creasingly modified by B-strain to overcome the loss of a benzyl radical resonance. The effect of the loss of a benzyl radical resonance between III and VI is reflected in the considerable difference in activation energy, which again is compensated for to a large degree by the very favorable entropy of activation of III. The rather high activation energy of III appears anomalous and is also consistent with the anomalous ultraviolet spectrum of this compound.[25] The loss of one benzyl radical resonance between VII and IV is reflected to a certain extent in the differences of the activation energies, but is more than compensated for by the quite favorable increase in the entropy of activation of IV.

The interpretation given above for the unsymmetrical and symmetrical alkyl azo compounds may also be applied in the same fashion to the linear azonitrile compounds.[3a-e] B-Strain is probably the major strain factor, although F-strain may assist to a lesser degree in accelerating the rate of decomposition of some of the azo compounds.

It should be realized, of course, that the arguments used for explaining the order of reactivity of the four unsymmetrical azo compounds listed in this work would still hold if the decompositions were occurring in a stepwise fashion with the rate determining step being the scission of the benzyl carbon–nitrogen bond, since the same relationships concerning B-strain and hyperconjugation are present among the four pertinent benzyl radicals.

Acknowledgment.—We wish to gratefully acknowledge the support of this work by the National Science Foundation, Grant NSF-1453. We also wish to thank Dr. R. G. Hiskey for his advice and help.

BROOKLYN 1, N. Y.

(25) C. G. Overberger and A. V. DiGiulio, THIS JOURNAL, **80**, 6562 (1958).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

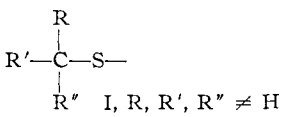
Stereochemistry of Raney Nickel Desulfurizations. I. The 1,3-Disubstituted Cyclohexane and the Bicyclo[2.2.1]heptane Systems

BY EUGENE E. VAN TAMELEN AND EDWIN A. GRANT[1]

RECEIVED OCTOBER 1, 1958

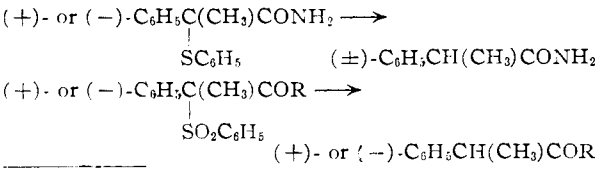
The synthesis and proof of stereochemistry of *trans*- and *cis*-3-methyl-3-mercaptocyclohexanols (IIIa and IIIb, respectively) are described. Suitable derivatives of IIIa and -b were reductively desulfurized with Raney nickel to give mixtures of diastereoisomeric 3-methylcyclohexanol derivatives: *cis*-S-benzyl ether O-β-naphthoate(IXb) → 37% *cis* and 63% *trans*; sulfone (Xb) of IXb → 43% *cis* and 57% *trans*; *trans*-S-benzyl ether O-β-naphthoate(IXa) → 56% *cis* and 44% *trans*; sulfone(Xa) of IXa → 46% *cis* and 54% *trans*. Phenyl 4-camphyl sulfide and the corresponding sulfone were prepared and were shown to give camphane on desulfurization.

Although the recent literature abounds in examples of the well-known Raney nickel desulfurization reaction, only a few of the reported cases provide information about the stereochemical fate of the carbon atom which becomes hydrogenolyzed. This gap in the body of results being accumulated is due in part to the infrequency of asymmetric S-*t*-carbinyl systems(I), a structural



I, R, R′, R″ ≠ H

type necessary for retention of asymmetry in a sulfur hydrogenolysis reaction. W. A. Bonner[2] has made a deliberate attempt to study the stereochemistry of the reaction by employing derivatives of 2-phenyl-2-mercaptopropionic acid, substances which conform to the specified type I. Each of the enantiomers of 2-phenyl-2-phenylmercapto-



propionamide (or the corresponding sulfoxide) gave on desulfurization racemic 2-phenylpropionamide. By contrast, the antipodal sulfones were converted to the expected products with 90% retention of optical activity; and although the relative configurations of starting material and product were not determined rigorously, inversion was indicated by the method of rotational trends. On the basis of these results, and others, Bonner[2] advanced a concerted mechanism involving coordination of the sulfone oxygen atom on the reagent, accompanied by backside displacement by hydrogen adsorbed on the metal surface. Because of the unusual nature of the Raney nickel desulfurization reaction, we felt it desirable to scrutinize stereochemically other systems and thereby extend and consolidate the grounds upon which mechanistic proposals can be developed.

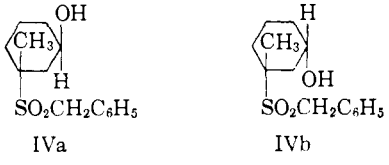
The 3-methyl-3-mercaptocyclohexanol system seemed attractive for desulfurization studies in that the oxygenated carbon atom would serve as a convenient and reliable reference point for gaining stereochemical information about changes at the 3-position; the anticipated desulfurization products, *cis* and/or *trans*-3-methylcyclohexanols, are well-characterized substances to which secure stereochemical assignments have been made.[3] Synthesis of the desired diastereoisomers was ac-

(1) Wisconsin Alumni Research Foundation Assigned Research Assistant.

(2) W. A. Bonner, THIS JOURNAL, **74**, 1034 (1952).

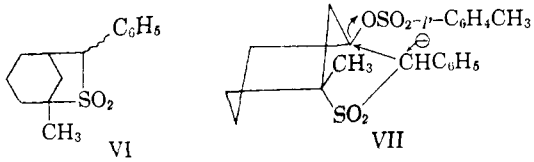
(3) H. L. Goering and C. Serres, Jr., *ibid.*, **74**, 5908 (1952).

complished through two variations of reaction scheme A. Conjugate addition of benzyl mercaptan to 3-methyl-2-cyclohexenone, carried out in benzene in the presence of Triton B hydroxide, afforded 3-methyl-3-benzyl-mercaptocyclohexanone (II, R = $C_6H_5CH_2$) as a distillable, low-melting solid, characterized as the semicarbazone. Although sodium borohydride reduction to the 3-methyl-3-benzylmercaptocyclohexanol structure (III, R = $C_6H_5CH_2$) was frustrated by prior elimination of benzyl mercaptan (a circumstance which could be demonstrated by the action of aqueous alkali or mineral acid alone), the desired conversion was effected in good yield by employing lithium aluminum hydride as the reducing agent. Perbenzoic acid oxidation of the unseparated diastereoisomeric alcohols gave a mixture of the corresponding sulfones IVa and IVb, which was

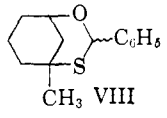


separated by chromatography and crystallization into two pure components, m.p.'s 98–100° and 135–135.5°. It was also possible to utilize hydrogen sulfide in place of benzyl mercaptan, the 3-methyl-3-mercaptocyclohexanols (III, R = H) being secured again through lithium aluminum hydride reduction. Alternately, a diastereoisomeric mixture of mercapto alcohols could be obtained by sodium and liquid ammonia reduction of the benzyl thioethers described above.

Stereochemical assignments to the mercapto alcohols were made possible through two separate approaches. In the first, the tosylates Va and Vb of the sulfones IVa and IVb were subjected to the action of base. Perhaps surprisingly, the tosylate of the higher-melting sulfone was recovered in 95% yield after its solution in methanolic sodium methoxide was refluxed for 36 hours.[4] On the other hand, the same basic reagent induced elimination of *p*-toluenesulfonic acid from the isomeric, lower-melting sulfone tosylate, with the formation in poor yield of a product, $C_{14}H_{18}O_2S$. The infrared spectrum of this substance revealed that the sulfone group was intact; perbenzoic acid titration showed no olefinic unsaturation. On the basis of these properties, and in consideration of reasonable reaction courses open to the starting material, the structure VI is assigned to the elimination product. The ring-closure which the lower-



melting, but not the higher-melting, tosylate undergoes, is best viewed as an intramolecular displacement with inversion of the tosyloxy function by the benzyl sulfone anion VII, and implies that the two reacting groups are *trans* related (IVa).[5] The stereochemical assignments which follow from the above observations were fully confirmed by cyclization experiments carried out on the free mercapto alcohols. The mixture of diastereoisomers was treated with benzaldehyde in benzene containing a catalytic amount of *p*-toluenesulfonic acid. Under optimum conditions, the *cis*-sulfhydryl alcohol was smoothly converted to the monothioacetal VIII, while the *trans* isomer did



not react significantly with benzaldehyde. Regeneration of the starting *cis*-cyclohexanol from the acetal was accomplished by heating in an aqueous dioxane solution with phenylhydrazine hydrochloride, under which conditions the acetal is cleaved, and the benzaldehyde is tied up irreversibly as the phenylhydrazone. The recovered *cis*-mercaptocyclohexanol was related to previously obtained members in the series by carrying out, successively, S-benzylation and perbenzoic acid oxidation; these transformations gave rise to sulfone alcohol, m.p. 135–135.5°, identical with the isomer IVb already assigned the *cis* configuration. A similar pair of steps served to convert the *trans*-mercapto alcohol to the isomeric, lower-melting sulfone alcohol IVa described earlier.

As expected, the free alcohols were found not suitable for stereochemical work, since on treatment with Raney nickel they suffered partial epimerization at the carbinol carbon, presumably the consequence of an oxidation–reduction mechanism. Therefore, the β-naphthoic acid esters were selected for use, and their effectiveness in preventing nickel-catalyzed equilibration of the alcoholic system was demonstrated by subjecting pure *cis*- and *trans*-3-methylcyclohexyl β-naphthoates to the desulfurization conditions used in later experiments; after saponification of recovered ester, each pure alcohol isomer was recovered in high yield.

Four substrates, the *trans*- and *cis*-3-methyl-3-benzylmercaptocyclohexyl β-naphthoates (IXa and IXb, respectively), and the corresponding sulfones Xa and Xb, were used in the desulfurization studies. In each case, the pure, crystalline ester

(4) Other examples of notably unreactive tosylates are cyclohexane *cis*-1,3-di-*p*-toluenesulfonate (M. F. Clarke and L. N. Owen, *J. Chem. Soc.*, 2103 (1950)) and *anti*-7-camphenyl tosylate (E. E. van Tamelen and C. I. Judd, THIS JOURNAL, **80**, 6305 (1958)).

(5) In this manuscript, the designation *cis* or *trans* refers to the relative configurations of the sulfur and oxygen functions, when both are attached to the cyclohexane ring.

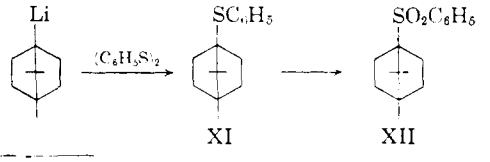
was dissolved in absolute ethanol, and after addition of a standard amount of fresh Raney nickel, the mixture was stirred and refluxed for 17–20 hours. After saponification of the desulfurized ester, the 3-methylcyclohexanol mixture was distilled and the proportion of isomers, shown in Table I, was determined by infrared spectral

TABLE I

Compound	Yield of ester, %	Yield of alcohol, %	Average proportion of *cis*-alcohol produced, %	Inversion of configuration, %
IXa	88	87	56	44
IXb	89	72	37	37
Xa	77	73	46	54
Xb	68	65	43	43

methods. In order to demonstrate that the isolation and analytical method developed was reliable and involved only minimal fractionation at any stage, a 3-methylcyclohexyl β-naphthoate mixture of known composition (67% *cis*) was exposed to the desulfurization conditions and carried through the identical sequence used in an actual desulfurization run; infrared analysis showed that the composition of the diastereoisomeric mixture was virtually unchanged (64% *cis*). Although the 3-methylcyclohexanol mixtures produced showed correct carbon–hydrogen analyses, the precision of the infrared analytical technique was not as high in some cases, as might reasonably be expected, thereby indicating either the presence of certain amounts of impurities, or uncontrolled variations in the desulfurization runs.

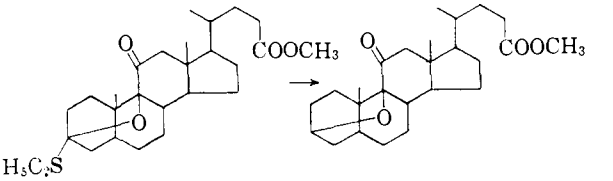
Unfortunately, the quantitative results of the desulfurization experiments do not appear to lend themselves to any straightforward mechanistic interpretation at the present time. Perhaps the most striking feature is the stereochemical indiscrimination displayed in the development of product. At the same time, the proportion of stereoisomers produced lies far from the equilibrium value,[6] and thus, in the cases studied herein, the desulfurizations are not thermodynamically controlled processes. The results obtained with the methylcyclohexanol system differ significantly from those secured in the phenylpropionic acid series; in particular, the high order of stereospecificity Bonner observed in working with α-benzenesulfonyl derivatives was not paralleled in the present work. The results described herein suggest that the nickel-induced hydrogenolysis of a sulfonyl group does not necessarily proceed with inversion of configuration at the attached carbon atom. This tenet can be demonstrated forcibly by reference to phenyl 4-camphyl sulfone (XII), which, because of its bridged skeleton, is sterically incapable of undergoing simple desulfurization with inversion. The bicyclic sulfone was prepared by



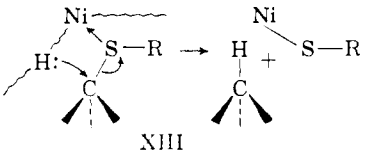
XI XII

(6) E. L. Eliel and R. S. Ro, THIS JOURNAL, **79**, 5992 (1957).

the treatment of 4-camphyllithium[7] with phenyl disulfide,[8] followed by oxidation of the resulting phenyl 4-camphyl sulfide (XI) with perbenzoic acid. Desulfurization proceeded smoothly, and camphane was secured in good yield from both the bicyclic sulfide and the sulfone. A bridgehead carbon atom in the (2.2.1)bicycloheptane system cannot easily accommodate a more or less completely developed positive charge; therefore this result, as well as the steroid case[9] reproduced below, suggests that, of the three possible sulfur-free



intermediates which might be involved—cation, anion, or free radical—the first is least likely. However, an SNi mechanism (*e.g.*, XIII), promoted by the energetically favorable formation of nickel



XIII

sulfide (*cf.* the release of nitrogen from diazotized 1-aminoapocamphane to give apocamphanol[10]), is not ruled out.

The intimate nature of Raney nickel desulfurizations is still obscure; however, the present evidence is not incompatible with the current preference for a reaction of the free radical type.

Experimental[11]

3-Benzylmercapto-3-methylcyclohexanone.—In a typical run 64 g. (0.515 mole) of redistilled benzyl mercaptan was dissolved in 100 ml. of benzene containing 5 g. of Triton B hydroxide and 55 g. (0.50 mole) of 3-methylcyclohexenone was added dropwise with stirring under an atmosphere of nitrogen. After three to five hours of additional stirring at room temperature, the mixture was extracted twice with water to remove the catalyst and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure along with unreacted benzyl mercaptan and 3-methylcyclohexenone. The product was distilled *in vacuo;* after a third redistillation, 68 g. (58%) was obtained as a colorless liquid, which slowly crystallized on standing in the cold; b.p. 152° (0.14 mm.), m.p. 31–33°, $n^{35}D$ 1.5618 (after three months at −20° in the dark, $n^{35}D$ 1.5633).

Anal. Calcd. for $C_{14}H_{18}OS$: C, 71.75; H, 7.75. Found: C, 72.21; H, 7.84.

The semicarbazone consisted of white needles (from aqueous ethanol), m.p. 171–171.5°.

Anal. Calcd. for $C_{15}H_{21}ON_3S$: C, 61.82; H, 7.27. Found: C, 62.28; H, 7.11.

***cis*- and *trans*-3-Benzylmercapto-3-methylcyclohexanol.**—A solution of 49.42 g. (0.211 mole) of the above thioether-ke-

(7) S. Winstein and T. G. Traylor, *ibid.*, **78**, 2597 (1956), and references cited therein.

(8) The reaction of 4-camphyllithium with benzenesulfenyl chloride involves nucleophilic attack, on halogen, giving 4-chlorocamphane and (presumably) lithium thiophenoxide.

(9) L. F. Fieser, H. Heymann and S. Rajagopalan, *ibid.*, **72**, 2307 (1950).

(10) P. D. Bartlett and L. H. Knox, *ibid.*, **61**, 3184 (1939).

(11) All melting points are corrected; boiling points are uncorrected.

tone in ethyl ether was added dropwise with stirring and cooling into a two-liter, three-neck round-bottom flask containing 11 g. (0.29 mole) of lithium aluminum hydride dissolved in 600 ml. of ethyl ether. After the addition was complete, the reaction flask was stirred at room temperature for an additional two to three hours, after which the excess hydride was decomposed with ethyl acetate. The reaction mixture was poured into ice-water, acidified with cold, 6 *N* sulfuric acid, saturated with solid sodium chloride, and extracted twice with diethyl ether. The combined ethereal extracts were washed with 25–30% sodium hydroxide solution, with water until neutral, and finally with saturated chloride solution. The solvent was dried over anhydrous sodium sulfate and removed under reduced pressure; the product, a colorless viscous liquid, was distilled under reduced pressure; b.p. 160–164° (0.17 mm.), $n^{30}D$ 1.5654, 38.42 g. (77%).

Anal. Calcd. for $C_{14}H_{20}OS$: C, 71.14; H, 8.5. Found: C, 71.22; H, 8.46.

Oxidation to the Sulfones. A solution of 16.8 g. (0.0718 mole) of the above thioether alcohols in 30 ml. of benzene was cooled in ice, and 530 ml. of perbenzoic acid solution (0.075 equivalent or 0.150 mole) was added slowly. The homogeneous solution was allowed to stand overnight at room temperature, after which time 10 ml. of crude cyclohexene was added to destroy the excess perbenzoic acid. The mixture was extracted three times with 5% sodium hydroxide solution. The organic layer was washed twice with water and, without preliminary drying, was evaporated under a current of air. The crude solid, 15 g. (78%), was chromatographed over 450 g. of silicic acid (previously washed thoroughly with acetone and dried at 70° under infrared lamps) using, as eluent, chloroform containing 0.75% ethanol, to yield, on evaporation of the solvent, 1.3 g. of white needles, m.p. 88–92°; 11 g. of white solid, m.p. 95–120°; and 2.2 g. of white plates, m.p. 134–135°. No distinct band separation was noted, even on increasing the alcohol content of the eluent. Recrystallization of the lowest melting material from benzene–petroleum ether raised its melting point to 98–100°. Recrystallization of the highest melting material from chloroform–petroleum ether raised its melting point to 135–135.5°. The sulfone isomers were identical with corresponding substances described below.

***cis-* and *trans*-3-Methyl-sulfhydrylcyclohexanols from Hydrogenolysis of the Benzylthioethers.**—Twenty-two grams (0.094 mole) of the mixture of 3-benzylmercapto-3-methylcyclohexanols was added slowly to 250 ml. of liquid ammonia which was stirred and cooled in a Dry Ice-bath. After 15–20 minutes of stirring to ensure complete solution, 6 g. (0.26 g.-atom) of sodium metal was added in small pieces. The mixture was then stirred for 45 minutes, after which time the cooling bath was removed and the ammonia allowed to evaporate with stirring. The semi-solid mass was again cooled in a Dry Ice-bath; absolute ethanol (10 ml.) was then added to destroy the excess sodium. One hundred ml. of 30% sodium hydroxide solution was added; the basic layer was extracted twice with benzene, and the resulting organic layers were discarded. The mercaptan was released from the basic solution in the cold with 12 *N* sulfuric acid and extracted quickly with chloroform. The chloroform solution was washed twice with water, dried over anhydrous sodium sulfate, and distilled at atmospheric pressure through a 3-foot column. The product was then distilled under reduced pressure and crystallized as a low melting solid (needles) in the cold receiver: 5.69 g. (41%), b.p. 129–130° (18 mm.), $n^{30}D$ 1.5118.

3-Methyl-3-sulfhydrylcyclohexanone.—In a typical run, 137.0 g. (1.24 moles) of 3-methylcyclohexenone was added dropwise with stirring at room temperature into a mixture of 1 kg. of chloroform and 60 ml. of triethylamine, which had been previously saturated with hydrogen sulfide. Stirring and introduction of gaseous hydrogen sulfide by means of a ground glass gas tube was continued throughout the addition of the ketone at such a rate that the solution remained saturated with hydrogen sulfide at all times. After the addition of the ketone was complete, hydrogen sulfide was bubbled into the solution at a very slow rate while the stirring was continued for an additional 8 to 10 hours. At the end of this time, the chloroform solution was extracted with two 500-ml. portions of 5% acetic acid solution (CARE must be exercised here as a large volume of hydrogen sulfide gas is released; therefore, a two-liter separatory funnel was used and the mixture of acetic acid and the chloroform solution was shaken only very gently at first). The mixture was extracted with water until neutral (5 to 10 washings required), then dried over anhydrous sodium sulfate, and the chloroform removed at atmospheric pressure through a 3-foot column. The product was distilled under reduced pressure through a short Vigreaux column and collected as a mobile, red liquid with a rather offensive odor: 72.97 g. (42.5%; by taking into account recovery of 3-methylcyclohexenone, the yield amounted to 95%). The red liquid, b.p. 123–125° (21 mm.), $n^{20}D$ 1.5087, gradually lost its color at room temperature and more slowly at 5° in the dark, but the refractive index remained constant.

Anal. Calcd. for $C_7H_{12}OS$: C, 58.29; H, 8.39. Found: C, 58.17; H, 8.30.

***cis-* and *trans*-3-Methyl-3-sulfhydrylcyclohexanol from Hydride Reduction of the Corresponding Ketone.**—In a three-liter, three-neck, round-bottom flask, surrounded with ice, 38 g. (1 mole) of lithium aluminum hydride was dissolved in 2 kg. of ethyl ether. A dilute solution of 72.97 g. (0.506 mole) of the sulfhydryl ketone in ethyl ther was added dropwise with stirring. After the addition was complete, and the mixture stirred for an additional 3 to 5 hours, the excess hydride was decomposed with ethyl acetate. The resulting semi-solid, gray mass was poured with vigorous stirring onto ice, acidified carefully with cold 6 *N* sulfuric acid, saturated with solid sodium chloride, and extracted twice with ether. The combined ether extracts were washed with 5% sodium bicarbonate solution, followed by saturated sodium chloride solution. Without preliminary drying, the ether was distilled through an efficient column at atmospheric pressure until the temperature reached 40–45°. The pot residue was then cooled and treated with 200 ml. of 30% sodium hydroxide solution. The basic solution was extracted twice with benzene, the organic layers discarded. The basic solution was then poured onto ice, and ice-cold 12 *N* sulfuric acid then added to congo red. The released mercaptan was quickly extracted with chloroform, the organic layer separated, washed with water, and dried over anhydrous sodium sulfate. The chloroform was distilled at atmospheric pressure through a 3-foot column; the product, under reduced pressure, was distilled as a colorless liquid which crystallized in long, white needles in the cold receiver, but remelted below room temperature: 43.24 g. (68%), b.p. 119–120° (9 mm.), $n^{30}D$ 1.5119. The infrared spectrum was identical with that obtained from the product of sodium and liquid ammonia treatment of *cis-* and *trans*-3-benzylmercapto-3-methylcyclohexanol.

Anal. Calcd. for $C_7H_{14}OS$: C, 57.49; H, 9.65. Found: C, 57.83; H, 9.12.

Separation of *cis-* and *trans*-3-Methyl-3-mercaptocyclohexanol.—One hundred grams (0.682 mole) of the mixture of sulfhydryl alcohols was dissolved in 250 ml. of benzene containing 2 g. of *p*-toluenesulfonic acid monohydrate. The solution was heated on the steam-bath, and 0.70 equivalent (51 g., 0.48 mole) of freshly distilled, purified benzaldehyde was added slowly with swirling. Within 5 minutes the solution turned milky white; gentle heating and swirling were continued for 10 additional minutes. The flask was then cooled in ice, and 30 ml. of 30% sodium hydroxide solution was added in three portions with cooling and swirling until the exothermic reaction subsided. The benzene solution was then extracted twice with 75-ml. portions of 30% sodium hydroxide solution, and the basic extracts were washed with benzene. The combined benzene layers were stored with excess base overnight, under nitrogen, to allow the Cannizzaro reaction to go to completion. The combined basic layers were poured onto ice, acidified with cold 12 *N* sulfuric acid solution and quickly extracted with chloroform. The chloroform solution was washed three times with 5% sodium bicarbonate solution to remove the benzoic acid, washed twice with water, and dried over anhydrous sodium sulfate. The solvent was distilled at atmospheric pressure through an efficient column; the product was distilled under reduced pressure and 49.44 g. (49%) was collected as a colorless liquid, b.p. 115–116° (8 mm.), $n^{30}D$ 1.5110. Qualitative infrared analysis of the product showed the presence of a small amount of the *cis* isomer. Therefore, the 49.44 g. (0.339 mole) was treated again with 20 g. (0.188 mole) of benzaldehyde in 25 ml. of benzene and worked up in the same way. On distillation of this retreated material, pure *trans*-3-methyl-3-sulfhydrylcyclohexanol was obtained as a colorless liquid, which crystallized spontaneously at

room temperature (m.p. 41–43°), b.p. 115.5° (7 mm.), $n^{30}D$ 1.5108 (supercooled), 20.80 g. (42%).

Anal. Calcd. for $C_7H_{14}OS$: C, 57.49; H, 9.65. Found: C, 57.95; H, 9.49.

The 1-Methyl-4-oxa-3-phenyl-2-thiabicyclo-2,2,1-nonane (VIII).—The combined benzene solutions, having been allowed to stand in contact with base overnight (see above), were extracted once more with 30% sodium hydroxide solution to ensure complete removal of all base-soluble material. After the benzene solution was washed with water and dried over anhydrous sodium sulfate, the benzene was removed under reduced pressure, and the reaction mixture distilled, yielding a forerun of 14.15 g., (b.p. 60–130° (0.03 mm.)) followed by 36.72 g. of the bicyclic derivative VIII, b. p. 130–131.5° (0.03 mm.), $n^{30}D$ 1.5684. On the basis of 20.8 g. of pure mercaptocyclohexanol recovered, the yield of the bicyclic product was 29%; on the basis of 49.44 g. of crude mercaptocyclohexanol recovered, the yield was 45.5%. A large amount of high-boiling material remaining in the pot, probably a mixture of mercaptals, was not investigated further.

Anal. Calcd. for $C_{14}H_{18}OS$: C, 71.76; H, 7.74. Found: C, 71.82; H, 7.57.

***cis*-3-Methyl-3-sulfhydrylcyclohexanol.**—All attempts to hydrolyze the monothioacetal VIII with aqueous mineral acid resulted in facile hydrolysis of the acetal, as evidenced by ultraviolet analysis of the benzaldehyde produced, but simultaneous destruction of the mercaptan in the acid medium.

To a solution of 43.5 g. (0.3 mole) of phenylhydrazine hydrochloride in 100 ml. of purified dioxane and 100 ml. of water contained in a 500-ml. erlenmeyer flask, was added 36.72 g. (0.156 mole) of the monothioacetal VIII. The flask was heated with swirling over a steam-bath for about 10 minutes, or until the original orange-pink color of the solution faded to a pale green. The heating and swirling were then continued for 15 additional minutes, after which the reaction mixture was cooled (benzaldehyde phenylhydrazone began to crystallize) and poured into a separatory funnel containing 300 ml. of ethyl ether. After the addition of 400 ml. of water, the mixture was extracted with ether. The combined ether layers were extracted twice with 100-ml. portions of 30% sodium hydroxide solution. The combined basic extracts were washed twice with benzene, poured onto ice, acidified with cold 12 *N* sulfuric acid solution, and quickly extracted with chloroform. The chloroform solution was washed with water and dried over anhydrous sodium sulfate. After distillation of the solvent, the product, on distillation under reduced pressure, was obtained as a colorless liquid which crystallized as a low melting solid (needles) in the cold receiver; 18.23 g. (80%), b.p. 124–124.5° (9 mm.), $n^{30}D$ 1.5128.

Anal. Calcd. for $C_7H_{14}OS$: C, 57.49; H, 9.65. Found: C, 57.44; H, 9.40.

S-Benzylation.—A solution containing 0.150 mole of sodium ethoxide was prepared by adding 3.45 g. (0.150 mole) of sodium metal in small pieces to 75 ml. of absolute ethanol with external cooling. After the addition of sodium was complete and the temperature of the solution no more than 5°, 21.80 g. (0.149 mole) of the above *cis*-mercaptoalcohol was melted and added slowly with stirring. When the temperature of the solution again reached 5°, and the solution protected from the air by nitrogen (stirring continuing), 18.7 g. (0.149 mole) of redistilled benzyl chloride was added dropwise with external cooling over a period of 2 hours. Sodium chloride began to cloud the solution almost immediately. After the addition of benzyl chloride was complete, the reaction mixture was allowed to stir under nitrogen and warm to room temperature during 2 to 3 hours. The mixture was then poured into benzene and extracted with water. The benzene was washed with 10 ml. of 30% sodium hydroxide solution, followed by one washing with water. The benzene solution was then dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The product was obtained by distillation as a colorless, viscous liquid, b.p. 153–155° (0.07 mm.), $n^{30}D$ 1.5660 (supercooled) which slowly crystallized and had m.p. 42–44°. This yield was 32.26 g. (92%).

Anal. Calcd. for $C_{14}H_{20}OS$: C, 71.14; H, 8.50, Found: C, 71.22; H, 8.46.

The S-benzylation of *trans*-3-methyl-3-mercaptocyclohexanol was carried out in a similar manner. After distillation, 21.13 g. (85%) of a colorless, viscous liquid which did not crystallize was obtained, b.p. 142–145° (0.05 mm.), $n^{30}D$ 1.5642.

Anal. Calcd. for $C_{14}H_{20}OS$: C, 71.14; H, 8.50. Found: C, 71.43; H, 8.38.

***cis*-3-Benzylsulfonyl-3-methylcyclohexanol.**—To a solution of 10 g. (0.0422 mole) of the *cis*-thioether alcohol in benzene was added with cooling a solution of perbenzoic acid in benzene, until, after 5 minutes standing, one drop of the reaction mixture liberated iodine from a solution of potassium iodide in acetic acid. The reaction mixture was then stoppered and allowed to stand overnight at room temperature. The excess perbenzoic acid was then destroyed with a few ml. of crude cyclohexene. The reaction mixture was extracted three times with 5% sodium hydroxide solution (a few ml. of chloroform was added to prevent the product from crystallizing in the separatory funnel); the third washing, on acidification, liberated no benzoic acid. The organic layer was then washed twice with water, and, without preliminary drying, was evaporated under a current of air to dryness, yielding 9.2 g. of crude solid. On recrystallization from chloroform-petroleum ether, 8.75 g. (77%) of large, white plates separated, m.p. 135–135.5°.

Anal. Calcd. for $C_{14}H_{20}O_3S$: C, 62.64; H, 7.51. Found: C, 62.91; H, 7.63.

The acid phthalate was prepared according to the directions of Hills[12] and was recrystallized from chloroform–petroleum ether, m.p. 187–188°

Anal. Calcd. for $C_{22}H_{24}O_6S$: C, 63.44; H, 5.80. Found: C, 63.75; H, 5.73.

The phenylurethan was recrystallized from chloroform–petroleum ether, m.p. 205–205.5°.

Anal. Calcd. for $C_{21}H_{25}O_4NS$: C, 65.09; H, 6.50. Found: C, 65.11; H, 6.73.

***trans*-3-Benzylsulfonyl-3-methylcyclohexanol** was prepared in 70% yield by the same method as that used for the preparation of the *cis* isomer (see above), except that, after evaporation of solvent, the oily product was recrystallized twice from benzene–petroleum ether, yielding long, white needles, m.p. 98–100°.

Anal. Calcd. for $C_{14}H_{20}O_3S$: C, 62.64; H, 7.51. Found: C, 62.34; H, 7.48.

***cis*-3-Benzylsulfonyl-3-methylcyclohexyl *p*-Toluenesulfonate.**—Two grams (0.00745 mole) of the *cis*-sulfone-alcohol was dissolved in anhydrous pyridine, and, after the solution was cooled in ice, excess *p*-toluenesulfonyl chloride was added. The reaction mixture was allowed to stand overnight in the cold, after which time the mixture was poured into ice-water. The product, which crystallized immediately, was filtered and dissolved in chloroform. Upon addition of petroleum ether to the dried chloroform solution, 1.95 g. (62%) of white solid separated, m.p. 175–175.5° dec.

Anal. Calcd. for $C_{21}H_{26}O_5S_2$: C, 59.69; H, 6.22. Found: C, 59.69; H, 6.39.

***trans*-3-Benzylsulfonyl-3-methylcyclohexyl *p*-toluenesulfonate** was prepared in anhydrous pyridine following the same procedure as used for the preparation of the *cis* isomer. One recrystallization from benzene–petroleum ether produced white, flocculent crystals in 76% yield, m.p. 146–147° dec.

Anal. Calcd. for $C_{21}H_{26}O_5S_2$: C, 59.69; H, 6.22. Found: C, 59.94; H, 5.97.

Conversion to the Bicyclic Sulfone VI.—A solution of 0.28 g. (0.00066 mole) of the sulfone tosylate Va in 30 ml. of absolute methanol was added to a solution of 0.54 g. (0.01 mole) of sodium methoxide in 5 ml. of absolute methanol. The homogeneous solution was refluxed for 3 hours, after which the solvent was evaporated, water added, and the precipitate filtered. The 100 mg. of crude solid obtained was dissolved in petroleum ether, decolorized with Norite, and cooled to −25°. After 12 hours the precipitate was collected, and the mother liquor evaporated to dryness. The white solid, 50 mg., obtained from filtration was not investigated. The solid obtained from the mother liquor had m.p. 80–88°; recrystallizations from methanol–water yielded

(12) H. W. J. Hills, J. Kenyon and H. Phillips, *J. Chem. Soc.*, 576 (1936).

TABLE II

Compound	Grams (mole)	Ni(H) used, g.	Abs. EtOH, ml.	Reaction time, hr.	Ester produced, g.	Yield, %	Alcohol produced, g.	Yield, %	Analyses, %[b]
IXb	3.10	13	80	18	1.94	88	0.72	87	73.32[a]
	(0.0083)								12.12
IXa	3.15	12	85	18	2.00	89	0.61	72	73.70
	(0.0084)								12.19
IXb	2.64	15	130	19	1.34	77	0.39	73	73.37
	(0.0065)								12.00
IXa	4.20	18	150	20	1.86	68	0.51	65	73.72
	(0.0103)								11.72

[a] Average of three determinations. [b] Calcd.: C, 73.60; H, 12.36.

25 mg. (15%) of bicyclic sulfone, m.p. 90–91°. The product did not consume perbenzoic acid under conditions where Δ^3-tetrahydrophthalic anhydride readily took up one equivalent.

Anal. Calcd. for $C_{14}H_{18}O_2S$: C, 67.19; H, 7.25. Found: C, 66.91; H, 7.32.

Preparation of β-Naphthoates.—The procedure in all cases was the same as up to the point where the solid β-naphthoate was obtained crude. The alcohol to be esterified was dissolved in anhydrous pyridine and a slight excess of pure β-naphthoyl chloride was added with cooling. After the initial heating subsided, the solution was stoppered tightly and allowed to stand overnight at room temperature. After 2 to 3 ml. of water was added to destroy the excess acid chloride, the entire solution was poured with vigorous stirring into excess 5% sodium carbonate solution containing much chopped ice. The mixture was allowed to stand in the cold until crystallization was complete. The crude solid was then filtered, washed with water, dissolved in the appropriate solvent, decolorized and filtered with Norit, and allowed to crystallize.

cis-**3-Methylcyclohexyl β-naphthoate** was recrystallized first from aqueous methanol, second from petroleum ether; m.p 59.5–60° (needles).

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.58; H, 7.52. Found: 80.82; H, 7.73.

trans-**3-Methylcyclohexyl β-naphthoate** crystallized from methanol as small, white plates, m p. 49.5–50°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.58; H, 7.52. Found: C, 80.60; H, 7.59.

cis-**3-Benzylmercapto-3-methylcyclohexyl β-naphthoate (IXb)** was first recrystallized from aqueous methanol, second from petroleum ether, m.p. 84–84.5°.

trans-**3-Benzylmercapto-3-methylcyclohexyl β-naphthoate (IXa)** crystallized very easily from absolute methanol as fine, white needles having m.p. 96–97°, but on remelting, after having solidified, had m.p. 103°.

Anal. Calcd. for $C_{25}H_{26}O_2S$: C, 76.90; H, 6.71. Found: for IXb: C, 76.87; H, 6.77. Found for IXa: C, 77.35; H, 6.61.

cis-**3-Benzylsulfonyl-3-methylcyclohexyl β-naphthoate (Xb)** was recrystallized several times from acetone–water mixtures and finally had m.p. 144.5°, with a transition point around 90–95°. (If the melting point tube was placed in the bath at 100° or more, the solid quickly melted, immediately resolidified, and had melting point 144.5°.) If the melting point tube was allowed to heat in the bath from room temperature, only slight softening was noted at around 95°, then complete melting at 144.5°.

trans-**3-Benzylsulfonyl-3-methylcyclohexyl β-naphthoate (Xa)** was first recrystallized from acetone water and then from benzene–petroleum ether twice; m.p. 136–136.5°.

Anal. Calcd. for $C_{25}H_{26}O_4S$: C, 71.06; H, 6.20. Found: for Xb: C, 71.02; H, 617. Found for Xa: C, 71.39; H, 6.14.

Control Experiments under Desulfurization Conditions.—Commercial 3-methylcyclohexanol (67% *cis*, 33% *trans*) was converted to a mixture of *p*-nitrobenzoates. After many recrystallizations from methanol–water at −10° to −20°, approximately 3 g. of pure *cis*- to 1 g. of pure *trans*-3-methylcyclohexyl *p*-nitrobenzoates were obtained. The melting points were identical with authentic samples,[13] and mixed melting points showed no depression. The pure alcohols were obtained by steam distillation from a boiling alkaline solution of the esters in 90–95% yield: pure *cis*, b.p. 90–91° (26 mm.), $n^{25}D$ 1.4556 (lit.[3] b.p. 80–84° (15 mm), $n^{25}D$ 1.4555); pure *trans*, b.p. 78–80° (13 mm.), $n^{25}D$ 1.4565 (lit.[3] b.p. 71–73° (10 mm.), $n^{25}D$ 1.4565). The infrared spectra of the alcohols were identical in all respects to those of authentic samples. These alcohols were used to prepare the β-naphthoates described above.

After either isomeric ester was treated with freshly prepared W-2 Raney nickel under reflux conditions with stirring in acetone, filtered (Filter-Cel), and freed of solvent by evaporation, a quantitative recovery of solid starting material was obtained. Melting points and mixed melting points were compared for each isomer.

A mixture of 3-methylcyclohexyl β-naphthoates (67% *cis*, 33% *trans*) was refluxed with Raney nickel in absolute ethanol with stirring for 18 hours, filtered, and worked up by the same method as outlined above. On distillation of the alcohols in the microdistillation apparatus, an 80% yield of 64% *cis*- and 37% *trans*-3-methylcyclohexanols was obtained (the mixture of alcohols analyzed by quantitative infrared comparisons, as outlined below).

The commercial mixture of *cis*- and *trans*-3-methylcyclohexanols (67% *cis* and 33% *trans*), when treated directly with Raney nickel in ethanol, was converted to a mixture of approximately 90% *cis*- and 10% *trans*-3-methylcyclohexanols. A sample of *cis*-3-benzylsulfonyl-3-methylcyclohexanol, when desulfurized under the same conditions, produced a mixture having nearly the same composition.

Desulfurization Studies—In each case the β-naphthoate was first *dissolved* in absolute ethanol to which was then added freshly prepared (less than two weeks old and stored in the cold) Raney nickel. After the mixture was stirred, and refluxed for 17–20 hours, the warm reaction mixture was filtered through a medium porosity, sintered glass funnel (200-ml. capacity), which had been previously packed with at least one-half inch of Filter-Cel and washed with absolute ethanol. The nickel cake was rinsed twice with boiling absolute ethanol. The solvent was evaporated under a current of air until the solution became turbid, after which the flask was gently heated with steam to again effect solution (addition of a few ml. of methanol was required), and the hot solution filtered into a tared beaker. The solution was again evaporated and dried carefully under high vacuum to constant weight. In each run, a colorless to pale yellow oil was obtained which was saponified as outlined in the control experiment described above. The resulting 3-methylcyclohexanols were distilled in a microdistillation apparatus into a tared, 1-dram vial, thus minimizing transfer losses. The mixtures of alcohols each had b.p. 78–82° (13 mm.).

Quantitative infrared data were obtained for the mixture of alcohols provided by each of the desulfurizations. In order to obtain empirical reference curves, authentic *cis* and *trans* alcohols as well as mixtures of each (25% *cis*, 50% *cis*, and 75% *cis*) were placed successively in a 0.044-mm., cell and scanned at low speed from 9 to 13 μ in a Baird double-beam automatic infrared spectrophotometer. Pure *cis*-3-methylcyclohexanol absorbs weakly at 11.7 and 12.3 μ while pure *trans*-3-methylcyclohexanol absorbs strongly at 11.7 and 12.3 μ. By plotting the log of the percentage transmission (I/I_0) against percentage composition, a nearly straight line was obtained from the five points used for each wave length. This plot was used in converting percentage transmission of a desulfurization product to percentage composition, the absorptions at both 11.7 and 12.3 μ being employed. The details of the desulfurization runs as well as the

(13) The authors are indebted to Dr. F. McCarron for authentic samples of *cis*- and *trans*-3-methylcyclohexyl *p*-nitrobenzoates.

carbon-hydrogen analysis of each product are given in Table II and the infrared results are compiled in Table III.

TABLE III

PERCENTAGE OF *cis* ISOMER PRODUCED

	Run 1		Run 2		Run 3		Run 4	
	11.7 μ	12.3 μ	11.7 μ	12.3 μ	11.7 μ	12.3 μ	11.7 μ	12.3 μ
IXb	39	37	36	37	33	34	37	37
IXa	60	57	56	54	62	58	51	54
Xb	44	38	47	39	49	44	46	39
Xa	45	37	48	40	56	42	..	..

4-Phenylmercaptocamphane (XI).—4-Camphyllithium was prepared following the procedure described by Winstein.[7] The 4-camphyllithium reagent in cyclohexane was filtered through the sintered glass funnel directly into a solution of cyclohexane containing 10 g. (7.2 g., 0.067 mole required) of phenyl disulfide. As the lithium reagent was added, the reaction mixture turned milky white, but very little heat was evolved. After the addition was complete, the mixture was heated under reflux for 2 to 3 hours. The reaction mixture was then cooled and added slowly to a solution of 5 g. of lithium aluminum hydride in ethyl ether to reduce the excess phenyl disulfide to thiophenol. After the reduction was complete, the excess hydride was destroyed with ethyl acetate, and the solution was poured slowly into excess 6 *N* sulfuric acid solution containing much chopped ice. After separation of the organic layer, the water layer was extracted twice with cyclohexane. The combined organic layers were then extracted five times with equal volumes of 5% sodium hydroxide solution, washed with water, and dried over anhydrous potassium carbonate. The solvent was removed at atmospheric pressure through a column, and the residue was heated gently in a subliming tube under reduced pressure (15 mm.). Unreacted 4-chlorocamphane, 2.75 g. (24% recovery), sublimed onto the walls of the tube and was carefully removed. The yellow residual oil was then distilled under reduced pressure. On redistillation, 10.2 g. (62%) of 4-phenylmercaptocamphane was obtained as a colorless oil, which could not be induced to crystallize, b.p. 119–121° (0.1 mm.), $n^{25}D$ 1.5557.

Anal. Calcd. for $C_{16}H_{22}S$: C, 78.00; H, 9.00. Found: C, 78.36; H, 8.90.

4-Benzenesulfonylcamphane (XII).—4-Phenylmercaptocamphane (1.7 g., 0.0069 mole) was treated with excess perbenzoic acid in the usual way; the reaction mixture was allowed to stand overnight at room temperature. After extraction of the benzoic acid and evaporation of the solvent under a current of air, the crude solid was recrystallized from benzene–petroleum ether, yielding 1.0 g. (52%) of long, white needles, m.p. 144–144.5°, which did not sublime.

Anal. Calcd. for $C_{16}H_{22}O_2S$: C, 69.05; H, 7.97. Found: C, 69.39; H, 7.80.

Desulfurization of 4-Phenylmercaptocamphane.—To a solution of 1.5 g. (0.0061 mole) of 4-phenylmercaptocamphane in 50 ml. of absolute ethanol was added 12 g. of Raney nickel. The mixture was refluxed with stirring for 20 hours, after which the solution was filtered (Filter-Cel), and the nickel cake rinsed twice with boiling absolute ethanol. The solution was transferred to a 500-ml. erlenmeyer flask (more than twice the required volume to contain the solution), 150 ml. of water was added, and the flask stoppered tightly and placed in the refrigerator. The small clumps of crystals which sublimed spontaneously onto the neck of the flask were scraped out on several occasions and resublimed. This procedure provided 0.45 g. (53%) of camphane, m.p. 153–154° (sealed tube), compared by mixed melting point with authentic camphane, 152–154° (sealed tube).

Desulfurization of 4-Benzenesulfonylcamphane.—To a solution of 0.4 g. (0.00143 mole) of 4-benzenesulfonylcamphane in 40 ml. of absolute ethanol was added 10 g. of Raney nickel. The mixture was refluxed with stirring for 17 hours. The reaction mixture was worked up in a manner identical with that used for the preceding desulfurization. Frequent removal of the crystals which sublimed onto the neck of the flask resulted, on resublimation, in collection of 0.12 g. (61%) of a white solid, m.p. 155° (sealed tube), which melted at 153–155° (sealed tube) when mixed with an equal portion of authentic camphane. The infrared spectra of this desulfurization product and authentic camphane, each dissolved in chloroform, were identical in every respect.

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[CONTRIBUTION FROM THE SUBDEPARTMENT OF SYNTHETIC CHEMISTRY IN RELATION TO MEDICAL RESEARCH, BANTING AND BEST DEPARTMENT OF MEDICAL RESEARCH, UNIVERSITY OF TORONTO]

Synthesis of L-α-Glycerylphosphoryl-L-serine[1]

BY ERICH BAER, DMYTRO BUCHNEA AND HARVEY C. STANCER

RECEIVED OCTOBER 23, 1958

L-α-Glycerylphosphoryl-L-serine is obtained by phosphorylation of D-acetone glycerol with phenylphosphoryl dichloride and quinoline, esterification of the resulting acetone L-α-glycerylphenylphosphoryl chloride with N-carbobenzoxy-L-serine benzyl ester in the presence of pyridine, and removal of the protective groups by two catalytic hydrogenolyses, and acid hydrolysis. The infrared spectra of L-α-glycerylphosphoryl-L-serine, L-α-glycerylphosphorylethanolamine and L-α-glycerylphosphorylcholine, the structural bases of the majority of the glycerolphosphatides, are reported.

Glycerylphosphorylcholine (GPC), glycerylphosphorylethanolamine (GPE) and glycerylphosphorylserine (GPS) occur widely in bound form in nature as moieties of lecithins, cephalins, plasmalogens and phosphatidylserines. GPC[2–8,11] and GPE[3,5,9–11] have been found to occur in biological materials in free form. Evidence for the occurrence of free GPS may be forthcoming soon. Whether the choline, ethanolamine and serine esters of L-α-glycerolyphosphoric acid are intermediates in the biological synthesis or in the degradation of glycerolphosphatides, or in both, has not yet been established with certainty. Evidence obtained by Dawson[11] appears to indicate that

(1) The synthesis of L-α-glycerylphosphoryl-L-serine was described in a thesis submitted in 1955 by Harvey C. Stancer to the Department of Pathological Chemistry of the University of Toronto, Canada, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. The present report incorporates improvements in the procedure introduced by Dr. Dmytro Buchnea.

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