[Contribution from the Baker Laboratory of Chemistry, Cornell University]

The Acid-catalyzed Rearrangement of Cinenic Acid. II.[1] Geronic Acid from 6-Hydroxy-2,2,6-trimethylcyclohexanone

By J. Meinwald and C. C. Cornwall

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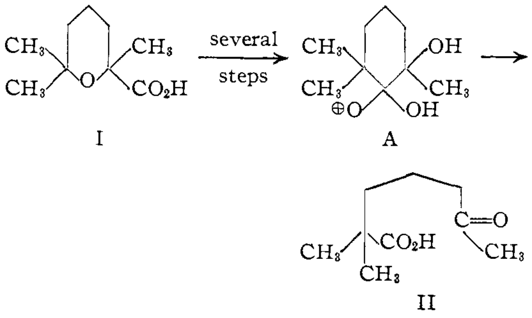
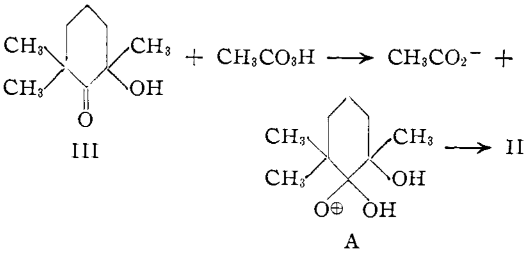
6-Hydroxy-2,2,6-trimethylcyclohexanone (III) has been prepared and subjected to peracetic acid oxidation. The formation of geronic acid (II) in this reaction is in accord with the mechanisms recently postulated for the "cinenic acid rearrangement."

An isotopic tracer study of the acid-catalyzed rearrangement of α-cinenic acid (I) to geronic acid (II) has demonstrated that the net change in this reaction is a carboxyl transfer.[1] This result is consistent with two types of mechanism, both of which postulate the formation of ion A as the immediate precursor of the geronic acid (see equation 1).



(1)

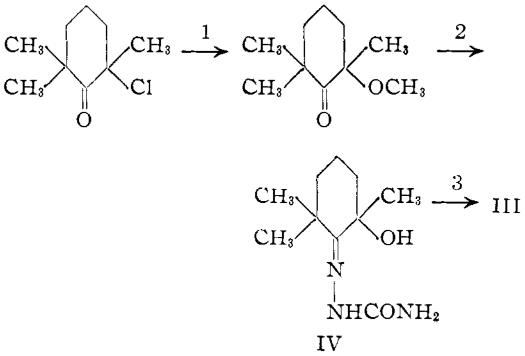
Inspection of A shows it to correspond to the product of the addition of an OH^+ fragment to 6-hydroxy-2,2,6-trimethylcyclohexanone (III). Since peracids are generally conceded to act as *quasi* OH^+ donors,[2] it was hoped that the reaction of the ketone III with peracetic acid would produce geronic acid if the previous speculations were valid (see equation 2).



(2)

In seeking a source of the ketol III, 6-chloro-2,2,6-trimethylcyclohexanone[3] was chosen as the starting material. Initial attempts to displace the halogen by some oxygenated function were abortive. Thus, prolonged refluxing of the chloroketone with potassium hydroxide and methyl formate in methanol[4] or with 3 *M* aqueous potassium hydroxide resulted in the recovery of unchanged starting material.[5] At this point a paper describing two preparations of the desired ketol III became available,[6] and it was decided to adopt one of the published procedures.

The method selected, represented in equation 3, consisted of (1) displacement of the chlorine in 6-chloro-2,2,6-trimethylcyclohexanone by methoxy, (2) conversion to the semicarbazone IV (which was found to have exchanged methoxy for hydroxy![6]), and finally (3) hydrolysis of the semicarbazone to the desired ketol III. The change of methoxyl into hydroxyl accompanying semicarbazone formation appeared unprecedented, but the experiments were nevertheless repeated in the hope of obtaining III. The product isolated after refluxing the chloroketone with sodium methoxide in methanol showed strong hydroxylic absorption as well as typical carbonyl absorption in its infrared spectrum. This product gave a semicarbazone which, after hydrolysis in the standard fashion, gave a regenerated ketone whose infrared spectrum was indistinguishable from that of the initial methoxide displacement product.



(3)

These results seemed to indicate that the compound isolated from the displacement reaction was itself the desired hydroxyketone III. This suspicion was strengthened by the observation that attempts to cleave the presumed methyl ether by treatment with aluminum chloride[7] or hydriodic acid yielded unchanged starting material and was finally confirmed by the fact that the same product

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[1] For the previous paper in this series see J. Meinwald, This Journal, **77**, 1617 (1955).

[2] For a brief survey of the mechanisms of peracid reactions see D. Swern in R. Adams, "Organic Reactions," Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 385–388.

[3] A convenient preparation of this chloroketone from 2,2,6-trimethylcyclohexanone has been described by A. Bell, T. H. Strickland and G. F Wright, *J. Org. Chem.*, **16**, 1742 (1951).

[4] A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 5.

[5] The possibility that the α-chloroketone might be rearranging under the basic conditions to give 1,2,2-trimethylcyclopentanecarboxylic acid was considered, but no acidic product could be isolated from either of these hydrolysis attempts.

[6] K. R. Bharucha, H. L. Cohen and G. F Wright, *J. Org. Chem.*, **19**, 1097 (1954).

[7] I. M. Hunsberger, R. Ketcham and H. S. Gutowsky, This Journal, **74**, 4839 (1952).

resulted from aerial oxidation of the lithium derivative of the chloroketone.[8]

6-Hydroxy-2,2,6-trimethylcyclohexanone (III), prepared by two independent methods, was now available for cleavage studies. The result of the peracetic acid oxidation was in accord with expectations: the ketol was cleaved to geronic acid (II), which was isolated and characterized as its 2,4-dinitrophenylhydrazone. Although this fact is insufficient proof that the ion A is the actual precursor of geronic acid in the cinenic acid rearrangement, it is in agreement with this postulate and lends experimental support to the hypothesis that when this ion is generated it does give rise to the anticipated keto-acid.

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Experimental

6-Chloro-2,2,6-trimethylcyclohexanone was prepared in 75–82% yield by treatment of 2,2,6-trimethylcyclohexanone[9] with phosphorus pentachloride according to the procedure of Bell, Strickland and Wright.[3]

Attempted Hydrolyses of 6-Chloro-2,2,6-trimethylcyclohexanone. A.—A mixture of 1.05 g. of potassium hydroxide, 7.5 ml. of absolute methanol and 4 ml. of methyl formate was refluxed for two hours.[4] Refluxing was discontinued, 2.6 g. of the chloroketone was introduced, and the refluxing resumed for another 16 hours. Removal of volatile components on the steam-bath, dilution with water and extraction with methylene chloride yielded a product whose infrared spectrum was indistinguishable from that of the starting material. Acidification of the aqueous layer followed by ether extraction yielded no acidic product.

B.—A mixture of 2.7 g. of chloroketone and 30 ml. of 3 *M* potassium hydroxide solution was refluxed for two days. Extraction of the reaction mixture led to the recovery of starting material. No acidic product was obtained by acidifying the aqueous phase and extracting with ether.

6-Hydroxy-2,2,6-trimethylcyclohexanone. A.—A solution containing 7.9 g. of 6-chloro-2,2,6-trimethylcyclohexanone, 5 g. of sodium methoxide and 50 ml. of methanol was refluxed for five hours.[6] Excess methanol was removed by distillation, the residue was diluted with water, and the product extracted with ether. After drying the extract and removing the ether, the product was distilled rapidly at 65–77° (9–10 mm.). The yield of the hydroxyketone was 45% (3.1 g.). The infrared spectrum of this material showed strong absorption at 2.90 and 5.85 μ, and differed considerably from the infrared spectra of both the chloroketone and 2,2,6-trimethylcyclohexanone.

The hydroxyketone was converted into a crude semicarbazone (m.p. 168–173°) in 48% yield, following the previously described procedure.[6] Hydrolysis of this derivative in the standard fashion led to the recovery of a ketone indistinguishable from the starting material (from inspection of infrared spectra).

B.—Several attempts to prepare a Grignard reagent from 6-chloro-2,2,6-trimethylcyclohexanone, using ether and ethylene glycol dimethyl ether as solvents and methyl iodide as an initiator, were unsuccessful. However, 10.8 g. of the chloroketone in 100 ml. of ether reacted with 0.5 g. of lithium ribbon over a period of several days. A stream of moisture and carbon dioxide-free air was passed through the cooled solution for ten hours. The mixture was then hydrolyzed with dilute hydrochloric acid and extracted with ether. 6-Hydroxy-2,2,6-trimethylcyclohexanone was recovered in 25% yield after the usual work up procedure. Its infrared spectrum was indistinguishable from that of the product formed in part A above.

"Hydrolysis" Attempts.—A mixture of 1.9 g. of 6-hydroxy-2,2,6-trimethylcyclohexanone, 6 g. of anhydrous aluminum chloride and 40 ml. of benzene was refluxed for two hours. The mixture was cooled, poured into dilute hydrochloric acid and ice and thoroughly extracted with ether. The organic layer was washed with aqueous sodium bicarbonate and dried. Removal of the solvent followed by vacuum distillation gave only unchanged hydroxyketone.

In another experiment the hydroxyketone was recovered unchanged after prolonged refluxing with hydriodic acid in acetic acid.

Dehydrohalogenation of 6-Chloro-2,2,6-trimethylcyclohexanone.—The pyridine dehydrohalogenation of 10 g. of 6-chloro-2,2,6-trimethylcyclohexanone was carried out as previously described,[6] to give a 90% yield of a product, b.p. 60–65° (9 mm.). The infrared spectrum showed carbonyl absorption at 5.97 μ, but no characteristic bands in the 11.25–11.40 μ region.

Peracid Cleavage of 6-Hydroxy-2,2,6-trimethylcyclohexanone.—A solution of 2.4 g. of 6-hydroxy-2,2,6-trimethylcyclohexanone in 10 ml. of 40% peracetic acid[10] was allowed to stand at 5° for five days. The reaction mixture was then neutralized with sodium carbonate solution and thoroughly extracted with ether in order to remove any non-acidic materials. The aqueous phase was acidified with 3 *N* sulfuric acid, and again extracted with ether. The ethereal extract was dried and the solvent removed by distillation. Treatment of the residue with excess 2,4-dinitrophenylhydrazine reagent gave a copious orange precipitate, which was collected by filtration and recrystallized from ethanol–water. The recrystallized derivative (2 g.) showed m.p. 128–132°; a mixture with authentic geronic acid 2,4-dinitrophenylhydrazone (m.p. 130–132°) showed m.p. 128–132°. The infrared spectra of the synthetic and authentic compounds were indistinguishable.

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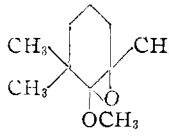
[8] The oxidation of this lithium derivative was carried out when the preparation of the corresponding Grignard compound could not be accomplished. The reasons for the discrepancies between the present work and that cited in reference 6 are not clear. One possibility is that the initial structure produced by the methoxide reaction is the epoxyether (i) or the hydroxyketal (ii), resulting from attack at the carbonyl rather than at the carbon–chlorine bond (*cf.* C. L. Stevens, W. Malik and R. Pratt, THIS JOURNAL, **72**, 4578 (1950)). Since the



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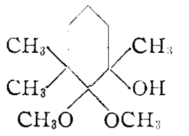
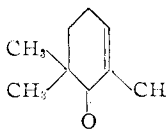


ii

product as isolated, however, shows unmistakable spectral indications of being a ketol, it would have to be further conjectured that either (i) or (ii) undergoes hydrolysis to III during the working up of the reaction mixture.

We also have had occasion to repeat the dehydrohalogenation of 6-chloro-2,2,6-trimethylcyclohexanone and would like to suggest the structure (iii) as the correct representation of the resultant unsaturated ketone. This material shows $\lambda_{\max.}^{\text{EtOH}}$ at 236 mμ, in slightly better



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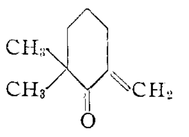

iv

agreement with this structure than with the previously assigned structure iv. In its infrared spectrum, the unsaturated ketone shows no characteristic terminal methylene absorption in the 11.25–11.40 μ region. Finally, structure iii is in accord with the earlier observation that the ketone gives rise to a 74% yield of α,α-dimethylglutaric acid on permanganate oxidation. In view of these data, the obtention of a 3% yield of formaldehyde by ozonolysis does not seem compelling evidence in favor of (iv). (*Cf.* reference 6.)

Although it is desirable that these various transformations be reinvestigated, it is not planned to undertake the task in this Laboratory, since the original objective in carrying out this research has been reached.

[9] We are indebted to Dr. B. A. Hems of Glaxo Company, Ltd., for a most generous gift of 2,2,6-trimethylcyclohexanone.

[10] The authors are indebted to the Buffalo Electro-Chemical Company, Inc., for a generous supply of this reagent.