia-8-*t*-butylspiro[4.5]decanes) I and II. The configuration of the compounds was assigned on the basis of n.m.r. spectra,[1,2] the chemical shifts of the CH_2S protons being −175 c.p.s. in I and −177 c.p.s. in II, whereas those of the CH_2O protons were −245 c.p.s. in I and −243 c.p.s. in II (all chemical shifts downfield from TMS at 60 Mc.p.s.). It was assumed that the higher field signals for both CH_2O and CH_2S corresponded to the equatorial methylene group and the lower field ones to the axial methylene group. This assumption was based on the signal positions found[3] for the 4-*t*-butylcyclohexyl methyl thioethers: IIIa, equatorial, −121.0 c.p.s.; IVa, axial, −119.5 c.p.s.; and for the corresponding ethers: IIIb, equatorial, −195.0 c.p.s.; IVb, axial, −193.0 c.p.s.[4]



I

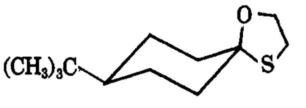
m.p. 74–75°

ν_{CH_2O} = −245 c.p.s.

ν_{CH_2S} = −175 c.p.s.

sulfoxide (V), m.p. 113–114°

sulfone (VII), m.p. 139–140°



II

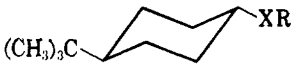
m.p. 1–2°

ν_{CH_2O} = −242 c.p.s.

ν_{CH_2S} = −177 c.p.s.

sulfoxide (VI), m.p. 124.5–125.5°

sulfone (VIII), m.p. 132–133°



IIIa, X = S

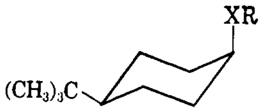
ν_{CH_3S} = −121.0 c.p.s.

IIIb, X = O

ν_{CH_3O} = −195.0 c.p.s.

IX, X = SO

m.p. 81–82°



IVa, X = S

ν_{CH_3S} = −119.5 c.p.s.

IVb, X = O

ν_{CH_3O} = −193.0 c.p.s.

X, X = SO

m.p. 89–90°

R = CH_3

Since we were in need of monothioketals of clearly defined configuration for several investigations under way in our laboratory,[5] and since equilibration of I and II had indicated[1,2,6] that, surprisingly, I was slightly more stable than II, we felt that additional evidence for the configurational assignments of I and II was desirable. This evidence has now been adduced by converting I and II to the corresponding sulfoxides (V and VI, respectively) by oxidation with a limited amount of perbenzoic acid and then studying the oxidation rates of the two sulfoxides with more perbenzoic acid.[7] Compound I was oxidized to a sulfoxide (V), whose oxidation rate was 9.43×10^{-3} l./mole sec. The product of oxidation was the sulfone VII. Compound II was similarly oxidized to its sulfoxide VI whose oxidation rate was 17.2×10^{-3} l./mole sec., the product of oxidation being the sulfone VIII. We feel that these oxidation rates strongly support the previous configurational assignment, since on general steric grounds[8] the axial sulfoxide function in V should certainly be more hindered and therefore less easily attacked than the equatorial sulfoxide function in VI. This assumption is further supported by the oxidation rates of the *trans*- and *cis*-4-*t*-butylcyclohexyl phenyl sulfoxides (IX and X). The *trans* (equatorial) isomer IX was oxidized at a rate of 16.2×10^{-3} l./mole sec., whereas the corresponding rate for the *cis* (axial) isomer (X) was 3.1×10^{-3} l./mole sec.

The sulfoxide of the parent compound, cyclohexanone ethylene monothioketal was a rather unstable liquid for which only an approximate oxidation rate of 12×10^{-3} l./mole sec. was obtained. As expected, the rate for the conformationally heterogeneous compound is in between that of the conformationally homogeneous models V and VI, although it is not so close to VI as might have been expected on the basis that sulfoxide has a greater conformational preference for the equatorial position (by 1.9 kcal./mole)[9] than ether (0.6 kcal./mole).[10]

The previously reached conclusion,[1,2,6] supported by the present configurational assignment, is that of the

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[1] E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Am. Chem. Soc.*, **84**, 2377 (1962).

[2] E. L. Eliel and L. A. Pilato, *Tetrahedron Letters*, 103 (1962).

[3] Data obtained by B. P. Thill.

[4] Data obtained by M. G. Gianni.

[5] *E.g.*, E. L. Eliel and S. Krishnamurthy, *J. Org. Chem.*, **30**, 848 (1965).

[6] See also M. Mertes, *ibid.*, **28**, 2320 (1963).

[7] Originally the oxidation rate of I and II itself with an excess of perbenzoic acid was investigated. However, since the oxidation under these circumstances is a two-stage reaction, the results were not readily interpretable.

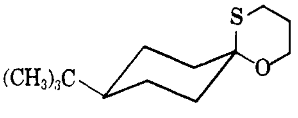
[8] D. H. R. Barton, *Experientia*, **6**, 316 (1950).

[9] This follows from the oxidation rate of phenyl *cis*-4-methylcyclohexyl sulfoxide which is 9.7×10^{-3} l./mole sec.; regarding the method, *cf.* E. L. Eliel, *J. Chem. Educ.*, **37**, 126 (1960).

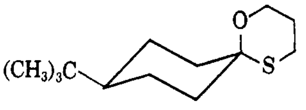
[10] E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, 97 (1962).

4-*t*-butylcyclohexanone ethylene monothioketals, the isomer with axial sulfur and equatorial oxygen is more stable by at least 200 cal./mole,[1,2] if not more.[6] This is contrary to other indications that sulfur is slightly larger than oxygen.[11,12] To throw further light on this situation, we have also synthesized the higher homologs XI and XII. These were readily obtained from 4-*t*-butylcyclohexanone[13] and 3-mercapto-1-propanol[1] and easily separated on Alcoa F-20 alumina. Isomer XI was more strongly adsorbed onto alumina, perhaps owing to the greater absorption affinity of the equatorial oxygen, and showed n.m.r. signals (at 60 Mc.p.s., relative to tetramethylsilane) at −161.2 c.p.s. (CH_2S) and −228.0 c.p.s. (CH_2O). Isomer XII, less strongly absorbed, showed signals at −167 and −224.4 c.p.s. Because XII had the sulfur methylene signal at lower field and the oxygen methylene signal at higher field than XI, XII was assigned the configuration with equatorial sulfur and axial oxygen, in analogy with the previous assignment,[1,2] now confirmed, for I and II.

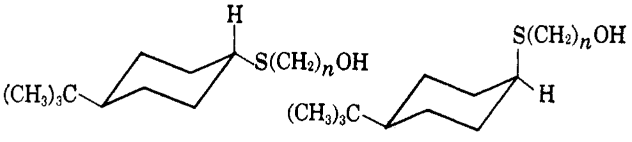
We had hoped to confirm the configurational assignment of XI and XII through oxidation rate measurements of the corresponding sulfoxides, as described above for I and II. Unfortunately, the sulfoxides corresponding to XI and XII were quite unstable and could not be obtained in a state of purity satisfactory for kinetic measurements.



XI
m.p. 50–51°
$\nu_{CH_2O} = -228.0$ c.p.s.
$\nu_{CH_2S} = -161.2$ c.p.s.



XII
m.p. 70–71°
$\nu_{CH_2O} = -224.4$ c.p.s.
$\nu_{CH_2S} = -167$ c.p.s.



XIII, $n = 2$ XIV, $n = 2$
XV, $n = 3$ XVI, $n = 3$

Compounds XI and XII were equilibrated by means of boron trifluoride etherate in ether solution.[1,2] The equilibrium mixture, according to column chromatographic analysis, infrared analysis, or gas chromatographic analysis contained 53–55% XII and 44–47% XI, indicating a preference of sulfur over oxygen to be equatorial by 75–100 cal./mole. This is opposite to the finding with the five-membered compounds I and II but in agreement with other determinations of the effective relative size of oxygen and sulfur in axially and equatorially substituted cyclohexanes.[11,12]

Although the configurational assignment of XI and XII based on n.m.r. spectra only cannot be considered conclusive, we believe our results are reasonable in that the six-membered ring compounds better reflect the true conformational preferences of oxygen and sulfur than the five-membered analogs I and II. The latter may not be good models because the geometry of the five-membered ring may require the axial substituent to bend outward, away from the *syn*-axial[14] hydrogen atoms in the cyclohexane ring. This bending outward relieves the compression of the sulfur atom with the *syn*-axial hydrogens more than that of the oxygen since the carbon–sulfur bond is longer than the carbon–oxygen bond and thus the sulfur moves through a larger distance for a given angle deformation (leverage effect).

Previous work[1] had indicated that I and II are reduced by lithium aluminum hydride–aluminum chloride to the same 4-*t*-butylcyclohexyl 2-hydroxyethyl thioether, $RSCH_2CH_2OH$ (R = 4-*t*-butylcyclohexyl), largely the *trans* isomer. This reduction has now been studied in greater detail, through synthesis of the previously unknown *cis*-4-*t*-butylcyclohexyl 2-hydroxyethyl thioether (XIV) from *trans*-4-*t*-butylcyclohexyl tosylate by displacement with ethyl mercaptoacetate $HSCH_2COOC_2H_5$ followed by lithium aluminum hydride reduction. Chromatographic analysis of the reduction products of either I or a mixture of I and II indicated the product to be a mixture of 78% of XIII (*trans*) and 22% XIV (*cis*). This ratio is close to that of the 4-*t*-butylcyclohexanols obtained in the reduction of 4-*t*-butylcyclohexanone with lithium aluminum hydride–aluminum chloride[15] (80:20) which is reasonable, since this reduction proceeds[16] *via* a sulfocarbonium ion $>C{=}S^+CH_2CH_2OAl^-Cl_3$ similar in structure to the ketone $>C{=}O$.

The reduction of either XI or XII with lithium aluminum hydride–aluminum chloride[1] similarly gave what appeared to be identical mixtures of *trans*- and *cis*-3-hydroxypropyl 4-*t*-butylcyclohexyl thioethers (XV and XVI) presumably *via* a common sulfocarbonium ion.[1,16] The exact composition of this mixture was not ascertained, but from n.m.r. spectra (see Experimental) it appeared that here also the equatorial isomer (XV) predominated over the axial (XVI). Not unexpectedly, hydroxysulfides XV and XVI were quite stable toward prolonged treatment with lithium aluminum hydride–aluminum chloride, in contrast to their lower homologs XIII and XIV which were readily reduced further to ethyl sulfides *via* cyclic sulfonium ions.[1]

Experimental

4-*t*-Butylcyclohexanone Ethylene Monothioketal Sulfoxide. From High-Melting Isomer (Compound V).—A standardized solution of perbenzoic acid in chloroform[17] (62 ml. containing 0.25 mole of peracid) cooled to about 15° was added, in small portions and with stirring, to a solution of 5 g. (0.232 mole) of I in 150 ml. of chloroform in a three-necked flask equipped with a thermometer, addition funnel, and stirrer which had also been cooled to −10 to −15° by means of an ice–salt bath. The temperature was maintained at −10° throughout the addition. The perbenzoic acid was consumed virtually instantaneously, as indicated by a starch–iodide paper test, except at the end when an excess was present. Saturated aqueous sodium hydroxide (100 ml.) was added, and the reaction mixture was transferred to a separatory funnel. The chloroform layer was separated washed with saturated sodium bicarbonate and with water, dried over magnesium sulfate, and concentrated at reduced pressure. The white, crystalline residue (5.25 g., 97%) melted at 108–110°;

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[11] E. L. Eliel and B. P. Thill, *Chem. Ind.* (London), 88 (1963).

[12] See also E. L. Eliel, L. N. Allinger, S. J. Angyal, and G. M. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, p. 44.

[13] Kindly donated by the Dow Chemical Co.

[14] See ref. 12, p. 43.

[15] E. L. Eliel and M. N. Rerick, *J. Am. Chem. Soc.*, **82**, 1367 (1960).

[16] B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **41**, 2671 (1963).

[17] G. Braun, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 431. Method modified according to J. M. Kolthoff, T. S. Lee, and M. A. Mairs, *J. Polymer Sci.*, **2**, 199 (1947).

its infrared spectrum showed the characteristic sulfoxide band at 1056 cm.$^{-1}$; carbonyl and sulfone bands were absent. Recrystallization from ethyl acetate raised the melting point to 113–114°.

Anal. Calcd. for $C_{12}H_{22}SO_2$: C, 62.56; H, 9.62. Found: C, 62.86, 62.58; H, 9.78, 9.90.

From Low-Melting Isomer (Compound VI).—The oxidation of 5 g. of II was effected in the same way as described for I and yielded 5.15 g. (95%) of VI free of carbonyl and sulfone bands. After recrystallization from ethyl acetate the material melted at 124.5–125.5°.

Anal. Calcd. for $C_{12}H_{22}SO_2$: C, 62.56; H, 9.62. Found: C, 62.76; H, 9.76.

Cyclohexanone Monothioketal Sulfoxide.—Cyclohexanone monothioketal[1] (15 g., 0.095 mole) in 250 ml. of chloroform was oxidized with 285 ml. of a chloroform solution of perbenzoic acid (0.01 mole) as described above. The product weighed 15.8 g. (95%) and melted at 50–52°. Recrystallization from ethyl acetate raised the melting point to 54–55°, unchanged by further recrystallization. The freshly crystallized material showed no carbonyl and sulfone bands in the infrared, but the compound is very unstable and carbonyl bands develop after short standing.

4-*t*-Butylcyclohexyl Phenyl Sulfoxide (*cis* Isomer X).—To a solution of 5 g. (0.0202 mole) of *cis*-4-*t*-butylcyclohexyl phenyl sulfide[18] in 150 ml. of ether and 50 ml. of methanol cooled below −10° was added 75 ml. (0.024 mole) of a 0.32 *M* standardized solution of perbenzoic acid in toluene, the temperature being maintained below −10° until the peracid was consumed (starch–iodide test). The solution was then washed with 10% aqueous sodium hydroxide followed by water, dried over magnesium sulfate, and concentrated at reduced pressure. The solid residue (5 g., 94% yield) had m.p. 86–87°, raised to 89–90° by recrystallization from ethyl acetate–pentane.

***trans* Isomer IX.**—The *trans* isomer was similarly prepared from the *trans* sulfide[19] in 93% yield, m.p. 81–82° after recrystallization from petroleum ether.

Anal. Calcd. for $C_{16}H_{24}SO$: C, 72.67; H, 9.15. Found for the *cis* isomer: C, 72.74; H, 8.95. Found for the *trans* isomer: C, 72.59; H, 9.09.

Cyclohexyl phenyl sulfoxide was similarly prepared in 91% yield from cyclohexyl phenyl sulfide,[19] except that the solvent was ether instead of ether–methanol. It melted at 57.5–58.5° after recrystallization from ethyl acetate–pentane.

Anal. Calcd. for $C_{12}H_{16}SO$: C, 69.18; H, 7.74. Found: C, 68.93; H, 7.49.

Kinetic Measurements.—Perbenzoic acid was prepared as described[17] and stored in ether solution. (It was found that chloroform solutions of the acid are unstable and soon develop chlorine, phosgene, and hydrochloric acid.) Shortly before use the perbenzoic acid was crystallized by concentrating the ether solution and adding pentane. It was then dissolved in redistilled analytical grade toluene. Equal amounts of this stock solution were pipetted into two 100-ml. volumetric flasks (one of which also had a mark at the 95-ml. level); one was made up to 100 ml. and the other to 95 ml. Both flasks, as well as a 25- or 50-ml. volumetric flask containing the stock solution of freshly recrystallized sulfoxide in toluene (about 0.02 *M*), were then immersed in a cryostat at 0 ± 0.1°. Five milliliters of the perbenzoic acid solution in the 100-ml. flask were quenched into aqueous potassium iodide (40 ml. of *ca.* 10% solution) containing *ca.* 5 ml. of acetic acid and the iodine liberated was titrated with 0.03 *N* sodium thiosulfate. From the thiosulfate titer, the amount of perbenzoic acid at zero time was calculated. Five milliliters of the stock solution of sulfoxide were then added by means of a quick-delivery pipet to the 95 ml. of peracid solution, zero time being taken when half the sulfoxide had been added. The reaction flask was immediately stoppered, shaken vigorously, and quickly returned to the cryostat. At appropriate times, 5-ml. aliquots of the solution were rapidly withdrawn from the flask by means of a quick-delivery pipet and immediately quenched, the time being recorded when the pipet was half-empty. Reactions were followed to 75–80% completion. In addition, infinity titers were determined and found to agree with the calculated value. Aliquots of the pure perbenzoic acid in the second volumetric flask were titrated from time to time as controls, but no blank consumption of peracid was noted. Eight or more well-spaced points were obtained in each run, and the rate constants were calculated by means of the integrated second-order rate equation

$$k = \frac{2.303}{t(a - b)} \log \frac{b(a - x)}{a(b - x)}$$

a and *b* being the initial concentrations of peracid and sulfoxide and *x* being the change in concentration of peracid consumed in the reaction. The rates are summarized in Table I.

TABLE I

Compd.	[PhCO$_3$H], mole/l.	[Sulfoxide], mole/l.	10 *k*, l./mole min.	10 *k* (av.)
V	0.04358	0.02215	5.64	
	0.04417	0.02215	5.66	
	0.05348	0.02198	5.50	
	0.06662	0.02215	5.86	5.66[a]
VI	0.5666	0.02045	10.2	
	0.4376	0.01853	10.4	10.3[a]
Cyclohexanone	0.05195	0.02070	*ca.* 7.16[b]	
ethylene	0.09244	0.02070	*ca.* 6.74[b]	
monothioketal	0.04183	0.02070	*ca.* 6.56[b]	*ca.* 7[a]
IX	0.0688	0.01575	0.968	9.72[c]
	0.02898	0.01521	0.970	
	0.02859	0.01509	0.971	
	0.03812	0.01575	0.965	
	0.04071	0.01552	0.989	
X	0.02508	0.01358	0.181	1.85[c]
	0.06706	0.01901	0.186	
	0.04140	0.01901	0.190	
	0.04375	0.01901	0.186[d]	
$PhSOC_6H_{11}$	0.02976	0.01941	0.958	9.50[c]
	0.03457	0.01918	0.950	
	0.03474	0.01922	0.944	
	0.03857	0.02005	0.948	

[a] Solvent, toluene. [b] Constant drifting during run, probably due to decomposition of sulfoxide. [c] Solvent, 90% aqueous isopropyl alcohol (by volume). [d] With added benzoic acid (0.082 mole/l.).

The sulfone VII (from sulfoxide V) was isolated in one of the runs and crystallized from methanol, m.p. 139–140°.

Anal. Calcd. for $C_{12}H_{22}SO_3$: C, 58.50; H, 8.99. Found: C, 58.85, 58.91; H, 8.95, 9.07.

The sulfone VIII (from sulfoxide VI) was similarly isolated, m.p. 132–133°.

Anal. Found: C, 58.77, 58.71; H, 8.94, 8.91.

4-*t*-Butylcyclohexanone Trimethylene Monothioketals (XI and XII).—A solution of 15.8 g. (0.1 mole) of 4-*t*-butylcyclohexanone[3] and 9.4 g. (0.1 mole) of 3-mercapto-1-propanol[1] in 50 ml. of benzene containing a few crystals of *p*-toluenesulfonic acid was boiled for 12 hr., the water (total 1.8 ml., 0.1 mole) being collected in a Dean–Stark trap. The reaction mixture was poured into 70 ml. of 10% aqueous sodium hydroxide and extracted with 80 ml. of ether. The organic layer was separated, washed with 1% aqueous sodium hydroxide and water, dried over potassium carbonate, and concentrated. After a forerun of ketone (1.3 g.) there was collected 11.6 g. (50%) of product, b.p. 120–128° (0.5 mm.) still containing carbonyl impurity. Redistillation gave a total of 9.7 g. collected between 110 and 116° at 0.4 mm. The material was chromatographed from hexane on 300 g. of Alcoa F-20 alumina. The head fractions (3.77 g.) crystallized: m.p. 63–66°, raised to 70–71° upon recrystallization from hexane (needles).

Anal. Calcd. for $C_{13}H_{24}OS$: C, 68.38; H, 10.59; S, 14.04. Found: C, 68.25; H, 10.48; S, 13.59.

The infrared spectrum of this material showed characteristic bands at 9.25, 9.68, 11.45, and 12.33 μ; carbonyl and hydroxyl were absent. N.m.r. signals (CCl_4 solution) were found at −167.0 (triplet) and −224.4 c.p.s. (triplet).

The intermediate fractions of the chromatogram (4.8 g.) were semisolid mixtures but the tail fraction (1.1 g.) was well crystalline: m.p. 43–46°, raised to 50–51° by recrystallization from hexane (flat prisms).

Anal. Calcd. for $C_{13}H_{24}OS$: C, 68.38; H, 10.59; S, 14.04. Found: C, 68.65; H, 10.53; S, 14.22.

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(18) E. L. Eliel and R. G. Haber, *J. Am. Chem. Soc.*, **81**, 1249 (1959).

(19) E. L. Eliel and R. S. Ro, *ibid.*, **79**, 5995 (1957).

Infrared bands were found at 9.25, 9.55, 10.40, 11.54 and 12.48 μ; n.m.r. signals at −161.2 (triplet) and −228.0 (triplet) c.p.s. (in CCl_4).

Equilibrations of Monothioketals XI and XII. High-Melting Isomer (1 Mole of Boron Trifluoride).—To a solution of 1.14 g. (0.005 mole) of XII in 200 ml. of ether, a solution of 1.1 g. (0.005 mole) of boron trifluoride etherate in 20 ml. of ether was added with vigorous stirring under a nitrogen atmosphere. The solution was boiled at reflux for 3 days and aliquots were withdrawn at the end of 1, 2, and 3 days. They were quenched in cold 10% aqueous sodium hydroxide, washed with 2% aqueous sodium hydroxide followed by water, dried over potassium carbonate, concentrated, and examined by infrared spectroscopy. It was evident that the samples withdrawn after 2 and 3 days were very nearly identical in composition. The entire reaction mixture was therefore worked up after 3 days in the manner described for the aliquots. The product recovered weighed 0.92 g. and its infrared spectrum most closely resembled that of a known 55:45 mixture of XII and XI. A portion of the product (0.7 g.) was subjected to column chromatography on alumina. This gave three fractions: A, 0.31 g., m.p. 65–67°, containing 93% XII according to infrared spectrum; B, 0.15 g., liquid, containing about equal amounts of XI and XII by infrared analysis; and C, 0.21 g., m.p. 46–47.5°, containing 97% XI according to infrared spectrum. Recrystallization of A from hexane gave pure XII, m.p. 70–71°, and recrystallization of C gave pure XI, m.p. 50–51°. The column chromatogram thus confirms a 55:45 (XII–XI) composition, even though separation of the isomers is incomplete. Finally gas chromatographic analysis[20] of the mixture on a Carbowax column at 200° indicated 53% XII and 47% XI.

Low-Melting Isomer (1 Mole of Boron Trifluoride).—Isomer XI (1.35 g.) was equilibrated as described for XII. Infrared and column chromatographic analysis indicated 55% XII and 45% XI; gas chromatographic analysis[20] indicated 53% XII and 47% XI.

High- and Low-Melting Isomer (Trace of Boron Trifluoride).—A solution of 0.96 g. (0.0042 mole) of XII and 0.05 g. (0.0002 mole) of boron trifluoride etherate in 3 ml. of ether was sealed in an ampoule under nitrogen and let stand for 6 months. Work-up as described above gave 0.93 g. of a colorless oil which was shown, by infrared spectroscopy and column chromatography, to contain XII and XI in a ratio of 55:45. When the same equilibration was effected starting with isomer XI, the product ratio XII–XI was 56:44.

***cis*-4-*t*-Butylcyclohexyl Carboxymethyl Sulfide and Its Ethyl Esters.**—Sodium (3.7 g., 0.161 g.-atom) was dissolved in 80 ml. of ethanol. To this solution was added 24 g. (0.2 mole) of ethyl mercaptoacetate followed by a solution of 25 g. (0.081 mole) of *trans*-4-*t*-butylcyclohexyl *p*-toluenesulfonate[15] in 150 ml. of ethanol. An additional 50 ml. of ethanol and about 10 ml. of water was added, and the reaction mixture was boiled at reflux under nitrogen for 3 days. Enough water was added to dissolve precipitated salts and reflux was continued for 2 additional days. The solution was then concentrated at reduced pressure, ether was added, and the precipitated salts were filtered and washed with ether. The ether solution was washed with brine and dried over magnesium sulfate. Concentration of the ether solution gave 13 g. (62%) of a crude liquid whose infrared spectrum was compatible with the assumed structure (*cis*-4-*t*-butylcyclohexyl carbethoxymethyl sulfide).

The solid material filtered above was suspended in saturated sodium chloride solution, filtered, washed with saturated sodium chloride, and then dissolved in water. The aqueous solution was acidified with 10% hydrochloric acid and extracted with ether; the ether extract was cleared with brine, dried over magnesium sulfate, and concentrated. The residue was crystallized from hexane to give 2.5 g. (13%) of the acid, m.p. 86–87°.

Anal. Calcd. for $C_{12}H_{22}SO_2$: C, 62.84; H, 9.66. Found: C, 62.47; H, 9.42.

***cis*-4-*t*-Butylcyclohexyl 2-Hydroxyethyl Sulfide.**—To a stirred solution of 1.85 g. (0.049 mole) of lithium aluminum hydride in 50 ml. of ether was added a solution of 12 g. (0.0465 mole) of the above crude *cis*-4-*t*-butylcyclohexyl carbethoxymethyl sulfide in 25 ml. of ether. The reaction mixture was stirred at room temperature for 2 hr. and worked up with 10% sulfuric acid in the usual way. The aqueous layer was twice extracted with 50 ml. of ether, and the combined ether solutions were washed with 10% aqueous sodium hydroxide, followed by brine. They were then concentrated to give 8.5 g. (85%) of white solid which, after recrystallization from pentane, melted at 38–39°. The infrared spectrum showed bands at 1055, 1020, and 868 cm.$^{-1}$; the n.m.r. spectrum showed a triplet (CH_2S) at −154.6 and a narrow peak (equatorial CHS) at −185.7 c.p.s.

Anal. Calcd. for $C_{12}H_{24}OS$: C, 66.61; H, 11.18. Found: C, 66.67; H, 11.07.

Reduction of 4-*t*-Butylcyclohexanone Ethylene Monothioketal (I) with Mixed Hydride.[1]—The hydride solution was prepared by dissolving 7.5 g. (0.052 mole) of aluminum chloride in 30–50 ml. of ether and adding a solution of 0.5 g. (0.0131 mole) of lithium aluminum hydride in an equal amount of ether at 0–10°. This was followed by slow addition of 10 g. (0.047 mole) of I in 30 ml. of ether. The reaction mixture was boiled at reflux for 2 hr., cooled, and worked up by the addition of water followed by 10% sulfuric acid. The layers were separated and the aqueous layer was extracted with ether twice. The combined ether layers were washed with saturated aqueous bicarbonate followed by saturated sodium chloride, dried over magnesium sulfate, and concentrated to give 9.5 g. (94%) of residue. The infrared spectrum of this material showed a strong band at 1010 cm.$^{-1}$ previously found[1] in *trans*-4-*t*-butylcyclohexyl 2-hydroxyethyl sulfide, but, in addition, weak bands or shoulders corresponding to the *cis* isomer appeared at 1055, 1020, and 868 cm.$^{-1}$ (see above). Similarly, the n.m.r. spectrum showed a strong triplet centered at −158 (at 60 Mc.p.s., relative to TMS) with a weak satellite at −155 c.p.s., the former being due, presumably, to equatorial CH_2S and the latter to axial CH_2S. A small peak, presumably due to equatorial C*H*S, was also found at −186.2 c.p.s., the major, axial C*H*S signal apparently disappearing under the CH_2S triplet. Separation of the mixture by column chromatograph was only partially successful, but gas chromatography (Carbowax 20M at 175°) showed four peaks, two small ones with retention times of 6 and 7 min. (partly overlapping), approximate ratio 76:24, and two large ones with retention times of 65 and 75 min. in a ratio of 22:78. The peak of retention time 65 min. was due to *cis*-4-*t*-butylcyclohexyl 2-hydroxyethyl sulfide (XIV), since, upon dilution of the sample with authentic *cis*-sulfide as described above, the 65-min. peak was greatly enhanced. It is believed that the larger 75-min. peak represents the corresponding *trans* sulfide (XIII). The 6-min. and 7-min. peaks are probably due to *trans*- and *cis*-4-*t*-butylcyclohexyl ethyl sulfide (formed by overreduction[1]), respectively.

The same product composition was obtained in reduction of a mixture of I and II.

Reduction of 4-*t*-Butylcyclohexanone Trimethylene Monothioketal with Lithium Aluminum Hydride–Aluminum Chloride.—To 50 ml. of cold (0°) anhydrous ether was added portionwise, with vigorous stirring, 4.47 g. (0.0355 mole) anhydrous aluminum chloride. After 0.5 hr., 9 ml. of 0.93 *M* ethereal lithium aluminum hydride solution (0.00837 mole) was added with stirring, followed after 0.5 hr. more, by a solution of 3.5 g. (0.0154 mole) of XII in 12 ml. of ether. The reaction mixture was boiled for 2 hr. at reflux, cooled, and decomposed with 50 ml. of 10% sulfuric acid; the ether phase was separated. The aqueous layer was extracted several times with ether and the combined ether layers were washed with water, 10% aqueous sodium hydroxide (nothing was obtained by acidification of the basic layer) and again water, dried over potassium carbonate, and concentrated. The residue (3.1 g.) upon distillation yielded 2.7 g. (60%) of 4-*t*-butylcyclohexyl 3-hydroxypropyl thioether, b.p. 118–119° (0.2 mm.), $n^{20}\text{D}$ 1.5028.

Anal. Calcd. for $C_{13}H_{26}OS$: C, 67.78; H, 11.38. Found: C, 67.57, 67.68; H, 11.44, 11.50.

The infrared spectrum of the compound showed strong hydroxyl absorption. The n.m.r. spectrum gave signals at −156.1 c.p.s., area 0.64, triplet (CH_2S and coincident axial CHS signal); −186 c.p.s., area 0.08 (equatorial CHS signal); −202 c.p.s. (variable with temperature, hence OH), area 0.25; −220 c.p.s., area 0.51, triplet (CH_2O). Assuming that an area of about 0.5 of the signal at −156.1 is attributed to CH_2S leaves 0.14 for axial H on the ring under sulfur. The corresponding peak for equatorial H is 0.08, thus the axial H–equatorial sulfide XV seemingly predominates over XVI although the data are not accurate enough to establish an exact ratio.

Reduction of either XI or a 50:50 mixture of XI and XII gave the same product, according to infrared and n.m.r. spectra, as pure XII. Use of a 100% excess of "mixed hydride" and extension of the reaction period to 42 hr. did not change the re-

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(20) Kindly carried out by Dr. S. Krishnamurthy.

action course; a mixture of XV and XVI was still obtained in about 95% (crude) or 83% (distilled) yield.

Acknowledgment.—Grateful acknowledgment is made to Petroleum Research Fund, administered by the American Chemical Society, and to the Donors of said fund for support under Grant No. 266-A, as well as to the National Science Foundation for support under Grant G-14251.

Octaarylporphyrins[1]

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Received August 24, 1964

A synthesis is described of 3,4-diarylpyrroles-2,5-dicarboxylic acids from benzils and dimethyl-N-acetyliminodiacetate catalyzed by sodium methoxide. Decarboxylation of the pyrrole diacids yields 3,4-diarylpyrroles. Aliphatic diketones except dimethyl oxalate do not undergo the pyrrole condensation. Octaarylporphyrins were synthesized in excellent yields from the Mannich bases of 3,4-diphenylpyrrole and 3,4-di-*p*-methoxyphenylpyrrole. Physical and spectral characteristics of these porphyrins and some of their metallo derivatives are described.

In connection with a study of substitution reactions of oxidized and reduced porphyrins,[3] it appeared desirable to prepare a symmetrically substituted model porphyrin because the number of theoretically possible positional isomers that could result would be kept at a minimum. A literature survey[4] indicated that only a few octaalkyl- and no octaarylporphyrins were known. The most outstanding characteristic of the symmetrically substituted octaalkylporphyrins is their low solubility in the usual organic solvents. This property is probably due to the tight crystalline packing of these molecules. Inspection of models of 1,2,3,4,5,6,7,8-octaphenylporphine[5] (V) revealed that the phenyl groups should take up conformations in which their planes are oriented 35 to 45° out of the plane of the porphyrin ring. This feature of the molecule was quite desirable for two reasons. The bulky out-of-plane phenyl groups would protect the methine bridges of the porphyrin ring from attack by oxidizing agents, thus permitting the oxidative removal of electrons from the π-orbitals of the macrocyclic ring system. In addition, the phenyl groups might cause a reduction in the tight crystalline packing of the molecules which would result in an increased solubility of the octaarylporphyrins as compared to the octaalkyl analogs.

Octaphenylporphine was synthesized from the previously unknown 3,4-diphenylpyrrole *via* the Linstead procedure.[4c] This pyrrole was prepared as outlined in Figure 1. When N-acetyliminodiacetate dimethyl ester was condensed with benzil in 10% sodium methoxide, a compound was isolated that had the expected properties of 3,4-diphenylpyrrole-2,5-dicarboxylic acid (I).[6] The pyrrole diacid shows the expected large carbonyl band in the infrared centered at 1680 cm.$^{-1}$. In addition to the OH stretching frequency due to the two carboxyl groups ranging from 2500–3000 cm.$^{-1}$, the compound has three absorption peaks in the NH stretching region at 3450, 3510, and 3600 cm.$^{-1}$. These may be due to the various hydrogen-bonded forms of the molecule.[7] Additional evidence for the suggested structure comes from the ultraviolet spectrum[8] ($\lambda_{\max}$ 245 and 284 mμ) and from the smooth, nearly quantitative decarboxylation of the diacid in ethanolamine to 3,4-diphenylpyrrole (II). The structure of II was confirmed by elementary analytical results, by the presence of an NH stretching frequency at 3390 cm.$^{-1}$ in the infrared, by the ultraviolet spectrum ($\lambda_{\max}$ 238 and 271 mμ), and from conversion of the pyrrole into magnesium octaphenylporphine (IV) as described below.

The scope of this pyrrole synthesis was extended by including the condensation of *p*-anisil, *p*-tolil, and *o*-tolil (see Figure 1). The yields with the first two compounds were high, but the low yield with *o*-tolil suggests steric hindrance of the *ortho*-methyl groups in the condensation. A variety of reaction conditions were unsuccessfully tried in an attempt to improve the yield with this diketone. The condensation could be made to take place with sodium hydride in benzene, but the yields were equally low. Only polymeric products resulted when the condensation with *o*-tolil was carried out with sodium hydride in xylene, sodium ethoxide in ethanol, or magnesium ethoxide in benzene.

Attempts to extend the pyrrole condensation with aliphatic diketones, such as biacetyl, failed because of the facile self-condensation of these compounds under basic conditions. However, dimethyl oxalate was an exception giving a 65% yield of 3,4-dihydroxy-2,5-dicarbomethoxypyrrole (Id). Recent spectroscopic evidence indicates that 3-hydroxypyrroles exist mainly in the keto form.[9] Compound Id was etherified with diazomethane to the corresponding 3,4-dimethoxy

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(1) Presented at the 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1961; Abstracts p. 97Q.

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(3) Mendel Friedman, Ph.D. Thesis, University of Chicago, March 1962.

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(5) The general term octaarylporphyrins will be used to name this porphyrin and analogous ones, but for specific porphyrins the term porphine will be used to describe the porphyrin ring system and octa, the eight substituents in the β-pyrrole positions.

(6) After the work on this pyrrole synthesis had been completed, K. Dimroth and U. Pintschovius [*Ann.*, **639**, 102 (1961)] published a similar pyrrole synthesis in which they use potassium *t*-butoxide as the catalyst. Their procedure results in a mixture of pyrroles due to transesterifications. These have to be separated chromatographically. None of the pyrroles described in this paper were prepared by these authors.

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