carbonyl peak at approximately 5.7 μ employing a Perkin-Elmer Model 21 recording infrared spectrophotometer. This method was chosen after repeated attempts to use the iodometric method of Silbert and Swern[18] proved unreliable with the later stages of a kinetic run.

The perester solutions in carbon tetrachloride were degassed, then sealed in thoroughly cleaned ampoules prepared from 9-mm. Pyrex tubing. The samples were immersed into an electrically heated oil bath controlled to ±0.2° by means of a Fisher-Serfass electronic relay. An equilibration time of 2 min. was allowed for the samples to reach bath temperature. At definite time intervals an ampoule was removed and immediately quenched by immersion in ice-water. The ampoules were stored at −70° until the completion of the kinetic run, then they were broken, and the sample was transferred directly to an infrared cell.

The rate constants determined are the average of at least two runs and are summarized in Table IV.

The energies of activation were calculated from a plot of the log of the rate constant *vs.* the reciprocal of the absolute temperature employing the method of least squares to determine the slope. The entropies of activation were calculated by the method of Foster, Cope, and Daniels.[20]

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(20) E. G. Foster, A. C. Cope, and F. Daniels, *J. Am. Chem. Soc.*, **69**, 1893 (1947).

The Products of Raney Nickel Desulfurization of Monothioketals[1]

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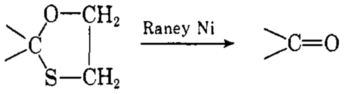
Desulfurization of the two stereoisomeric 4-*t*-butylcyclohexanone ethylene monothioketals (I) with Raney nickel in benzene at room temperature gave 4-*t*-butylcyclohexanone (53–55%), *cis*-4-*t*-butylcyclohexyl ethyl ether (12–14%), 4-*t*-butylcyclohexanone diethyl ketal (6–11%), 4-*t*-butylcyclohex-1-enyl ethyl ether (16%), and 4-*t*-butylcyclohexene (7–12%), in addition to much ethane and a little ethylene. Product composition was independent of the stereochemistry of the starting material. Similarly, the two 3-cholestanone ethylene monothioketals (II) gave 3-cholestanone (43–47%), 3α-ethoxycholestane (11–12%), 3-ethoxy-2-cholestene (20–21%), 3-cholestanone diethyl ketal (7–8%), and 2-cholestene (4–5%). The two isomers of 4-*t*-butylcyclohexanone trimethylene monothioketal (III) gave 4-*t*-butylcyclohexanone (47–48%), *cis*-4-*t*-butylcyclohexyl *n*-propyl ether (12%), 4-*t*-butylcyclohex-1-enyl *n*-propyl ether (16%), 4-*t*-butylcyclohexanone di-*n*-propyl ketal (7%), and 4-*t*-butylcyclohexene (7%). The recovery of the three-carbon fragment as propane (with traces of propylene and cyclopropane) was low in this case.

Desulfurization by Raney nickel, discovered but 25 years ago,[2] has become a reaction of considerable preparative significance.[3,4] One of its useful applications is in the removal of a protective monothioketal function to regenerate a ketone.[5] The course and mechanism of this reaction has been investigated by Djerassi and co-workers.[6,7]



These authors found[7] that in benzene solution one of the products of the Raney nickel treatment of monothioketals is the ethyl ether formed by simple hydrogenolytic removal of the sulfur atom. From the then only known 3-cholestanone ethylene monothioketal (m.p. 135–136°) they obtained, as the only ether product, 3α-ethoxycholestane (axial ethoxy group). From this finding it was inferred[7] that the starting monothioketal had the oxygen in the α- and the sulfur in the β-configuration, from which inference, in turn, conclusions were drawn regarding the mechanism of monothioketal formation. The implication that desulfurization involves retention of configuration in this case must be subject to doubt, however, since it has been shown[8] that the reaction is, in most instances, not stereospecific. Having at our disposal *both* stereoisomers of 3-cholestanone monothioketal[9a] (Figure 1: IIb,[9b] m.p. 112–113°, and IIa,[9b] 135–136°) as well as both stereoisomeric monothioketals of the simple model compound 4-*t*-butylcyclohexanone (Figure 1, Ia and Ib) of known configuration[9–11] we decided to reinvestigate the stereochemistry of thioketal hydrogenolysis.

In summary, the present results, discussed in greater detail below, indicate that *both* stereoisomeric 3-cholestanone monothioketals (Figure 1, II) give 3α-ethoxycholestane (axial ethoxyl) as the sole saturated ether product. Similarly, both 4-*t*-butylcyclohexanone ethylene monothioketals (Figure 1, I) give *cis*-4-*t*-butylcyclohexyl ethyl ether (axial ethoxyl) without any of the *trans* isomer and both 4-*t*-butylcyclohexanone trimethylene monothioketals (Figure 1, III)[11] give *cis*-4-*t*-butylcyclohexyl *n*-propyl ether uncontaminated by its stereoisomer. The reaction is therefore "stereoconvergent" (*i.e.*, both stereoisomeric starting materials give the same stereoisomeric product) rather than stereospecific (meaning that each stereoisomeric starting material gives the corresponding stereoisomeric product) as previously surmised.[7]

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(1) We gratefully acknowledge support of this work by a National Institutes of Health Grant (GM-08848) and by a grant-in-aid from Merck Sharp & Dohme, Inc. This paper is taken from the Ph.D. Dissertation of S. Krishnamurthy.

(2) J. Bougault, E. Chattelain, and P. Chabrier, *Compt. rend.*, **208**, 657 (1939); *Bull. soc. chim. France*, [5] **7**, 781 (1940).

(3) R. Mozingo, D. E. Wolf, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).

(4) See the following reviews: H. Hauptmann and W. F. Walter, *Chem. Rev.*, **62**, 347 (1962); G. R. Pettit and E. E. vanTamelen, *Org. Reactions*, **12**, 356 (1962).

(5) J. Romo, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **73**, 4961 (1951).

(6) C. Djerassi, M. Gorman, and J. A. Henry, *ibid.*, **77**, 4647 (1955).

(7) C. Djerassi, M. Shamma, and T. Y. Kan, *ibid.*, **80**, 4723 (1958).

(8) W. D. Bonner and co-workers, papers cited in E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 394–396.

(9) (a) E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Am. Chem. Soc.*, **84**, 2377 (1962). (b) Tentative structure assignment based on n.m.r. data: L. A. Pilato, Ph.D. Dissertation, University of Notre Dame, 1962.

(10) E. L. Eliel and L. A. Pilato, *Tetrahedron Letters*, 103 (1962).

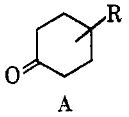
(11) E. L. Eliel, E. W. Della, and M. Rogić, *J. Org. Chem.*, **30**, 855 (1965); see also ref. 12 and 13.

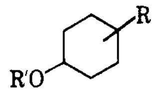
(12) M. Mertes, *ibid.*, **28**, 2320 (1963).

(13) E. L. Eliel, *Record Chem. Progr.*, **22**, 129 (1961).

TABLE I

RANEY NICKEL DESULFURIZATION PRODUCTS[a]


A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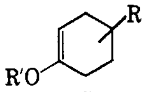
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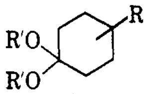
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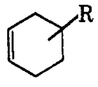
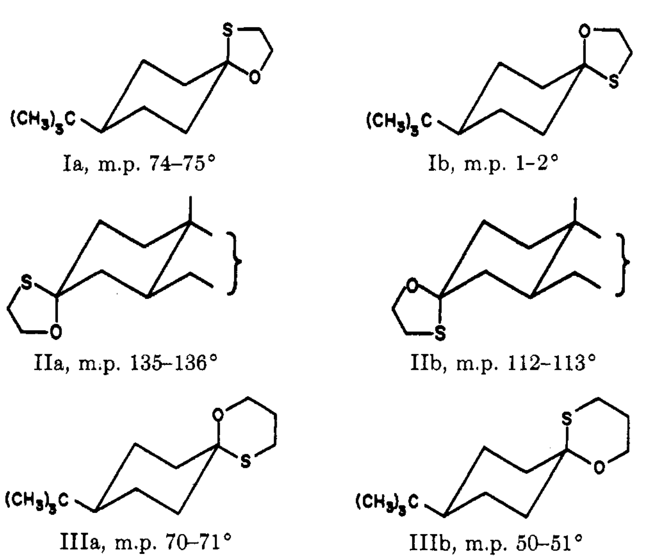

E

Starting material	% yield Ketone A	Ether B	Enol ether C	Ketal D	Olefin E
Ia[b]	53.4	14.1	15.5[c]	6.1[c]	11.5
Ib[b]	54.7	12	15.5[c]	10.5[c]	6.8
IIa[d]	43	11	20	7	5
IIb[d]	47	11.5	21	8	4
IIIa[e]	48	12	15.5[c]	6.5[c]	7
IIIb[e]	47	12		21.5	7
Ia[f]	60	12	5	5	Not analyzed
Ia[g]	12	0	0	83	0
IIa[h]	58.3	0	0	21.3	0
Ia[i]	39	9[j]	0	0	Not analyzed
Ia[k]	69	0	0	0	0

[a] In benzene, 2 hr., room temperature unless otherwise indicated. [b] R = 4-*t*-Bu; R′ = Et. Analysis by gas chromatography with internal standard. [c] Apportionment by column chromatography. [d] R = cholestane residue; R′ = Et. Analysis by column chromatography. Reaction time 24 hr. [e] R = 4-*t*-Bu; R′ = *n*-Pr. Analysis by isolation and gas chromatography. [f] Toluene distilled from catalyst prior to reaction. Analysis by column chromatography. [g] Ethanol added to benzene. [h] Solvent acetone; 6 hr. at reflux. [i] 6 hr. at reflux. Other products formed: *trans*-4-*t*-butylcyclohexanol, 27%; *cis*-4-*t*-butylcyclohexanol, 12%. [j] Also 1.5% *trans* ether. [k] Reflux, 5 hr.; Raney nickel deactivated by boiling with acetone. Product contained traces of 4-*t*-butylcyclohexanols.

In the process of studying the reaction of the monothioketals shown in Figure 1 with Raney nickel, several interesting observations were made which are summarized in Table I. First of all, it was found that the desulfurization of monothioketals proceeds smoothly and in reproducible fashion in benzene at room temperature; the products from stereoisomeric starting materials are nearly identical and the product distribution for the three different starting materials (I, II, and III) is remarkably similar. Secondly, control experiments (see Experimental) indicate that none of the reaction products is altered by further treatment with Raney nickel in benzene at room temperature. This is significant since it was also found that under more stringent conditions (benzene at reflux) the products are apparently *not* stable and, in particular, that alcohols (presumably formed by reduction of the ketone) appear among the products, although they are not formed in desulfurization under milder conditions. Since many Raney nickel desulfurizations reported in the literature[4] were effected at the reflux temperature of the solvent used (56° or above), it appears probable that some of the products isolated were artifacts of the reaction of the primary products with Raney nickel or with solvent. Thirdly, by a combination of gas chromatographic and column chromatographic methods, it has now been possible to account for over 80% of the products in all cases. In fact, in the desulfurization of the 4-*t*-butylcyclohexanone monothioketals where gas chromatographic analysis with an internal standard was employed, 100% of the product has been accounted for. Thus there is no possibility that any of the products from Ia and Ib were missed and, in view of the analogy of the results, it is unlikely that any products from II and III were overlooked either.


Ia, m.p. 74–75°

Ib, m.p. 1–2°

IIa, m.p. 135–136°

IIb, m.p. 112–113°

IIIa, m.p. 70–71°

IIIb, m.p. 50–51°

Figure 1.

The major product of desulfurization of all the six monothioketals (I–III) shown in Figure 1 is the corresponding ketone, formed in 43–55% yield. This agrees well with the 34–58% yield of ketone previously reported[7] in the desulfurization of IIa. Also obtained were the axial (*cis*- or α-, ethyl or *n*-propyl) ethers in yields of 11–14% which is within the range (10–31%) previously observed.[7] However, the present investigation also yielded three products not previously reported. One is the ethyl or *n*-propyl enol ether corresponding to the starting ketone, formed in 15–21% yield. A second one is the diethyl or di-*n*-propyl ketal of the starting ketone, formed in 6–9% yield. The final new product is olefin (4-*t*-butylcyclohexene or 2-cholestene) obtained in 4–12% yield.

The reason why these products were not found previously may be twofold. One is that two of them—the enol ether and the ketal—are quite sensitive to acid, being readily converted to ketone. This conversion may have taken place during column chromatography on acid-washed alumina; in the present work, either column chromatography on basic alumina or gas chromatography was employed to analyze the products. Even so, the ketal is not stable to gas chromatography, being converted to enol ether in the process of analysis; column chromatography was the only method at our disposal to analyze the ketal and enol ether separately. The second reason why enol ether and ketal did not appear in previous investigations may lie in the fact that they are apparently not stable to treatment with Raney nickel at elevated temperatures (see Table I), seemingly being converted to ethyl ethers and ketone and/or the corresponding alcohols. The possibility that the different product composition at higher temperatures reflects a large difference in activation energy for the different products on the catalyst surface is not entirely ruled out, however.

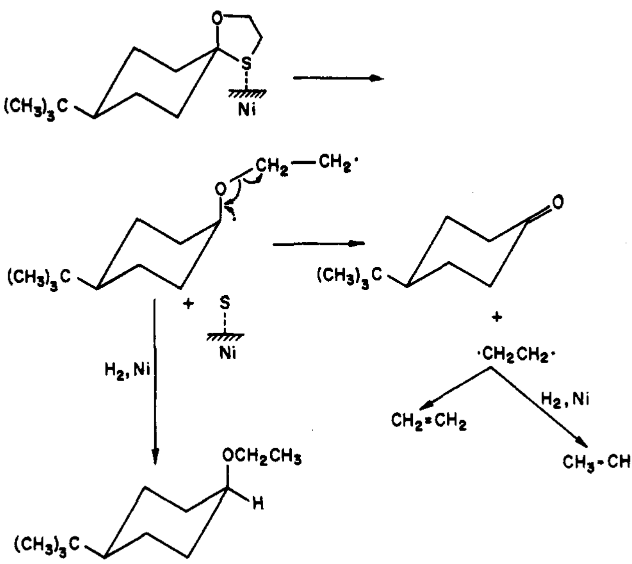


Figure 2.

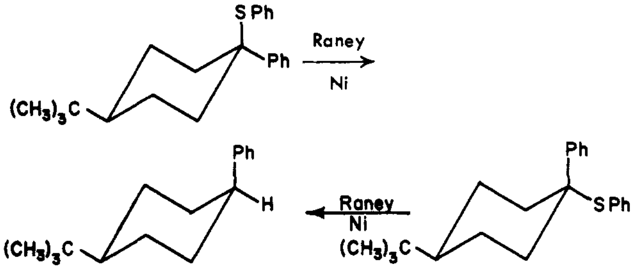


Figure 3.

The gaseous products obtained from I and III were also collected and investigated by gas chromatography to account for the fate of the ethyl or propyl moieties eliminated from I and III in the process of forming 4-*t*-butylcyclohexanone. It was found that the gas from I was mainly ethane containing only little ethylene, and *ca.* 75% of the C_2 fragment lost from the solid and liquid monothioketals was accounted for as ethane. Contrariwise, only about 40% of the C_3 fragment lost in ketone formation from III was accounted for as propane (containing only traces of propylene and cyclopropane).

Attempts were made to look for cyclohexane, the possible dimerization product of the trimethylene diradical eliminated from III. However, even carrying out the reaction in toluene instead of benzene (so as to make possible enrichment of any cyclohexane formed by distillation prior to gas chromatographic analysis), no cyclohexane could be found.

The appearance as ethane rather than ethylene of the C_2 fragment eliminated from I and propane rather than propylene or cyclopropane of the C_3 fragment from III in the formation of 4-*t*-butylcyclohexanone may be compared to previous results recorded[7] in the desulfurization of monothioketals derived from higher mercaptoethanols (such as 3,3-diphenyl-1-mercapto-2-propanol and 4,4-diphenyl-1-mercapto-3-butanol). In the earlier work, saturated hydrocarbons were always obtained from the six-membered monothioketals (oxathianes). From the five-membered monothioketals (oxathiolanes), sometimes saturated and sometimes unsaturated hydrocarbons resulted, the implication being (Table I in ref. 7) that deactivation of the Raney nickel (by boiling with acetone prior to reaction) promotes olefin formation whereas active Raney nickel gives rise to paraffin.

In the cases studied previously,[7] the potential olefin has its double bond conjugated with at least one aromatic ring. The extra stability of the double bond thus provided may favor olefin over paraffin formation, other things being equal.

We shall now turn to the mechanistic implications of the present work. In doing so we must point out that our work does not prove or even afford strong support for any particular mechanism of Raney nickel desulfurization of monothioketals; the most that may be said is that the results can be interpreted in terms of the currently favored[4] radical mechanism of Raney nickel desulfurization and that the experimental observations provide some previously unsuspected subtleties which any reaction mechanism must take into account.

For formation of the ketone we favor the previously proposed[5-7] diradical mechanism (Figure 2). The ethylene diradical may be adsorbed on the catalyst as formed and pick up two adsorbed hydrogen atoms to yield ethane, the observed major gaseous product. Alternatively (but less likely), ethylene may be formed first but be efficiently adsorbed on the catalyst and hydrogenated further to ethane. The previous observation[7] that olefin formation is enhanced *vis-a-vis* paraffin formation on deactivated catalysts is compatible with either explanation. Either the substituted ethylene diradical is desorbed (as olefin) from the activated catalyst before it picks up hydrogen, or, if olefin is formed, the deactivated catalyst is not able to hydrogenate it efficiently. In the case of a trimethylene radical, formation of propylene or cyclopropane is unlikely and the diradical presumably stays (or becomes) absorbed on the catalyst until it is hydrogenated to propane. Unfortunately, our work gives no clue as to the reason for the poor recovery of the C_3 fragment from oxathiolanes. Similar observations, have, however, been made previously.[7]

The same diradical which gives rise to the ketone may also give rise to the ethyl (or *n*-propyl) ether (Figure 2). The fact that the axial ether was formed exclusively is somewhat surprising. It suggests that the diradical formed in the primary act of desulfurization is sufficiently free to reorient itself on the catalyst, so that the hydrogen eventually attaches itself from the less hindered equatorial side. This hypothesis is in accord with observations on the 1-phenyl-1-thiophenoxy-4-*t*-butylcyclohexanes[14] (Figure 3) both of which, upon Raney nickel desulfurization, give largely *cis*-1-phenyl-4-*t*-butylcyclohexane. Apparently conflicting evidence, however, comes from the desulfurization of *p*-menthylene sulfide (Figure 4) which, to the extent that it proceeds by a simple hydrogenolysis of the sulfur–carbon bonds, gives rise to *cis*- and *trans*-*p*-menthane in about equal amounts.[15] This particular situation is complicated, however, by the fact that the cyclohexane ring in the starting material is in the boat form and it is possible that the intermediate diradical reacts partly in the boat form and partly in either of the two chair forms formed by ring inversion.

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[14] E. W. Garbish, private communication.

[15] A. W. Weitkamp, *J. Am. Chem. Soc.*, **81**, 3434 (1959).

The enol ether may also arise from the intermediate diradical either by an intramolecular hydrogen transfer (Figure 5, A) or by a hydrogen transfer to and from the catalyst (Figure 5, B). Attempts to distinguish between these two possibilities by study of the ethylene monothioketal of 2,2,6,6-tetradeuteriocyclohexanone failed since, because of the isotope effect, the enol ether was obtained from the labeled compound in quantity insufficient for adequate study by n.m.r.

The origin of the olefin (4-*t*-butylcyclohexene or 2-cholestene) is relatively obscure. Formal pathways can be devised for formation of the olefin, together with alcohol, from the diradical intermediate but they are not mechanistically very attractive. It is of interest that in all cases the yield of olefin and of ketal are quite comparable. A possible mechanism for ketal formation based on this finding is shown in Figure 6. The equilibrium between the monothioketal and ketal is normally nearly entirely on the side of the former, but is shifted toward the latter through removal of the sulfur. The assumption that ethanol split out in the formation of the olefin is responsible for the formation of the diethyl ketal is supported not only by the approximate equivalence of the olefin and ketal yields but also by an experiment in which ethanol was deliberately added to a solution of 4-*t*-butylcyclohexanone ethylene monothioketal in benzene prior to treatment with Raney nickel (Table I). In this case, 4-*t*-butylcyclohexanone diethyl ketal was the major product (85%, the remainder being 4-*t*-butylcyclohexanone).

The possibility that ethanol used in the storage of Raney nickel might be involved in the formation of the ketal was ruled out in three different ways. Firstly the diethyl ketal was formed in all runs from I and II in approximately constant yield, even though, after decantation of the ethanol from the catalyst and addition of benzene, part of the benzene was always distilled to remove all ethanol by azeotropic distillation. Secondly, in one case where the Raney nickel catalyst was boiled with toluene to remove ethanol more efficiently, the diethyl ketal was nevertheless formed. Thirdly, as already mentioned, the trimethylene monothioketals III gave rise to di-*n*-propyl ketal, not to diethyl ketal or mixed ethyl propyl ketal.

It is of some interest that formation of ketals and enol ethers followed by hydrolysis during work-up might account for the formation of alcohols (corresponding to the thioethanol moiety of the monothioketal) along with ketones observed by previous investigators[6,7] who have been somewhat puzzled by the appearance of an extra oxygen atom (ketone plus alcohol from monothioketal) in their products. However, the pertinent experiments[6,7] were mostly carried out in acetone or methyl ethyl ketone at reflux and our experiments in benzene or benzene–ethanol at room termperature have no *direct* bearing on the results. Because acetone deactivates Raney nickel[7] (probably by dehydrogenating it, being partially reduced to isopropyl alcohol), making experiments at room temperature problematic and also because of the danger of transketalization, we have not studied acetone as a solvent extensively in the present work. In one experiment where a Raney nickel catalyst deactivated by boiling with acetone was used in benzene at reflux to desulfurize Ia, the only product isolated was 4-*t*-butylcyclohexanone (69%); in another single experiment, desulfurization of IIa in boiling acetone gave 3-cholestanone diethyl ketal (21%) as well as 3-cholestanone (58%).

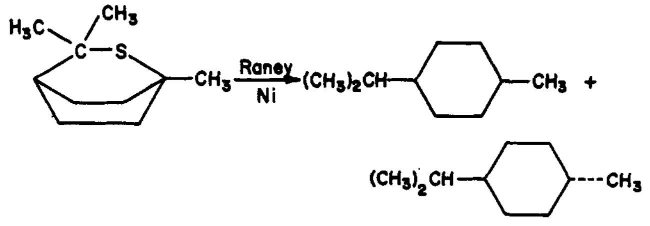

Figure 4.

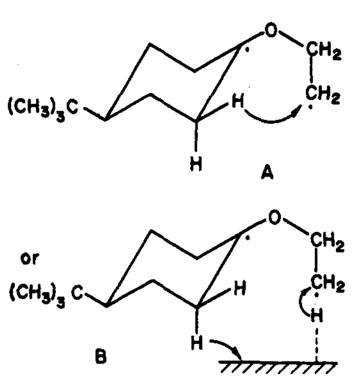

Figure 5.

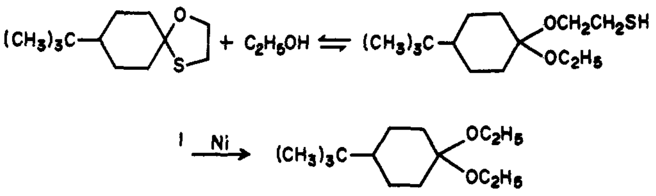

Figure 6.

Authentic specimens of all reaction products obtained in this work were prepared by known methods to establish retention times and response ratios in gas chromatograms and to compare infrared spectra. Of interest are the formation of the 4-*t*-butylcyclohexyl ethyl and propyl ethers from the corresponding acetates or propionates by the method of Pettit[16] (reduction with lithium aluminum hydride–boron trifluoride or diborane–boron trifluoride) and the formation of 3α-ethoxycholestane (43% yield) along with 2-cholestene from 3β-cholestanyl *p*-toluenesulfonate and sodium ethoxide in ethanol.

Experimental

Raney Nickel.—W-2 Raney nickel was prepared by the method of Mozingo[17] shortly before use and stored under ethanol. The ethanol was decanted and replaced by benzene and the benzene was distilled until its boiling point was maintained constant for some time. In the sequel, it is assumed that 1 ml. of settled catalyst is equivalent to 0.6 g. of nickel.

Desulfurizations. 4-*t*-Butylcyclohexanone Monothioketal. A. Solid Isomer (Ia).—To *ca.* 200 g. of Raney nickel in 600 ml. benzene was added 20 g. (0.094 mole) of Ia,[9] m.p. 74–75°, and the suspension was stirred vigorously for 2 hr. The catalyst was then filtered carefully on a sintered-glass funnel and washed several times with benzene. The combined filtrate was concen-

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[16] G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, **25**, 875 (1960); **26**, 4557 (1961).

[17] R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 181.

trated at reduced pressure; the residue weighed 14 g. and contained no sulfur as shown by a sodium fusion test. Analysis and identification of the reaction products was effected in two different ways.

In the first method, the product was dissolved in hexane and chromatographed, using a 5-ft.-long column containing 1 lb. of basic (Alcoa F-20) alumina. Thirty-seven fractions (about 100 ml. each) were eluted with hexane, all of them being free of ketone as indicated by infrared spectrum. The remainder of the material on the column was then removed by washing the column with benzene. Fractions 1–9 contained negligible residue. Fractions 10–12 contained two compounds (infrared bands at 6.1 and 8–10 μ), evidenced by gas chromatography. Fractions 13–24 contained a single compound (infrared bands at 6.1, 8.4, and 12.8 μ), and fractions 25–35 contained another compound (infrared-bands in the 9–10-μ region), which, after rechromatography, weighed 1.2 g. (5.6%). The infrared spectrum of this compound was identical with that of the diethyl ketal of 4-*t*-butylcyclohexanone (*vide infra*). Fractions 10–12 were rechromatographed and thus separated into two compounds. One weighing 1.7 g. (9.8%) appeared homogeneous on a gas chromatogram and had an infrared spectrum identical with that of an authentic specimen of *cis*-4-*t*-butylcyclohexyl ethyl ether (see below). The other fraction was identical with the material in the original fractions 13–24, total weight 2.4 g. (14.1%). This compound had an infrared spectrum identical with that of 4-*t*-butylcyclohexanone enol ether (see below) and, upon treatment with aqueous alcoholic hydrochloric acid followed by 2,4-dinitrophenylhydrazine, gave the phenylhydrazone of 4-*t*-butylcyclohexanone, m.p. 150° (lit.[18] m.p. 151.1–152.5°), undepressed by admixture with an authentic sample. The 4-*t*-butylcyclohexanone eluted with benzene weighed 7.6 g. (52%) and its infrared spectrum was identical with that of an authentic sample.

In a repeated experiment, the total nonketonic material (fractions 10–35) was treated with hydrochloric acid in dioxane on the steam bath for 0.5 hr. to destroy the enol ether and ketal. The reaction mixture was poured into water, extracted with ether, cleared with water and aqueous sodium carbonate, dried over sodium sulfate, concentrated, taken up in hexane, and chromatographed on alumina. In this case only two fractions were obtained, one weighing 0.9 g. (6.9%) and having identical infrared spectrum as 4-*t*-butylcyclohexene,[19] the other being the same *cis*-4-*t*-butylcyclohexyl ethyl ether previously isolated.

For more accurate analysis, the reaction mixture after concentration and addition of an internal standard (*trans*-4-*t*-butylcyclohexyl acetate) was subjected to gas chromatography on a Carbowax column at 150°, helium flow rate 30 p.s.i. Retention times and response ratios were established using the authentic samples to be described below. The analysis indicated 4-*t*-butylcyclohexene (retention time 2 min.), 11.5%; *cis*-4-*t*-butylcyclohexyl ethyl ether (9 min.), 14.1%; diethyl ketal and enol ether of 4-*t*-butylcyclohexanone (19 min.), 21.7%; and 4-*t*-butylcyclohexanone (38 min.), 53.4%. No other peaks, except for traces of benzene were detected. Unfortunately, a separate analysis of the ketal and enol ether proved impossible by gas chromatography, since the ketal is converted to enol ether on the column, as shown by injection of authentic samples. The apportionment of these compounds in Table I is based on the column chromatogram.

In an experiment where 3 g. of the solid monothioketal was desulfurized with 30 g. of Raney nickel in 200 ml. of benzene at 6-hr. reflux, the products, analyzed by gas chromatography (without internal standard), as shown in Table I contained *trans*- as well as *cis*-4-*t*-butylcyclohexyl ethyl ether and *cis*- and *trans*-4-*t*-butylcyclohexanol; no ketal or enol ether of 4-*t*-butylcyclohexanone survived. An experiment carried out for 2 hr. at reflux gave 38% ketone, 24% *trans* alcohol, 7% *cis* alcohol, 11% *cis* ether, 2.5% *trans* ether, and 3% ketal plus enol ether. Clearly the latter two compounds disappear as the reaction conditions are made more stringent and alcohols appear, the ketone possibly being an intermediate in the transformation of the former into the latter. *trans* ether may result from hydrogenation of enol ether. However, these conclusions are quite tentative and require further experimental support.

In an experiment in which 2.5 g. of monothioketal in 200 ml. of benzene was reduced for 5 hr. with 25 g. of Raney nickel previously deactivated by boiling 2 hr. with 150 ml. of acetone, the product was largely 4-*t*-butylcyclohexanone (1.24 g., 69%) which, according to gas chromatographic analysis, contained only traces of the corresponding *cis* and *trans* alcohols.

In one experiment toluene was used as a solvent instead of benzene to ensure more certain removal of ethanol (from Raney nickel preparation) by codistillation. The toluene was then decanted and replaced by benzene. From 5 g. of monothioketal Ia and 50 g. of Raney nickel were thus obtained by column chromatography 2.17 g. of 4-*t*-butylcyclohexanone (60%), 0.22 g. of *cis*-4-*t*-butylcyclohexyl ethyl ether (5%), 0.29 g. of 4-*t*-butylcyclohexanone diethyl ketal (5%), and 0.57 g. of 4-*t*-butylcyclohexanone enol ethyl ether (12%). The material balance is somewhat low, possibly due to losses on chromatography, but the ketal is clearly formed in this case.

Deliberate addition of 5 ml. of ethanol prior to desulfurization of 5 g. of Ia (otherwise as described above) gave the following products by column chromatography: 4-*t*-butylcyclohexanone diethyl ketal, 4.78 g. (83%), and 4-*t*-butylcyclohexanone, 0.54 g. (12%).

B. **Liquid Isomer (Ib).**[9]—The desulfurization was carried out exactly as described for Ia. The crude products weighed 14.2 g. Both column chromatographic and gas chromatographic separation of the products was effected, as described for the solid isomer, with the results given by Table II.

TABLE II

	Column chromatogram		
Product	Wt. recovered, g.	% isolated	Gas chromatogram,[a] % yield
4-*t*-Butylcyclohexene	0.86	6.7	6.8
cis-4-*t*-Butylcyclohexyl ethyl ether	1.51	8.8	12
4-*t*-Butylcyclohexanone ethyl enol ether	2.2	13.1	26
4-*t*-Butylcyclohexanone diethyl ketal	1.15	5.2	
4-*t*-Butylcyclohexanone	6.95	48.3	54.7

[a] Using *trans*-4-*t*-butylcyclohexyl acetate as internal standard.

Control Experiments.—(1) 4-*t*-Butylcyclohexanone (1 g.) and Raney nickel (10 g.) in 50 ml. benzene were stirred for 2 hr. at room temperature. After filtration and concentration, gas chromatography and infrared examination indicated that the ketone was unchanged. (2) The ethyl enol ether of 4-*t*-butylcyclohexanone (5 g.) was stirred with 50 g. of Raney nickel in 200 ml. benzene for 2 hr. at room temperature. Infrared examination of the product after concentration suggested that the ethyl enol ether was unchanged by this treatment. The result was the same when ethanol was added to the benzene. (3) The diethyl ketal of 4-*t*-butylcyclohexanone (5 g.) was stirred with 50 g. of Raney nickel in 200 ml. of benzene for 2 hr. at room temperature. Concentration and infrared spectroscopy disclosed that the ketal was recovered nearly unchanged, with but a trace of ketone having been formed.

4-*t*-Butylcyclohexanone Trimethylene Monothioketal.[13] High-Melting Isomer.—Monothioketal IIIa[13] (10 g., 0.044 mole) was stirred for 2 hr. with 100 g. of Raney nickel in 250 ml. of benzene at room temperature. Filtration of the catalyst and concentration yielded 6.7 g. of oil which was analyzed in two ways.

Column chromatography on basic (Alcoa F-20) alumina from hexane yielded 18 fractions of *ca.* 70 ml. each, following which the ketone was eluted with benzene. The chromatogram was monitored by infrared and gas chromatographic analysis. Fractions 1–3 (infrared absorption at 6.1 μ) appeared to contain two components. The crude eluate was treated with a little hydrochloric acid in dioxane at steam-bath temperature for 30 min. to destroy any enol ether. The solution was poured into water and extracted with ether which was cleared with water and sodium bicarbonate solution, dried over sodium sulfate, and concentrated. The residue was rechromatographed from hexane giving *ca.* 0.4 g. (6%) of material whose infrared spectrum indicated it to be 4-*t*-butylcyclohexene. Fractions 4–12 absorbed at 6.1, 8.4, 9–10, and 12.8 μ in the infrared and contained two compounds. Rechromatography gave 1.3 g. (14.7%) of the propyl enol ether of 4-*t*-butylcyclohexanone, infrared bands at 6.1, 8.4, and 12.8 μ, identical in spectrum with an authentic specimen (see below). The remainder of the material (0.9 g., 11%) was treated with hydrochloric acid–dioxane as described above to give pure *cis*-4-*t*-

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

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

butylcyclohexyl *n*-propyl ether, identified by comparison of infrared spectrum with that of an authentic sample (see below). Fractions 13–18 on rechromatography yielded 0.7 g. (5.7%) of material identical in infrared spectrum with the di-*n*-propyl ketal of 4-*t*-butylcyclohexanone (see below). The 4-*t*-butylcyclohexanone eluted with benzene weighed 3.2 g. (44%). Gas chromatography (Carbowax, 165°) of the crude material indicated approximately the following yields of products (uncorrected for differences in weight–area response): 4-*t*-butylcyclohexene, 7%; *cis*-4-*t*-butylcyclohexyl *n*-propyl ether, 12%; di-*n*-propyl ketal and propyl enol ether of 4-*t*-butylcyclohexanone, 22%; and cyclohexanone, 48%.

When the desulfurization was carried out in boiling benzene (6-hr. reaction time), the approximate yields of products from 5 g. of IIIa were *cis*-4-*t*-butylcyclohexyl *n*-propyl ether, 0.37 g. (9%); 4-*t*-butylcyclohexanone, 1.61 g. (47%); *cis*-4-*t*-butylcyclohexanol, 0.31 g. (9%); and *trans*-4-*t*-butylcyclohexanol, 0.51 g. (15%). Here, also, more vigorous conditions led to formation of alcohols at the expense of enol ether and ketal.

Low-Melting Isomer.—The desulfurization of 3 g. of IIIb[13] with 30 g. of Raney nickel in 100 ml. of benzene at room temperature (2 hr.) was carried out as described above for IIIa. The crude product (2.01 g.) was subjected to an approximate analysis by gas chromatography which indicated the following yields: 4-*t*-butylcyclohexene, 0.12 g., 6.5%; *cis*-4-*t*-butylcyclohexyl *n*-propyl ether, 0.29 g., 12%; *n*-propyl enol ether and di-*n*-propyl ketal of 4-*t*-butylcyclohexanone, approximately 22% (exact analysis not possible, as the gas chromatogram did not distinguish between the two species); and 4-*t*-butylcyclohexanone, 0.97 g., 45%. More vigorous conditions (6 hr. reflux) here also produced *cis*-4-*t*-butylcyclohexanol, 7%; and *trans*-4-*t*-butylcyclohexanol, 14%; in addition to cis-4-*t*-butylcyclohexyl *n*-propyl ether, 9.5%; and 4-*t*-butylcyclohexanone, 49%.

Gas Analyses.—In one experiment, the gas evolved in the desulfurization of 1 g. (4.7 mmole) of Ia was collected in a gas buret over water. The volume at 27° (739.5 mm.) was 47 cc. or 1.80 mmoles. This is a 38 mole % yield compared with a 48–53% yield of ketone in similar experiments (*vide supra*). Thus the mole ratio of gaseous product to ketone is about 0.75. In another experiment, the suspension of nickel in benzene was frozen, the ketal Ia (1.5 g.) in a little benzene was added, and the air-tight apparatus was evacuated. The benzene was then thawed and the reaction mixture was stirred magnetically for 2 hr. at room temperature, the gases being collected in an expansion bulb. The gas was then distilled into a liquid nitrogen-cooled receiver and analyzed mass spectrometrically. The gas consisted of ethane, ethylene, carbon dioxide, nitrogen, oxygen, and benzene vapor with a high ratio of ethane/ethylene. Gas chromatographic analysis indicated that the gas was very largely (>98%) ethane with a little ethylene.

From 1 g. (4.4 mmoles) of IIIa there was obtained only 21.5 cc. of gas at 739.5 mm. and 26°, *i.e.*, 0.82 mmole or 19 mmole %. This compares to a 45–48 mole % yield of ketone; the mole ratio gas/ketone is only about 0.4. The gas was analyzed by gas chromatography as described above and found to be mainly propane with a very small amount of cyclopropane and a trace of propylene.

3-Cholestanone Ethylene Monothioketal. High-Melting Isomer.—A solution of 10 g. of IIa[9] in 300 ml. of benzene was stirred with 100 g. of Raney nickel for 24 hr.[20] The catalyst was filtered and washed with chloroform and the combined filtrate was concentrated to give 8.31 g. of crude solid which was analyzed by chromatography on basic alumina using hexane as solvent. Eleven fractions of 100 ml. each were collected, the separation being monitored by infrared analysis. At the end, the remaining material was eluted with chloroform, which yielded 3.7 g. (43%) of 3-cholestanone, m.p. 129–130° (lit.[21] m.p. 129–129.5°), identical in infrared spectrum with an authentic sample. The early fractions (4–7) were rechromatographed to give three fractions: A, m.p. 70–74°; B, m.p. 54–59°; and C, m.p. 75–80°. Compound C had strong absorption bands at 6.1, 8.4, and 12.8 μ and, upon recrystallization from ethanol containing a little pyridine, gave 2.03 g. (20%) of 3-ethoxy-2-cholestene, m.p. 83–84° (lit.[22] m.p. 87–88°), undepressed by admixture with an authentic specimen (see below) with which it was identical in infrared spectrum. A and B were combined, heated on the steam bath with ethanolic hydrochloric acid for 0.5 hr., poured into water, and extracted repeatedly with ether. The ether was dried over sodium sulfate and distilled and the residue was chromatographed from hexane to give, as first fraction, 0.415 g. (5%) of 2-cholestene (glistening needles), m.p. 75–76° (lit.[23] m.p. 75–76°), undepressed by admixture of an authentic sample; its infrared spectrum was identical with that of the authentic sample and that reported in the literature.[24] Fractions 2–4 of the above chromatogram yielded viscous oils which solidified on standing overnight and, upon recrystallization, yielded 1.02 g. (11%) of 3α-ethoxycholestane, m.p. 63–63.5°, undepressed by admixture of an authentic specimen (see below) with which it was identical in infrared spectrum.

Anal. Calcd. for $C_{29}H_{52}O$: C, 83.58; H, 12.58. Found: C, 83.42; H, 12.29.

Fractions 8–11 of the original chromatogram yielded solid residues which were recrystallized from ethanol containing a little pyridine to give 0.72 g. (7%) of 3-cholestanone diethyl ketal, m.p. 67–69° (lit.[22] m.p. 68–69.5°), undepressed by admixture with an authentic specimen (see below) with which it was identical in infrared spectrum.

When the reaction was repeated starting from 2 g. of IIa in 150 ml. of acetone with 20 g. of Raney nickel (6 hr. reflux), the only compound eluted from the chromatogram with hexane was 3-cholestanone diethyl ketal, 0.434 g. (21.3%), m.p. 67–69° after one recrystallization. Chloroform elution produced 1.01 g. (58.3%) of 3-cholestanone.

Low-Melting Isomer.—The desulfurization of 2.5 g. of IIb[9] with 25 g. of Raney nickel in 75 ml. of benzene was carried out as described for IIa above. Column chromatography (as described) gave 0.084 g. (4%) of 2-cholestene, m.p. 75–76°; 0.265 g. (11.5%) of 3α-ethoxycholestane, m.p. 63–63.5; 0.537 g. (21%) of 3-ethoxy-2-cholestene, m.p. 83–84°; 0.205 g. (8%) of 3-cholestanone diethyl ketal, m.p. 68–69.5°; and 1.01 g. (47%) of 3-cholestanone, m.p. 129–130°.

Preparation of Authentic Materials. ***trans*-4-*t*-Butylcyclohexyl Ethyl Ether. A.**—*trans*-4-*t*-Butylcyclohexanol[18] (9 g.) was acetylated with 15 ml. of acetic anhydride and 15 ml. of pyridine on the steam bath. After 1 hr. the excess reagents were distilled at reduced pressure and the residue was taken up in ether, washed successively with 2 *N* hydrochloric acid, 1 *N* sodium hydroxide, and water, and dried over sodium sulfate. Distillation yielded 9.1 g. (80%) of *trans*-4-*t*-butylcyclohexyl acetate, b.p. 118° (15 mm.), lit.[25] b.p. 110° (16 mm.).

In a three-necked flask equipped with a stirrer and reflux condenser were placed 3.8 g. (0.1 mole) of lithium aluminum hydride and 300 ml. of dry ether. The suspension was stirred and placed in an ice bath, and a solution of 9.9 g. (0.05 mole) of the above *trans* acetate in 117 g. (1.25 moles) of redistilled boron trifluoride etherate was added over the course of 1 hr. Stirring and cooling were continued for 45 min., after which the reaction mixture was refluxed for 2 hr. It was cooled and treated with cold, dilute hydrochloric acid, the layers were separated, and the ether layer was washed successively with 1 *N* hydrochloric acid, saturated aqueous sodium bicarbonate, and water. The product was a mixture of *trans*-4-*t*-butylcyclohexanol and its ethyl ether. It was chromatographed on alumina from hexane and the eluate was concentrated to give 3.1 g. (34%) of *trans*-4-*t*-butylcyclohexyl ethyl ether, b.p. 204–205° (745 mm.), n^{20}_{D} 1.4460.

Anal. Calcd. for $C_{12}H_{24}O$: C, 78.27; H, 13.04. Found: C, 78.50; H, 12.91.

B. Alternative Method.—The *trans* alcohol (7.8 g.) was dissolved in 30 ml. of dry ether in a flask equipped with a stirrer and cooled in an ice bath. Boron trifluoride etherate (2 ml.) was added, followed by a cold solution of diazoethane prepared by treating 8.19 g. of N-nitroso-N-ethylurea with 50% aqueous potassium hydroxide.[26] The diazoethane solution was added slowly with stirring, the yellow color disappearing rapidly. At the end of the addition the mixture was stirred for 2 hr. more, washed with water, dried over sodium sulfate, concentrated, chromatographed from hexane on alumina, concentrated, and dis-

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[20] After 4 hr., about 60% of the monothioketal remained unchanged.

[21] A. L. Wilds and C. Djerassi, *J. Am. Chem. Soc.*, **68**, 1712 (1946).

[22] A. Serini and H. Köster, *Ber.*, **71**, 1766 (1938).

[23] K. Hattori, *J. Pharm. Soc. Japan*, **57**, 708 (1937); *Chem. Abstr.*, **32**, 187^7 (1938).

[24] H. Rosenkrantz, A. J. Milhorat, and F. Farber, *J. Biol. Chem.*, **195**, 510 (1962).

[25] N. B. Chapman, R. E. Parker, and P. J. A. Smith, *J. Chem. Soc.*, 3634 (1960).

[26] G. F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

tilled. There was obtained 4.1 g. (56%) of the *trans* ether identical in infrared spectrum with the material described above.

***cis*-4-*t*-Butylcyclohexyl Ethyl Ether.**—This ether was obtained in 33% yield from *cis*-4-*t*-butylcyclohexanol[27] by reduction of the acetate as described for the *trans* isomer above: b.p. 206–207° (745 mm.), $n^{20}\text{D}$ 1.4486.

Anal. Calcd. for $C_{12}H_{24}O$: C, 78.27; H, 13.04. Found: C, 78.24; H, 12.75.

4-*t*-Butylcyclohexanone Diethyl Ketal.[28]—A solution of 0.5 g. of ammonium nitrate, 11.7 g. (0.079 mole) of 4-*t*-butylcyclohexanone, and 14.8 g. (0.1 mole) of triethyl orthoformate in 50 ml. of absolute ethanol in a flask equipped with a downward condenser was heated briefly on a steam bath. An exothermic reaction set in and ethyl formate distilled. When the reaction subsided, heating was resumed for a few minutes and again the reaction became exothermic. The reaction mixture was let stand overnight and concentrated at reduced pressure with slight warming. The residue was poured into dilute sodium hydroxide solution (2 g. of NaOH in 150 ml. of water) and extracted with ether. The ether was washed with 10% sodium hydroxide and water, dried over sodium sulfate, and concentrated to yield a slightly orange oil which was chromatographed on basic alumina from hexane to give 11.8 g. (70%) of the diethyl ketal of 4-*t*-butylcyclohexanone. Attempted distillation (at 30 mm.) led to decomposition so the chromatographed material was freed of solvent by prolonged pumping and drying in a vacuum desiccator. The infrared and n.m.r. spectra were compatible with the assigned structure.

Anal. Calcd. for $C_{14}H_{28}O_2$: C, 73.69; H, 12.28. Found: C, 73.27; H, 12.28.

1-Ethoxy-4-*t*-butylcyclohexane.—The above ketal (15.2 g., 0.066 mole) and a few crystals of *p*-toluenesulfonic acid were placed in a 50-ml. distilling flask attached to a condenser and fraction collector. The flask was heated at 30-mm. pressure and the products which distilled were collected. Heating was stopped when the contents of the flask became discolored. The main fraction of the distillate (following a forerun which was discarded) appeared, according to infrared spectrum, to contain enol ether contaminated with ketone. It was chromatographed from hexane on basic alumina and distilled to give 8.5 g. (70%) of product, b.p. 106–110° (23 mm.).

Anal. Calcd. for $C_{12}H_{22}O$: C, 79.12; H, 12.09. Found: C, 78.84; H, 11.97.

***cis*-4-*t*-Butylcyclohexyl *n*-Propyl Ether.**—This ether was prepared from *cis*-4-*t*-butylcyclohexanol, propionic anhydride, lithium aluminum hydride, and boron trifluoride in essentially the same fashion as described above for the corresponding ethyl ether (method A), except that the crude ethereal solution of the propionate, after drying was directly subjected to reduction. From 10 g. (0.064 mole) of *cis* alcohol there was obtained 6.1 g. (50%) of *cis*-4-*t*-butylcyclohexyl *n*-propyl ether, b.p. 120° (33 mm.).

Anal. Calcd. for $C_{13}H_{26}O$: C, 78.27; H, 13.13. Found: C, 78.59; H, 13.33.

4-*t*-Butylcyclohexanone Di-*n*-propyl Ketal.[29]—A mixture of 30.8 g. (0.2 mole) of 4-*t*-butylcyclohexanone, 24 g. of *n*-propyl alcohol, 50 mg. of *p*-toluenesulfonic acid, and 200 ml of benzene was boiled at reflux in a 500-ml. flask equipped with a Dean–Stark trap. After 3 hr., an additional 15 g. of 1-propanol was added and boiling was continued for an additional hour after which time no more water separated. The reaction mixture was washed with sodium hydroxide solution and water, dried over sodium sulfate, and concentrated at reduced pressure. The residual oil was chromatographed from hexane on basic alumina and the solvent was removed by prolonged pumping and drying in a vacuum desiccator. The residual ketal weighed 20 g. (40%), and its infrared and n.m.r. spectra were compatible with the assigned structure.

Anal. Calcd. for $C_{16}H_{32}O_2$: C, 75.01; H, 12.50. Found: C, 74.91; H, 12.60.

1-Propoxy-4-*t*-butylcyclohexene.—The *n*-propyl enol ether was prepared from 25.6 g. (0.1 mole) of the above di-*n*-propyl ketal in the same fashion described for the lower homolog (*vide supra*) except that chromatography was not needed. The crude product was distilled directly to give 11.7 g. (60%) of product, b.p. 240–243° (745 mm.), infrared spectrum (bands at 6.1, 8.4, and 12.8 μ), and n.m.r. spectrum compatible with the assigned structure.

Anal. Calcd. for $C_{13}H_{24}O$: C, 79.58; H, 12.25. Found: C, 79.02; H, 12.35.

3-Cholestanone Diethyl Ketal.—An authentic specimen of this ketal was prepared from 3.68 g. (0.01 mole) of 3-cholestanone (from chromic acid oxidation of commercially available 3β-cholestanol[30]), 1.5 g. of triethyl orthoformate, and 0.1 g. of ammonium nitrate in 25 ml. of absolute ethanol in essentially the same way as described for 4-*t*-butylcyclohexanone diethyl ketal above. The crude product weighed 3.5 g. (75%) and, after chromatography from hexane on basic alumina, melted at 68–69.5° (lit.[22] m.p. 68–69.5°). Its infrared spectrum was compatible with the assigned structure.

3-Ethoxy-2-cholestene.—Attempted preparation of this enol ether by heating of the diethyl ketal in xylene[22] was unsuccessful; the ketal was recovered unchanged. The method of Julian, *et al.*,[31] was therefore adapted. To a solution of 4 g. (0.0104 mole) of 3-cholestanone in 20 ml. of dioxane was added 4 ml. of triethyl orthoformate followed by a solution of 1 drop of concentrated sulfuric acid in 1 ml. of dioxane. The solution was boiled at reflux for 0.5 hr., 0.5 ml. of pyridine was added, and the solvent was removed by distillation at reduced pressure. Work-up in the usual way, chromatography, and crystallization from ethanol (with a little pyridine) gave 3.4 g. (80%) of 3-ethoxy-2-cholestene, m.p. 83–85° (lit. m.p. 87–88°), prominent infrared bands at 6.1, 8.4, and 12.8 μ. Treatment with warm ethanolic hydrochloric acid yielded 3-cholestanone, m.p. 128–129°.

3α-Ethoxycholestane and 2-Cholestene.—3β-Cholestanyl *p*-toluenesulfonate, m.p. 134–135° from ethyl acetate–petroleum ether (lit.[32] m.p. 134–135°), was prepared in 80% yield by the usual procedure from 3β-cholestanol (0.02 mole) and *p*-toluenesulfonyl chloride (0.03 mole) in pyridine (75 ml.).

Boiling of 5.3 g. (0.1 mole) of the above *p*-toluenesulfonate with sodium ethoxide from 0.25 g. of sodium (0.011 g.-atom) and 250 ml. of absolute ethanol for 5 hr. left 0.9 g. (17%) of unchanged starting material which crystallized from the solution. The solution was filtered, diluted with water, and extracted with ether. The residue from the ether extract, upon chromatography on neutral alumina (150 g.), gave a total of 0.37 g. (10%) of 2-cholestene, m.p. 75–76° (lit.[23] m.p. 75–76°), infrared spectrum identical with that published[24]; and a total of 1.8 g. (43%) of 3α-ethoxycholestane, m.p. 63–63.5° after crystallization from ethanol. (The literature[7] reports the ether as a liquid.) The infrared spectrum of the ether was identical with that of the analytical sample obtained from Raney nickel desulfurization of Ia (*vide supra*). There was also obtained 0.2 g. (5%) of which appeared to be 3α-cholestanol, m.p. 178–180° (lit.[33] m.p. 186–187°), infrared absorption at 3.04 μ (KBr disk). Acetylation yielded material of m.p. 93–94° after crystallization from methanol (reported[33] for 3α-cholestanyl acetate, m.p. 95.5–96°).

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[27] E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, **79**, 5992 (1957).

[28] Method of J. A. VanAllan, *Org. Chem.*, **32**, 5 (1952).

[29] *Cf.* R. E. McCoy, A. W. Baker, and R. S. Gohlke, *J. Org. Chem.*, **22**, 1175 (1957).

[30] W. F. Bruce, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 139.

[31] P. L. Julian, E. W. Meyer, W. J. Karpel, and W. Cole, *J. Am. Chem. Soc.*, **73**, 1982 (1951).

[32] W. Stoll, *Z. physiol. Chem.*, **207**, 147 (1932).

[33] C. W. Shoppee, *J. Chem. Soc.*, 1138 (1946).