stants of *trans*-1,4-cyclohexanecarboxylic acid, the method described by Speakman was employed.[42]

Apparent Constants in Ethanol–Water Solvent (50% by Volume).—Fifty ml. of 0.10 molar solutions of the 4-X-cyclohexanecarboxylic acids was titrated to the half-point of neutralization. Readings were taken at the half-neutralization point on the *p*H scale of a Beckman model G *p*H meter calibrated against aqueous buffer solutions using glass and saturated potassium chloride–calomel electrodes. The pK_a's were calculated assuming unit activities and *p*H meter readings equal to the logarithm of the reciprocal of the hydrogen ion concentration.[9] The results of the above measurements are shown in Table I.

Alkaline Hydrolysis of *trans*-Methyl 4-X-Cyclohexanecarboxylates in Methanol–Water Solvent (50% by Weight).—The pure ester was dissolved in the methanol–water mixed solvent (50% by weight) to make 250 ml. of about 0.1 molar solutions. Sodium hydroxide solutions of equivalent strength were prepared in each case. Fifty-ml. portions of the base and ester were placed in a thermostat until the desired temperature was achieved. The reaction was started by pouring the ester solution rapidly into the sodium hydroxide solution and shaking thoroughly and the time of mixing recorded.

Five-milliliter samples were withdrawn and titrated after about 3 minutes and at regular intervals until the reaction was completed. The sample was discharged as rapidly as possible into a known excess of 0.02703 *N* hydrochloric acid. The solution was titrated with standard sodium hydroxide using precautions to exclude carbon dioxide.

The concentration of sodium hydroxide at the beginning of the experiment was calculated from the original solutions and the volume of the mixture. All concentrations are expressed in moles per liter. The value of the specific reaction rate constant (k) was determined by finding the slope of the best straight line passing through the points obtained from plotting $1/c$ *vs.* t. The method of least squares was used to obtain the best slope from these points. The results for the hydrolysis of the methyl esters at these temperatures are shown in Table III.

To obtain the hydrolysis constants of *trans*-methyl 4-carbomethoxycyclohexanecarboxylate, the procedure described by Frost and Schwemer was employed.[43] For this purpose, the hydrolysis was performed in a solution 0.200 molar in potassium chloride (in 50% by weight aqueous methanol) to swamp any effects due to changes in ionic strength as the diacid anion was produced. Although the salt is thought to have little effect upon the hydrolysis constant of the first ester group, it affects the second constant appreciably. Consequently, the constant for the hydrolysis of the salt of the monoester was corrected to zero ionic strength by use of the equation[44]

$$\log k = \log k_0 + 2Z_AZ_B\alpha\sqrt{\mu}$$

The constant α (0.82) was evaluated for 25° from universal constants and a value of 56.28 for the dielectric constant of the mixed solvent.[45]

The correction ($\Delta pk = 0.33$) yields the value of 1.55×10^{-3} for k_0, the hydrolysis constant for the ester anion at zero ionic strength. Although this extrapolation is rather large, it is not unreasonable. The use of the above equation for extrapolation is probably justified because of the rather highly aqueous nature of the reaction medium. A more detailed study of salt effects would be required for an accurate extrapolation.[46,47] Fuller details of the measurements and calculations are recorded in reference 1.

Reactivity of the 4-X-Cyclohexanecarboxylic Acids toward Diphenyldiazomethane.—The rates of reaction of the acids with diphenyldiazomethane were measured spectrophotometrically at 24.91 ± 0.05° following the procedure reported by Roberts, McElhill and Armstrong.[48]

Acknowledgments.—This work was generously supported, initially by a grant from the Research Corporation and subsequently by the National Science Foundation (Research Grant NSF-G-1440). The authors are grateful for this assistance.

We wish to thank, also, Professor Donald Noyce for providing information on the preparation of *trans*-4-chloro- and 4-methoxycyclohexanecarboxylic acids prior to publication.

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[42] J. C. Speakman, *J. Chem. Soc.*, 855 (1940).

[43] A. A. Frost and W. C. Schwemer, THIS JOURNAL, **74**, 1268 (1952).

[44] S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 427.

[45] P. S. Albright and L. J. Gosting, THIS JOURNAL, **68**, 1061 (1946).

[46] R. L. Burnett and L. P. Hammett, *ibid.*, **80**, 2415 (1958).

[47] F. H. Westheimer, W. A. Jones and R. A. Lad, *J. Chem. Phys.*, **10**, 478 (1942), and ref. 36.

[48] J. D. Roberts, E. A. McElhill and R. Armstrong, THIS JOURNAL, **71**, 2923 (1949).

FAYETTEVILLE, ARK.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY]

The Relative Stabilities of *cis* and *trans* Isomers. VII. The Hydrindanes[1,2]

BY NORMAN L. ALLINGER AND JAMES L. COKE

RECEIVED SEPTEMBER 3, 1959

The equilibrium constant for the reaction *cis*-hydrindane ⇄ *trans*-hydrindane has been measured in the liquid phase over the temperature range 466–638°K. From the data the thermodynamic quantities for the isomerization under these conditions were calculated to be: ΔH^{552} −1070 ± 90 cal./mole; ΔS^{552} −2.30 ± 0.10 e.u. The applicability of the method to the determination of the thermodynamic constants for such a reaction on a small scale has been established.

Introduction

Knowledge concerning the relative stabilities of *cis* and *trans* isomers of fused ring compounds is of general interest and is especially important in natural product work where stereochemistry is often assigned by analogy with related simpler systems. A previous paper described the determination of the thermodynamic quantities for the *cis–trans* isomerization of the fundamental decalin system, and discussed the usefulness of such data.

The relative "stability"[3] of the *cis* and *trans* isomers in various hydrindane systems is affected by many variables and cannot be summarized in any simple way. This complexity, relative to the decalins, results in part from the fact that the parent hydrindanes are of nearly equal stability, and minor structural changes can have appreciable effects.

The pertinent thermodynamic data available

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[1] This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund.

[2] Paper VI, THIS JOURNAL, **81**, 4080 (1959).

[3] "Stability" is always used in this paper in reference to free energy and not to enthalpy.

for the hydrindanes themselves are limited to heats of combustion.[4-6] The best value for the enthalpy of the reaction *cis*-hydrindane $\rightleftarrows$ *trans*-hydrindane is -0.74 ± 0.52 kcal./mole (unspecified state and temperature).[5,7] *trans*-2-Hydrindanone has a lower heat of combustion than does the *cis* isomer,[4] while the *cis* form of 1-hydrindanone predominates over the *trans* at equilibrium.[8] Reasons which have been advanced as responsible for these apparent inconsistencies include the 2-alkyl ketone effect,[9] and the effect of entropy.[10] It seems likely that both of these effects are important in the present cases. When the 8-methylhydrindane systems are considered, the generalization can be made that *cis* isomers are more stable, and this is usually true both in simple bicyclic systems and in more complicated fused systems, such as the C/D rings in steroids and the nor-A/B rings in steroids and triterpenes. The effect of the methyl is qualitatively similar to that of the corresponding group in 9-methyldecalin.[11] There are exceptions to the generalization, however.[12]

All this has led to the statement that in the hydrindane series an angular methyl has no effect on the relative stabilities of *cis* and *trans* isomers[13] and to the general belief that *cis*-hydrindanes are more stable than the corresponding *trans* isomers.[12] This confusion has been discussed[10] and appears to be due in part to the fact that a differentiation between free energies and heat contents has usually not been made in the past.[14] It is shown in the present work that above 466°K. *cis*-hydrindane is more stable than *trans*-hydrindane and predominates at equilibrium, but below this temperature the *trans* form is more stable. This is due to the fact that *cis*-hydrindane has a greater entropy than the *trans* isomer and at a sufficiently high temperature the entropy becomes the controlling factor.

The objectives of the present work were first to refine the experimental method used for determining the thermodynamic constants of the decalins[2] and then to determine the thermodynamic quantities for the reaction *cis*-hydrindane $\rightleftarrows$ *trans*-hydrindane.

Results

In the present work equilibrium between *cis*- and *trans*-hydrindane was established by heating samples of hydrindane with a palladium-on-carbon catalyst in sealed tubes until equilibrium was reached. Equilibrium was brought about by the dehydrogenation–hydrogenation action of the catalyst. At each of the several temperatures studied a number of samples of hydrindane were equilibrated at the same time. That equilibrium was attained was shown by the fact that the same mixture was obtained from both isomers. The temperature range covered in the investigation was from 466 to 638°K.

Some simplifications in the experimental procedure were introduced in the light of earlier experience. The method was successfully adapted to a much smaller scale so as to be more generally useful for compounds which are not readily available in large quantity. The volume of the liquid phase was made large relative to the volume of the gas phase. The amount of material in the gas phase was therefore completely negligible over the temperature range used, and the difference in the equilibrium composition in the gas and liquid phases resulting from a difference in vapor pressure of the two isomers did not have to be taken into account. Again this simplification is most important for less well known compounds for which no vapor pressure data are available. A summary of the data is given in Table I.

TABLE I

EQUILIBRATION DATA FOR *cis*-HYDRINDANE $\rightleftarrows$ *trans*-HYDRINDANE

t, °K.	% *cis* (liq.)	*t*, °K.	% *cis* (liq.)
466	50.15	550	54.45
492	51.42	606	56.55
517	52.75	638	57.84

A plot of ln K against $1/T$ was made and a line was fitted to the points by the method of least squares. The thermodynamic quantities were determined from the intercept at $1/T = 0$ which gave $\Delta S/R$ and from the slope which gave $-\Delta H/R$. The values obtained were ΔS^{552} -2.30 ± 0.1 e.u. and ΔH^{552} -1070 ± 90 cal./mole. The agreement of ΔH with the previously reported[6] value of -740 ± 520 cal./mole is good.

Discussion

Conformational analysis also furnishes an explanation as to why the difference in heat content between the *cis*- and *trans*-hydrindanes is smaller than the corresponding difference between *cis*- and *trans*-decalin. In the case of the decalins either isomer can exist in a strainless conformation with all the bond angles normal, and the enthalpy difference can be accounted for as being due exclusively to *gauche* butane interactions. These considerations apply qualitatively to the hydrindanes, but in addition the six-membered ring in a hydrindane is in a deformed chair conformation.[15]

The five-membered ring is more nearly planar than a six-membered ring, and therefore in *cis*-hydrindane an axial bond and an equatorial bond of the adjacent ring juncture atoms in the six-membered ring must be twisted toward one another. With *trans*-hydrindane, the corresponding twist involves two equatorial bonds. It is generally

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[4] (a) W. Hückel, *Ann.*, **533**, 1 (1937); W. Hückel, M. Sachs, J. Yantschulewitsch and F. Nerdel, *ibid.*, **518**, 155 (1935).

[5] W. G. Dauben and K. S. Pitzer in "Steric Effects in Organic Chemistry," edited by M. S. Newman, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 37, footnote 58.

[6] The authors are indebted to Dr. S. S. Todd and Dr. D. W. Scott for informing them prior to publication of work done on the entropies of the hydrindanes at the U. S. Bureau of Mines.

[7] Throughout this paper the signs of the thermodynamic quantities are those for the isomerization in the direction *cis*-hydrindane, *trans*-hydrindane and all numerical values refer to the liquid phase at the temperature stated.

[8] R. P. Linstead, *Ann. Rep. Chem. Soc.* (*London*), 305 (1935).

[9] W. Klyne, *Experientia*, **12**, 119 (1956).

[10] N. L. Allinger, *J. Org. Chem.*, **21**, 915 (1956).

[11] R. B. Turner, THIS JOURNAL, **74**, 2118 (1952).

[12] See the discussion by A. S. Dreiding, *Chemistry & Industry*, 992 (1954).

[13] W. E. Bachmann, A. Ross, A. S. Dreiding and P. A. S. Smith, *J. Org. Chem.*, **19**, 222 (1954).

[14] See also the discussion by R. M. Gascoigne, *J. Chem. Soc.*, 876 (1958).

[15] E. L. Eliel and C. Pillar, THIS JOURNAL, **77**, 3600 (1955).

conceded that the latter process involves more energy,[16] and the best evidence for this conclusion now comes from the present study on the hydrindanes. Other evidence, such as easy acetonide formation from *cis*- but not *trans*-1,2-cyclohexanediol, has supported a corresponding statement with regards to free energy, but since entropy changes were previously unknown, no definite statements could be made regarding energy or heat content.

Both *cis*- and *trans*-hydrindane exist as racemates, so the entropy of mixing is the same for both isomers. The *cis* isomer has a symmetry number of 1, but the *trans* isomer may have a symmetry number of 1 or 2, depending on whether and how the five-membered ring is puckered.[17]

In the former case the entropy of isomerization would be predicted to be zero, and in the latter case, −1.4 e.u. The observed entropy difference is found to have neither of these values. The entropy of the *cis* isomer is found to be larger than that of the *trans* by 2.3 e.u. This relatively large value may be due to the fact that the five-membered ring is more stretched, and probably more nearly flat in the *trans* isomer than in the *cis*. Presumably, therefore, the *cis* isomer can show a larger partial psuedo-rotation in the five-membered ring analogous to that found in cyclopentane,[18] and this extra freedom would lead to an increased entropy for that isomer.

The seemingly anomalous case of the 1-hydrindanone can be understood from the increase in the heat content of the *trans* form over that found in the hydrocarbon which is expected to result from the 2-alkyl ketone effect.

It has been shown that for a number of hydrindanes containing an angular methyl group the *trans* isomer has the greater free energy.[19,20] The effect of the angular methyl here must be much like that of the methyl in 9-methyldecalin.[11] In the latter case the number of *gauche* butane interactions is one greater for the *cis* isomer than for the *trans*, and the two isomers are predicted to have rather similar energies. The available experimental data[21] are consistent with this conclusion. With the hydrindane system the *cis* isomer has a free energy approximately the same as that of the *trans* even without the angular methyl, and presumably the effect of the methyl is to raise the free energy of the *trans* still higher.

The stabilities of steroidal hydrindane systems are more complicated, and cases must be examined individually. Such studies will be reported in subsequent papers.

Experimental

Indane.—Commercial indene was reduced to indane in 255-ml. portions using 1 g. of platinum oxide in a 500-cc. Parr hydrogenator at a hydrogen pressure of from 30–50 p.s.i. at room temperature. One equivalent of hydrogen was taken up and the product was isolated and distilled.

Hydrindane.—Indane was reduced to hydrindane in 150-ml. batches using 3 teaspoons of freshly prepared W-2 Raney nickel in absolute ethanol. The reduction was carried out in a 260-cc. Magna Dash bomb at a hydrogen pressure of from 700–1550 p.s.i. at 160° over a 12-hour period. Three equivalents of hydrogen was taken up. The crude material was fractionally distilled at atmospheric pressure using a 4-foot helix-packed column. The material which boiled at 159.5–167°, $n^{25}\mathrm{D}$ 1.4615–1.4702, was used for equilibration.

Pure *cis*-Hydrindane.—The fractions from the distillation of hydrindane which had a boiling point of 167° and $n^{25}\mathrm{D}$ 1.4700–1.4702 were combined and redistilled using a 4-foot helix-packed column. The *cis* isomer was shown to be pure by gas phase analysis and had b.p. 166.5° (746 mm.), $n^{25}\mathrm{D}$ 1.4700. The reported[4] constants are b.p. 166° (760 mm.), $n^{20}\mathrm{D}$ 1.4713, n^{20}_{He} 1.4713.

Pure *trans*-Hydrindane.—The fractions from the distillation of hydrindane which had a boiling point of 159.5–163° and $n^{25}\mathrm{D}$ 1.4615–1.4636 were combined and redistilled using a 4-foot helix-packed column. The *trans* isomer was shown to be pure by gas phase analysis and had b.p. 160° (741 mm.), $n^{25}\mathrm{D}$ 1.4616. The reported[4] constants are b.p. 159° (760 mm.), n^{20}_{He} 1.4639.

Equilibration.—The equilibrations were carried out using four 0.5-ml. samples of hydrindane at each temperature. One sample was pure *cis*, one pure *trans* and two were a mixture of *cis*- and *trans*-hydrindane. The samples were placed in ampoules of 7-mm. Pyrex tubing along with 100 mg. of 10% palladium-on-charcoal. The total volume of solid and liquid material in the tubes was about two-thirds of the total volume of the tubes. The ampoules containing hydrindane and catalyst were then sealed and placed inside metal tubes which were placed in an electrically heated jacket. The temperature was maintained at the desired point for 3.5 hours at the highest temperature and 200 hours at the lowest temperature. At the end of the reaction time the metal tubes were removed from the heating jacket and plunged into an ice-bath. When the sealed tubes were cold they were opened, centrifuged, and the liquid was pipetted away from the catalyst and sealed in glass ampoules. The samples remained sealed in glass until analyzed. The temperature at each equilibration was measured by means of a Leeds and Northrup calibrated potentiometer using an iron–constantan thermocouple inserted in one of the metal tubes. The temperature fluctuated over about a 3° temperture range quite rapidly, completing a cycle in 6 minutes, due to the heater turning off and on. Since this fluctuation was quite rapid compared to the time required to reach equilibrium, the average temperature of the cycle was used as the reaction temperature. This temperature was constant within the experimental error of the potentiometer.

Analysis.—The analysis of each sample was carried out by gas chromatography. The column used was nine feet long and was made of one-eighth inch copper tubing. The column was packed with a mixture of 21.5 g. of the tris-β-cyanoethylation product of glycerine and 26 g. of 60–90 mesh firebrick. The analyses were carried out at 100° and a helium flow rate of 15 ml./min. The retention times of *cis*- and *trans*-hydrindane were 26 min. and 19 min., respectively. The separation was complete. The ratio of isomers in the mixture was taken as equal to the ratio of the products of the band height and the half-band width as determined graphically. Each time samples were run a standard sample of hydrindane was run which was known to contain 51.43% by weight of the *cis* isomer. This standard sample gave 51.61, 51.31, 51.25, 51.21% *cis* isomer. The deviation of the average of these from the known value is only 0.08%. This is within the experimental error so no correction factor was applied. Each equilibrated sample was analyzed at least twice and the average deviation of percentages of each isomer for all duplicate analyses was ±0.10%.

The values of ΔH and ΔS for the reaction *cis*-hydrindane $\rightleftarrows$ *trans*-hydrindane were determined from the slope and the intercept of a line drawn by the method of least squares through points obtained from a plot of $\ln K$ against $1/T$. The values along with estimated probable errors are ΔH^{552} -1070 ± 90 cal./mole and ΔS^{552} -2.30 ± 0.10 e.u.

The effect of pressure on the isomerization could not be calculated, since the pressure was not known, but was probably negligible.[2]

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[16] Reference 5, p. 37.

[17] J. E. Kilpatrick, K. S. Pitzer and R. Spitzer, This Journal, **80**, 6697 (1958); **69**, 2483 (1947).

[18] J. P. McCullough, *J. Chem. Phys.*, **29**, 966 (1958).

[19] K. Dimroth and H. Jonsson, *Ber.*, **74**, 520 (1941).

[20] W. E. Bachmann and A. S. Dreiding, This Journal, **72**, 1323 (1950).

[21] (a) A. Ross, P. A. S. Smith and A. S. Dreiding, *J. Org. Chem.*, **20**, 905 (1955); (b) F. Sondheimer and D. Rosenthal, This Journal, **80**, 3995 (1958).

It was shown that no correction was needed for material in the gas phase during equilibration by equilibrating one sample with seven times as much free space as the other samples. The composition of this sample was identical with the others equilibrated at the same temperature. It was also shown that the method could be adapted to a smaller scale by equilibrating a sample of pure *cis*- and a sample of pure *trans*-hydrindane using 0.10 ml. of hydrindane and 20 mg. of 10% palladium-on-charcoal in 4-mm. Pyrex tubing. The results of these small scale runs were identical with those on a larger scale at the same temperature.

DETROIT 2, MICH.

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

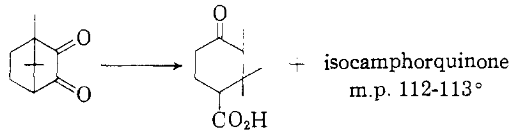
The Structure of Isocamphorquinone

BY SAMUEL G. LEVINE[1,2]

RECEIVED SEPTEMBER 26, 1959

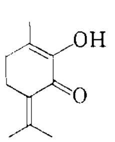
Isocamphorquinone has been shown to have the structure V.

Isocamphorquinone was first described by Manasse and Samuel[3] as an easily resinified product, $C_{10}H_{14}O_2$, resulting from the action of a cold fuming sulfuric acid mixture on camphorquinone (I). Also produced in this reaction was a keto-carboxylic acid, $C_{10}H_{16}O_3$, which has since been clearly identified[4] as 2,2,3-trimethyl-4-keto-cyclohexanecarboxylic acid (II).

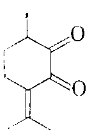


I II

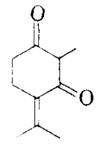
Isocamphorquinone was found[5] to yield a urethan and a benzoate as well as an oxime and a phenylhydrazone—the derivatives, in each case, resulting from condensation with a single equivalent of reagent. In addition, the compound could be titrated as a mono-acid and gave various positive tests indicating olefinic, enolic and reducing properties. Based on these and certain other experiments (*vide infra*), Manasse and Samuel[5] assigned the dienolone structure III to isocamphorquinone[6]; the corresponding diketo modification IV was proposed by Bredt[7] during the same period. In the present communication it is shown that isocamphorquinone is in fact a tautomer of 2-methyl-6-isoproylidenecyclohexane-1,3-dione (V).



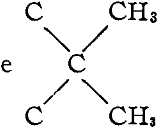
III

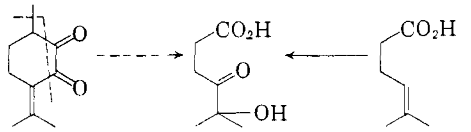


IV



V

The early ascription of a monocyclic carbon skeleton to isocamphorquinone resulted from its ease of oxidation by cold, dilute permanganate solution. The main product of this reaction was a keto-acid, m.p. 97–98° (semicarbazone, m.p. 199–200°), formulated by Bredt as 5-hydroxy-5-methyl-4-ketohexanoic acid (VI). Although this assignment originally rested only on the simultaneous isolation of succinic acid and acetone as "further decomposition products," its correctness has been shown by later work. Thus, Staudinger and co-workers[8] have prepared 5-methyl-Δ^4-hexenoic acid (VII) which, on permanganate oxidation, produced acetone, succinic acid and a hydroxyketo-acid $C_7H_{12}O_4$, m.p. 97° (semicarbazone, m.p. 198–200°), in close agreement with Bredt's data. The above experiment led, then, to the suggestion[7a] that the dimethylcarbinyl bridge of camphorquinone is broken in isocamphorquinone for, were it still present, the stable  $\begin{matrix} C & & CH_3 \\ & C & \\ C & & CH_3 \end{matrix}$ moiety should have been found intact in the permanganate oxidation product. That this grouping is here the precursor of an isopropylidene function (as in III or IV) was early inferred from the production of acetone, in high



III VI VII

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[1] U. S. Public Health Service pre-doctoral fellow 1952–1953. Present address: Eastern Regional Research Laboratory, U. S. Department of Agriculture, Philadelphia 18, Pa.

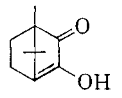
[2] Abstracted from the Ph.D. Thesis of Samuel G. Levine, Harvard University, December, 1953. The author is happy to acknowledge with thanks the guidance of Professor R. B. Woodward during the course of this research.

[3] (a) O. Manasse and E. Samuel, *Ber.*, **30**, 3157 (1897); (b) **31**, 3258 (1898).

[4] R. N. Chakravarti, *J. Chem. Soc.*, 1565 (1947).

[5] O. Manasse and E. Samuel, *Ber.*, **35**, 3829 (1902).

[6] It may be of interest that the first structure assigned (ref. 3b) by these authors was i, the hypothetical enolic form of isocamphorquinone.



i

Their later rejection (ref. 5) of this prohibitively strained structure was due to the failure of isocamphorquinone to yield camphor glycol on reduction.

[7] (a) J. Bredt, F. Rochussen and J. Monheim, *Ann.*, **314**, 389 (1901). (b) Isocamphorquinone is represented as Bredt's structure (IV) in J. L. Simonsen, "The Terpenes," Vol. II, Cambridge University Press, Cambridge, 1939, p. 469, and in E. H. Rodd, "The Chemistry of Carbon Compounds," Vol. II, part B, Elsevier Publishing Co., New York, N. Y., 1953, p. 613.

[8] H. Staudinger, W. Kreis and W. Schilt, *Helv. Chim. Acta*, **5**, 743 (1922).