

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

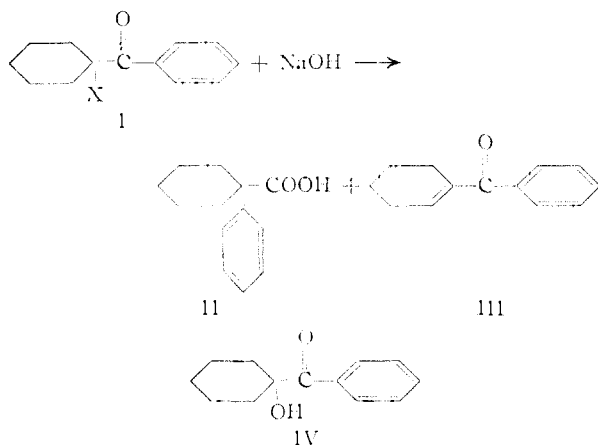
The Formation of 1-Phenylcyclohexanecarboxylic Acid from α -Halocyclohexyl Phenyl Ketones

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RECEIVED JANUARY 7, 1952

A study of the conditions necessary for the rearrangement of α -halocyclohexyl phenyl ketone (I) to 1-phenylcyclohexanecarboxylic acid (II) is reported. Reaction of the α -haloketone (I) with a strong base such as hydroxide ion in a homogeneous medium is rapid with the formation of α -hydroxycyclohexyl phenyl ketone (IV) and *no* acid (II) by rearrangement. In an inert solvent the heterogeneous reaction of the α -haloketone (I) with sodium hydroxide is slow and produced the α -hydroxyketone (IV) with some rearranged acid (II). The yield of the acid depends upon the solvent and temperature of the reaction. Conditions are reported for the formation of the acid (II) in useful yield (53%). A solution of the α -haloketone (I) in a water-dioxane mixture that contained *no* strong base slowly liberated halide ion to give the rearranged acid (II). The α -haloketone (I) with silver nitrate in an ethanol-water solution also gave rearrangement.

In 1939 Tchoubar and Sackur² reported that α -chlorocyclohexyl phenyl ketone (I, X is Cl) gave a 30 to 40% yield of 1-phenylcyclohexanecarboxylic acid (II) when allowed to react for 12 hours in ether with powdered sodium hydroxide. The remainder of the reaction mixture was reported to be 1-cyclohexenyl phenyl ketone (III). The forma-



tion of the acid, which could not proceed by a cyclopropanone type intermediate³ or an intermediate formed by enolization of the ketone was considered to proceed by a semipinacolic type rearrangement.

Since the haloketone (I) was found to react rapidly with alcoholic sodium methoxide with the exclusive formation of the epoxyether⁴ and *no* rearranged acid derivative, an investigation of the rearrangement of the haloketone was undertaken to determine the conditions necessary for rearrangement. The results indicate that sodium hydroxide will react rapidly with the haloketone (I) in a homogeneous reaction medium to give the α -hydroxyketone (IV) and *no* rearrangement products. The haloketone will react slowly with sodium hydroxide in a heterogeneous reaction mixture to give the hydroxyketone (IV) and some 1-phenylcyclohexanecarboxylic acid (II), the yield of which depends upon the solvent and the temperature. Further, in a refluxing water-dioxane solu-

tion containing *no* strong base the α -haloketone slowly liberated halide ion to yield the rearranged acid (II) and 1-cyclohexenyl phenyl ketone (III). In an ethanol-water solution silver nitrate also caused rearrangement with the formation of an acid derivative. From this latter reaction 1-cyclohexenyl phenyl ketone (III) also could be isolated.

α -Chlorocyclohexyl phenyl ketone (I, X is Cl), in which the position of the chlorine atom was shown by rapid formation of the epoxyether,³ was treated with sodium hydroxide in ether, the directions of Tchoubar² being followed as closely as possible. The yield of 1-phenylcyclohexanecarboxylic acid (II) in each of seven experiments was 6-9% in contrast to the 30-40% recorded by Tchoubar. The neutral fraction, which gave a semicarbazone melting at 212° in agreement with Tchoubar, later crystallized, and proved to be an 83% yield of α -hydroxycyclohexyl phenyl ketone (IV). The structure of IV previously had been proven in this Laboratory⁴ by independent synthesis and the melting points of mixtures of the known ketone with IV as well as the respective semicarbazones were not depressed. Since Tchoubar² reported the neutral fraction as 1-cyclohexenyl phenyl ketone (III) this ketone was prepared independently.⁵ III gave a semicarbazone melting at 212° but depressed the melting point of the semicarbazone derivative of the neutral fraction of the reaction described above.

When the α -chloroketone was allowed to react with finely divided sodium hydroxide in refluxing toluene, a 51% yield of rearranged acid (II) could be isolated along with 39% of hydroxyketone. Under the same conditions the bromoketone gave 34% of acid and 54% of ketone.

Using refluxing xylene in the above experiments gave 53% II and 25% IV from the α -chloroketone. From the α -bromoketone a 39% yield of II and 36% of IV was obtained.

The α -hydroxycyclohexyl phenyl ketone (IV) was shown not to be the precursor of the rearranged acid (II) since under the conditions of the reaction, IV gave *no* rearrangement.

In a homogeneous dioxane-water reaction mixture the haloketone (I) reacted rapidly with sodium hydroxide to yield 82% of α -hydroxyketone (IV) and *no* acid of rearranged carbon skeleton. A small amount of benzoic acid was isolated but this

(1) Presented at the Organic Division of the 118th Meeting of the American Chemical Society, Sept., 1950. Supported in part by the Ethyl Corporation, Detroit, Michigan.

(2) B. Tchoubar and O. Sackur, *Compt. rend.*, **208**, 1020 (1939).

(3) R. B. Loftfield, *This Journal*, **73**, 4707 (1951).

(4) C. L. Stevens and E. Farkas, *ibid.*, **74**, 618 (1952).

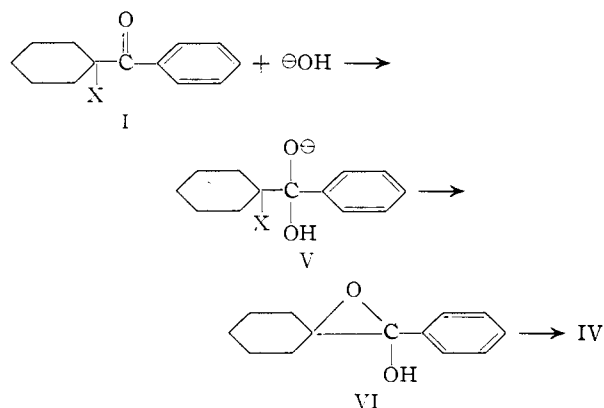
(5) R. E. Christ and R. C. Finson, *ibid.*, **59**, 893 (1937).

acid was shown to arise from the cleavage of the hydroxyketone (IV) by the base.

The haloketone (I) when dissolved in a water-dioxane mixture and heated to reflux slowly liberated halide ion and after 11% of the halide ion had formed 2.2% of 1-phenylcyclohexanecarboxylic acid could be obtained. From the neutral fraction 76% of starting haloketone was recovered. When the original solution was heated until 75% of halide ion had been liberated, a 7.8% yield of 1-phenylcyclohexanecarboxylic acid was obtained. From the neutral fraction in this experiment 1-cyclohexenyl phenyl ketone could be identified and titration of an aliquot with bromine indicated 60% of unsaturated compound had formed. An experiment in which the reaction was subject to the isolation procedure immediately showed that the sodium bicarbonate extraction reagent did not cause the formation of the rearranged acid or the unsaturated ketone.

After the α -haloketone was allowed to react with silver nitrate in a refluxing ethanol-water mixture, an 18% yield of acid (II) could be isolated from saponification of the non-ketonic neutral product. From the ketonic fraction 1-cyclohexenyl phenyl ketone could be isolated and titration of an aliquot of this fraction with bromine indicated 68% of unsaturated compound.

The rapid formation of the hydroxyketone in the homogeneous reaction of sodium hydroxide with haloketone (I) undoubtedly proceeded by attack of the hydroxide ion on the carbonyl group with the elimination of halide ion to form the internal hemiacetal (VI) which immediately forms the stable hydroxyketone (IV). An infrared spectrum of IV in



carbon disulfide (Fig. 1) indicates a carbonyl group as well as a hydroxyl group.

This formation of the hydroxyketone (IV) is analogous to the exclusive rapid formation of the stable epoxyether (VII) when the haloketone (I) is treated with sodium methoxide in homogeneous solution. These results are in accord with the evidence presented by Lane⁶ which indicated that in the example studied of a pinacolic type displacement of a halogen, the order of participation of neighboring groups was $\text{C}\beta\text{-O}^- \gg \text{C}\beta\text{-C}_6\text{H}_5 > \text{C}\beta\text{-OH}$. Structure V is unique in that all of these groups are on one carbon atom.

The formation of the acid in hydroxylic media

(6) J. F. Lane and D. R. Walters, *THIS JOURNAL*, **73**, 4238 (1951).

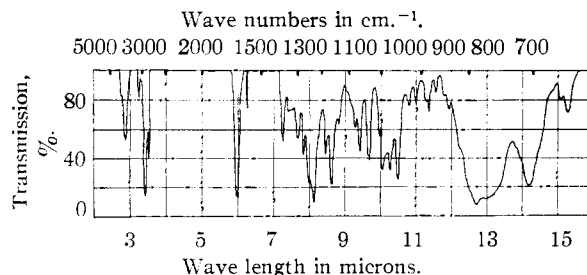
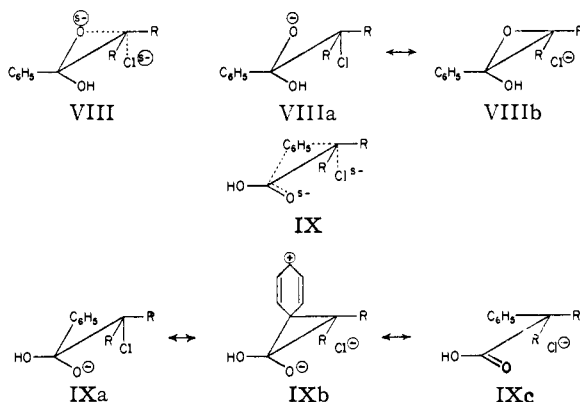


Fig. 1.—Infrared absorption spectrum of α -hydroxycyclohexenyl phenyl ketone (IV) in carbon disulfide (compensated).

alone or in the presence of AgNO_3 can be satisfactorily explained by a mechanism similar to the one of Cope and Graham⁷ which involves initial hemiacetal formation or hydration of the carbonyl group followed by a pinacol type rearrangement.

Present theory is not sufficient to explain the high yield (53%) of acid (II) from rearrangement in the reaction of solid sodium hydroxide with α -haloketone. The work of Curtin⁸ and associates has indicated that in a pinacol type rearrangement the migrating and departing groups and the two contiguous carbon atoms must be planar with the groups *trans*. The formation of hydroxyketone in a water-dioxane solution of sodium hydroxide and the rearrangement to acid with solid sodium hydroxide in toluene or xylene can be interpreted on the basis of differences in the transition states of the two reactions. According to this interpretation the following resonance forms are presumably important contributors to the transition states, one of which (VIII) leads to oxide formation and the other (IX) to rearranged acid. When reaction occurs in a good solvating solvent then VIII, which has an opti-



mum charge distribution, is the preferred transition state. If reaction occurs on a sodium hydroxide surface then the transition state is solvated almost entirely by a single sodium ion which should be as close as possible to the negative charge of the transition state. Under these conditions transition state IX becomes important and the product contains rearranged acid.

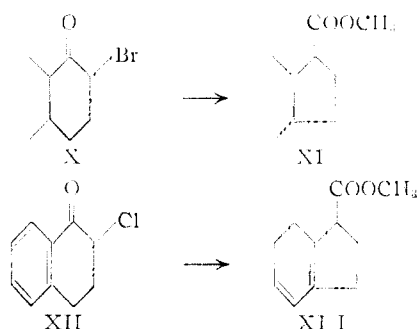
Other examples of rearrangements of α -haloketones to acids which cannot proceed through a cyclopropanone intermediate, *i.e.*, the 17b-bromo-D-homoandrostane-3(β)-ol-17-one acetate⁹ (X)

(7) A. C. Cope and E. S. Graham, *ibid.*, **73**, 4702 (1951).

(8) Curtin, *et al.*, *ibid.*, **72**, 961 (1950); **73**, 992, 3453 (1951).

(9) D. A. Prins and C. W. Shoppee, *J. Chem. Soc.*, 494 (1946).

which gave 3% of XI or the 2-chloro-1-tetralone (XII) which is reported¹⁶ to give XIII, may proceed in a manner similar to the conversion of I to II



although in these examples α -elimination of hydrogen halide followed by rearrangement is possible.

Experimental

Reaction of the α -Chlorocyclohexyl Phenyl Ketone with Sodium Hydroxide in Ether.—A mixture of 3.6 g. (90 millimoles) of sodium hydroxide pellets and 200 ml. of ether was stirred in a Morton¹¹ type Hi-Speed¹² stirring apparatus for 15 minutes, after which time the sodium hydroxide was finely divided. The mixture was then transferred to a 500-ml. flask equipped with a Hershberg¹³ type stirrer and 10 g. (45 millimoles) of chloroketone (I) added. After stirring for 48 hours, water was added and the ether layer separated. Evaporation of the ether layer gave a neutral oil. After standing several days the oil crystallized and proved to be 7.6 g. (83%) of α -hydroxycyclohexyl phenyl ketone (IV), m.p. 47–49°. This ketone was shown to be identical by mixture melting point determination with the ketone⁴ previously prepared. A semicarbazone of this ketone, m.p. 211–212°, proved to be identical with the semicarbazone of authentic IV.

The aqueous layer was acidified and the precipitated acid filtered and dried, m.p. 110–118°. The impurity could be extracted from this precipitated acid with boiling water and proved to be benzoic acid, m.p. 120–121°. The benzoic acid was proved by mixture melting point determination and amounted to about 20 mg. The hot water insoluble acid was recrystallized from low-boiling petroleum ether and proved to be 0.72 g. (8%) of 1-phenylcyclohexanecarboxylic acid,^{14,15} m.p. 123–124°.

Anal. Calcd. for C₁₃H₁₆O₂: C, 76.44; H, 8.08. Found: C, 76.32; H, 8.06.

An authentic sample of 1-phenylcyclohexanecarboxylic acid kindly supplied by Dr. F. H. Case¹⁵ had m.p. 123–124°. A melting point of a mixture was not depressed, m.p. 123–124°.

An amide¹⁶ prepared from a sample of both acids had m.p. 95–97°, and the melting point of a mixture was not depressed.

Six other experiments using from 3 to 20 g. of starting chloroketone and various sizes of sodium hydroxide pellets gave similar results.

α -Bromocyclohexyl phenyl ketone gave similar products. From 27 g. (0.1 mole) of bromoketone and 10 g. (0.25 mole) of sodium hydroxide, 1.2 g. (5.7%) of 1-phenylcyclohexanecarboxylic acid, m.p. 123–124°, and 16.2 g. (79%) of crystalline α -hydroxycyclohexyl phenyl ketone were obtained under conditions similar to those as described above.

Cyclohexenyl Phenyl Ketone (III).—This ketone was prepared in 33% yield, b.p. 128–134° (1 mm.); n_D^{25} 1.5430, from benzoyl chloride and cyclohexene in the presence of aluminum chloride according to the directions of Fison.⁵

(10) M. Mousseron and Nguyen Phuoc Du, *Compt. rend.*, **218**, 281 (1944).

(11) A. A. Morton and L. M. Redman, *Ind. Eng. Chem.*, **40**, 1190 (1948).

(12) From Secor Scientific Equipment Corp., 73 Pond St., Waltham 54, Massachusetts.

(13) E. B. Hershberg, *Ind. Eng. Chem., Anal. Ed.*, **8**, 313 (1936).

(14) M. Rubin and H. Wishinsky, *This Journal*, **68**, 828 (1946).

(15) F. H. Case, *ibid.*, **66**, 715 (1934).

The pure 1-cyclohexenyl phenyl ketone is a solid, m.p. 32–34°.

The semicarbazone of this ketone had a melting point of 209–211°.

Anal. Calcd. for C₁₁H₁₅ON₃: C, 69.11; H, 7.04. Found: C, 68.72; H, 7.49.

A mixture melting point of this semicarbazone with the semicarbazone from the neutral fraction of the reaction of α -chlorocyclohexyl phenyl ketone with sodium hydroxide in ether was greatly depressed, m.p. 180–190°.

Rearrangement of α -Haloketone in a Water-Dioxane Mixture.—A solution of 5.06 g. (0.019 mole) of α -bromocyclohexyl phenyl ketone in 150 ml. of dioxane and 80 ml. of water was heated at reflux. After 17 hours, titration of an aliquot indicated that 11% of bromide ion had been formed. Most of the excess solvent was removed under reduced pressure and the remaining mixture was extracted with four 50-ml. portions of ether. The ether solution was extracted with sodium carbonate solution and the latter upon acidification gave 88 mg. (2.2%) of 1-phenylcyclohexanecarboxylic acid, m.p. 121–122°. This isolation procedure, when carried out before reflux, gave no acid. The remaining ether solution was evaporated to dryness and the resulting material recrystallized from low boiling petroleum ether to give 3.97 g. (76%) of starting ketone, m.p. 50–51°.

It was necessary to heat the original reaction mixture for 65 hours to liberate 75% of halide ion. Following the procedure outlined above 0.31 g. (8%) of rearranged acid could be isolated. In this experiment the neutral fraction was dissolved in petroleum ether and after an aliquot had been withdrawn, the solution was cooled to give 0.2 g. of pure 1-cyclohexenyl phenyl ketone, m.p. 32–34°, mixture melting point 32–34°. Distillation of the remaining neutral fraction gave 1.2 g. of liquid, b.p. 95–100° (0.2 mm.), the infrared spectrum of which was virtually identical with that of 1-cyclohexenyl phenyl ketone. Titration of the aliquot of original neutral material with bromine indicated the presence of 60% of unsaturated compound.

Homogeneous Reaction of α -Haloketone with Sodium Hydroxide in a Water-Dioxane Mixture.—To a solution made by mixing 1.0 g. (25 millimoles) of sodium hydroxide, 40 ml. of dioxane and 25 ml. of water, was added 3.0 g. (13.6 millimoles) of α -chlorocyclohexyl phenyl ketone. After refluxing for one-half hour, the reaction was poured onto 150 g. of ice. This mixture was extracted four times with 50-ml. portions of ether. After evaporation of the combined ether layers, 2.3 g. (82%) of crude crystalline α -hydroxycyclohexyl phenyl ketone was obtained, m.p. 44–45°.

Titration of an aliquot of the water layer for chloride ion indicated 98% of the chloroketone had reacted. Acidification of the water layer gave no precipitate of acid, but through a continuous extraction of the acidic water layer with ether, 0.18 g. (11%) of benzoic acid was isolated, m.p. 120–121°.

To show that the hydroxyketone was the precursor of the benzoic acid, 3.0 g. (14.7 millimoles) of the hydroxyketone was allowed to react under the same conditions as described above. After 24 hours at the reflux temperature, 40 mg. (2.2%) of benzoic acid was isolated without the aid of a continuous extractor.

Rearrangement of α -Haloketone in Refluxing Toluene or Xylene in the Presence of Sodium Hydroxide.—A mixture of 3.6 g. (90 millimoles) of sodium hydroxide which had previously been finely ground with a Morton¹¹ type Hi-Speed Stirrer, 10 g. (45 millimoles) of α -chloroketone (I) and 250 ml. of toluene was stirred and heated to reflux for 30 hours. After the mixture cooled, water was added and the layers separated. Acidification of the water layer gave 3.6 g. (51%) of 1-phenylcyclohexanecarboxylic acid, m.p. 122–123°.

After the toluene was distilled from the organic layer, the resulting oil was dissolved in low-boiling petroleum ether from which a total of 3.7 g. (39%) of hydroxyketone (IV) could be isolated in crystalline form.

Under the same conditions 2.9 g. (72 millimoles) of sodium hydroxide and 10 g. (36 millimoles) of α -bromoketone gave 2.5 g. (34%) of acid (II) and 3.9 g. (54%) of hydroxyketone (IV).

Using xylene in place of toluene, the chloroketone gave 53% of acid (II) and 25% of hydroxyketone (IV) while the bromoketone gave 39% of acid and 36% of hydroxyketone.

Reaction of Silver Nitrate in an Ethanol-Water Solution with the α -Bromoketone (I).—The α -bromoketone (5.36 g.

0.02 mole) was dissolved in 120 ml. of 95% ethanol. To this solution was added 3.5 g. (0.02 mole) of silver nitrate dissolved in 80 ml. of a solution of 60 parts ethanol and 40 parts water. After the resulting reaction mixture was heated to reflux for one hour, the precipitated silver bromide was filtered and washed. After drying, the silver bromide weighed 3.6 g. (97%).

Most of the organic solvent was evaporated under reduced pressure and the remaining mixture was extracted with ether. After the ether was evaporated the neutral organic material was separated into a ketonic and non-ketonic fraction using Girard¹⁶ reagent. The non-ketonic

(16) M. E. Smith, B. Chase and R. Rhodes, *THIS JOURNAL*, **66**, 1547 (1944).

fraction was saponified using the procedure of Rubin¹⁴ for esters of II to give 0.74 g. (18%) of 1-phenylcyclohexanecarboxylic acid, m.p. 123–124°.

After an aliquot had been withdrawn, the remaining neutral ketonic fraction was distilled to give 0.8 g. of pure 1-cyclohexenyl phenyl ketone, m.p. 32–34°, the melting point of which was not depressed by addition of an authentic sample. Titration of the aliquot of neutral material with bromine indicated the presence of 68% of unsaturated compound. An infrared spectrum of the neutral ketonic fraction indicated no significant amount of α -hydroxyketone (IV) had formed.

DETROIT 1, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

The Configuration of Isocamphenilanol¹

BY WYMAN R. VAUGHAN AND RANDOLPH PERRY, JR.

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Evidence is presented for the assignment of an *endo* configuration to the lower melting isomer of the epimeric pair of alcohols related to camphenilanic and isocamphenilanic acids. The names camphenilanol and isocamphenilanol are suggested for the corresponding alcohols.

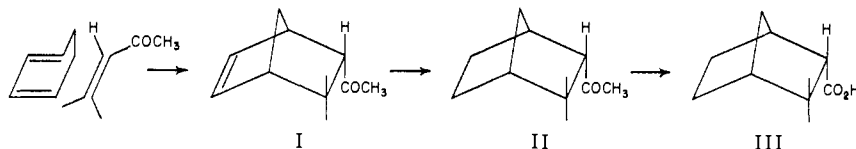
The confusion arising from an early study² of the acids obtained by oxidation of camphene and camphene derivatives was only partially resolved by the explicit demonstration of the *endo* configuration of isocamphenilanic acid.³ While this proof of configuration inferentially established the identity of camphenilanic acid^{2,4} there appeared to be no satisfactory way of relating the apparently stereoisomeric camphenanic and isocamphenanic acids to these substances. The esters of all four acids gave the same alcohol on reduction with sodium and alcohol thus suggesting the stereoisomeric character of the acids as opposed to structural differences, and this appeared to be confirmed by saponification of the ester of isocamphenanic acid, which afforded a mixture of camphenilanic and isocamphenilanic acids. In view of this evidence and the nature of the steric problem it is only possible to conclude that camphenanic acid, too, must constitute another such mixture.⁵

Inasmuch as esters of the pure acids as well as of mixtures of them appeared to give the same alcohol on sodium and alcohol reduction, nothing could be said of the configuration of this alcohol (m.p. 77°, acid phthalate m.p. 153°).² A presumably epimeric, lower melting alcohol^{6,7} had been prepared by reduction of the enolacetate of camphenilanaldehyde, but here again conclusions as to configuration are equivocal.

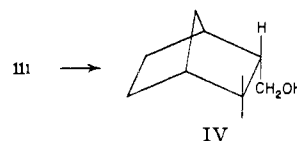
Recently the two epimeric alcohols were prepared for the first time in substantially pure state and

with adequate data on derivatives to enable comparative identification. However, unequivocal assignment of configuration was not possible, since the reactions used⁸ were essentially those previously described^{2,6} and thus are subject to the same objections. It is only possible to infer that since the yield and purity of the higher melting alcohol (81°) obtained by sodium and alcohol reduction of methyl camphenilamate (*exo*) are superior to those reported for similar reduction of the epimeric isocamphenilamate (*endo*), the higher melting isomer probably has the *exo* configuration.

In connection with other studies in this field the present investigators had occasion to prepare one of these alcohols by a route which leaves no doubt as to its configuration. Mesityl oxide was allowed to react with cyclopentadiene, produced *in situ* by thermal depolymerization of the dimer, and the resulting unsaturated ketone (I) was reduced catalytically to the saturated ketone (II) which then was converted to isocamphenilanic acid (III) by the haloform reaction. The acid thus obtained corresponded in all respects with that more directly produced by the addition of β , β -dimethylacrylic acid to cyclopentadiene followed by reduction.⁸



Reduction of III by lithium aluminohydride afforded an excellent yield of an alcohol, IV, melting at 58–60°. Purification through the acid phthal-



(1) Presented in part before the Organic Division of the American Chemical Society at Buffalo, March 26, 1952.

(2) G. G. Henderson and M. M. J. Sutherland, *J. Chem. Soc.*, **105**, 1710 (1914).

(3) G. Komppa and O. Komppa, *Ber.*, **69B**, 2606 (1936).

(4) J. Bredt and W. Jagelki, *Ann.*, **310**, 112 (1900).

(5) Cf. P. Lipp, private communication, "Beilstein," Vol. V. 1 Suppl., p. 83.

(6) F. W. Semmier, *Ber.*, **42**, 962 (1909).

(7) P. Lipp, H. Dessauer and E. Wolf, *Ann.*, **525**, 271 (1936).

(8) W. Hüchel and H. Schultze, *ibid.*, **575**, 32 (1951).