

The sulfamic acid and pyridine reagent and also the sulfur trioxide pyridine addition compound convert optically active *s*-butyl alcohol to salts of

hydrogen *s*-butyl sulfate with retention of configuration and maintenance of optical purity.

EVANSTON, ILLINOIS

RECEIVED DECEMBER 27, 1948

[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

Analogs of Dihydroionone

BY E. C. HORNING, M. G. HORNING AND E. JANE PLATT¹

The structural relation between ionone and irone has recently been defined through the proof of structure and synthesis of *dl*- α -irone by Ruzicka. Both α - and γ -irone possess a characteristic fresh violet odor, and this is evidently a specific property of the 6-methyl- α - and γ -ionone structure; 6-methyl- β -ionone (β -irone) has an ionone odor. The saturation of the exocyclic double bond in compounds of this group generally leads to complete or almost complete loss of odor, but cyclohexene unsaturation is less necessary for odor. This is indicated by the fact that the condensation product of dihydrocyclocitral and acetone has an intense odor.

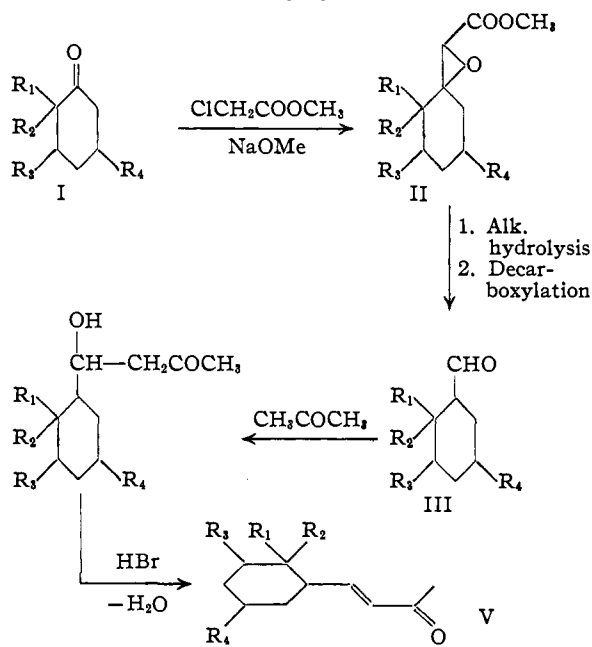
The location of the methyl groups is an important factor in determining the character of the odor in these compounds, and we have been interested in a study of several analogs of dihydroionone in which the ring methyl groups are modified in number and position, and in which exocyclic unsaturation is retained. The general method employed for the preparation of these compounds is shown in Fig. 1. Model experiments carried out with 3,5-dimethylcyclohexanone (I, $R_1R_2 = H$, $R_3R_4 = \text{methyl}$) indicated that the Darzens method gave a satisfactory over-all yield of the corresponding hexahydrobenzaldehyde. The glycidic ester was obtained in 78% yield; hydrolysis under alkaline conditions gave the glycidic acid in 99% yield of crude material, and this gave on pyrolysis a 65% yield of the aldehyde. The condensation of 3,5-dimethylhexahydrobenzaldehyde with acetone was carried out in the usual way,² but the result was a mixture which included the aldol product, and it was necessary to carry out a separate dehydration step (with hydrobromic acid) to obtain the unsaturated ketone.

These steps were repeated with 2,3-dimethylcyclohexanone (I, $R_2R_4 = H$, $R_1R_3 = \text{methyl}$) and with 2,2,3-trimethylcyclohexanone (I, $R_4 = H$, $R_1R_2R_3 = \text{methyl}$). The introduction of methyl groups in positions adjacent to the carbonyl group led to greatly lowered yields in the Darzens procedure. An attempt to obtain 2,2,3,6-tetramethylhexahydrobenzaldehyde (for the proposed preparation of a dihydroirone) was not successful. The introduction of three α -methyl substituents into a cyclohexanone struc-

ture (as in 2,2,3,6-tetramethylcyclohexanone) provides sufficient steric hindrance to prevent completely the Darzens condensation.

The dihydroionone analogs obtained in this way did not possess a floral odor, except for 1-(2',2',3'-trimethylcyclohexyl)-1-butenone-3, and in this case the odor was not violet-like.

Most of the necessary cyclohexanones were made by methylation methods. 2,3-Dimethylcyclohexanone was prepared from 3-methyl-4-carbomethoxy-2-cyclohexen-1-one by sodamide alkylation, followed by hydrolysis, decarboxylation and catalytic reduction. Using the enol ether method,³ with potassium amide alkylation, 2,2,3-trimethylcyclohexanone was prepared from 2,3-dimethylcyclohexanone. A potassium amide alkylation of 2,2,3-trimethylcyclohexanone provided 2,2,3,6-tetramethylcyclohexanone.



Acknowledgment.—We are indebted to Mrs. Sarah M. Woods for the analyses reported here.

Experimental

All melting points are corrected.

Methyl 5,7-Dimethyl-1-oxaspiro[2,5]octane-2-carboxylate.—A mixture of 108 g. (0.86 mole) of 3,5-di-

(3) Johnson and Posvic, *THIS JOURNAL*, **69**, 1361 (1947).

(1) Rohm and Haas Research Assistant.

(2) "Organic Syntheses," **23**, 78 (1943).

methylcyclohexanone⁴ and 103 g. (0.95 mole) of methyl chloroacetate was cooled to 5° in a 500-ml. three-necked flask equipped with a stirrer and a reflux condenser protected with a calcium chloride tube. There was added, in one portion and with good stirring, sodium methoxide prepared from 21.7 g. (0.95 mole) of sodium. The sodium methoxide was heated at 100° under 10–15 mm. pressure (aspirator) for one hour, and crushed to a powder before use. A vigorous reaction occurred immediately; the creamy suspension was stirred in an ice-bath for two and one-half hours, and then allowed to stand at room temperature, without stirring, for twelve hours. The reaction was completed by heating on a steam cone, with stirring, for two hours. The mixture was treated with 150 ml. of ice-water and 150 ml. of ether; the layers were separated and the aqueous solution extracted with two 100-ml. portions of ether. The combined ether extracts were washed with 100-ml. portions of 5% sodium carbonate solution and water, and dried over magnesium sulfate. After removal of the ether, the glycidic ester was distilled *in vacuo* through a short column; yield, 133 g. (78%) of colorless ester, b. p. 130–131° (16 mm.).

Anal. Calcd. for C₁₁H₁₈O₃: C, 66.64; H, 9.15. Found: C, 66.84; H, 9.30.

5,7-Dimethyl-1-oxaspiro[2,5]octane-2-carboxylic Acid.—A 65.3 g. (0.33 mole) quantity of the glycidic ester was hydrolyzed with aqueous alcoholic potassium hydroxide. The yield was 60.0 g. (99%) of crude glycidic acid. This acid did not crystallize, although it was extremely viscous. It was not characterized further, but was subjected immediately to pyrolytic decomposition.

3,5-Dimethylhexahydrobenzaldehyde.—The crude glycidic acid (60.0 g.) was placed in a Claisen distilling flask equipped with a thermometer and a wire stirrer, and arranged for distillation under about 100–150 mm. pressure. Approximately 5 g. of powdered copper was added. With good stirring and careful heating, the decomposition occurred smoothly and the aldehyde distilled from the flask at about 170–180° (*ca.* 150 mm.). The distillate was dissolved in ether; the ether solution was washed with saturated sodium bicarbonate solution, and dried. A crude yield of 29.4 g. (65%) of the aldehyde was obtained. This material was used directly in the acetone condensation reaction. Further purification may be effected by distillation under reduced pressure, although the aldehyde appeared to undergo considerable decomposition when redistilled. A colorless sample, b. p. 69–71° (14 mm.), was obtained in this way.

Anal. Calcd. for C₉H₁₆O: C, 77.08; H, 11.50. Found: C, 77.26; H, 11.58.

The semicarbazone was recrystallized from methanol, m. p. 169–171°.

Anal. Calcd. for C₁₀H₁₆ON₃: C, 60.88; H, 9.71. Found: C, 60.78; H, 9.52.

1-Hydroxy-1-(3',5'-dimethylcyclohexyl)-butanone-3.—The condensation of 3,5-dimethylhexahydrobenzaldehyde with acetone was carried out essentially according to the method of Russell and Kenyon.² From 29.4 g. of crude aldehyde there was obtained 26.1 g. (68%) of condensation product, b. p. 135–150° (10 mm.). This material was a light yellow oil which partially solidified on cooling. By trituration with ether-pentane, and chilling in Dry Ice, there was obtained 5.0 g. of colorless crystalline solid, m. p. 65–66°. This was recrystallized from ether-pentane without change in melting point.

Anal. Calcd. for C₁₂H₂₀O₂: C, 72.68; H, 11.19. Found: C, 72.90; H, 11.11.

The product of condensation was evidently a mixture which included the aldol form, and in later experiments crude condensation products were dehydrated directly.

1-(3',5'-Dimethylcyclohexyl)-1-butenone-3.—The dehydration of 1-hydroxy-1-(3',5'-dimethylcyclohexyl)-butanone-3 was accomplished using 48% hydrobromic acid. To 2.55 g. of the liquid condensation product, described

above, in 110 ml. of dry toluene was added 6 drops of 48% hydrobromic acid. The material was distilled at atmospheric pressure, and 80 ml. of toluene and water was collected. This step was repeated with an additional 80 ml. of dry toluene. To the residual solution there was added 60 ml. of water and 12 g. of sodium bisulfite; the mixture was maintained under vigorous reflux for four hours. After cooling, the aqueous layer was separated and the organic layer washed with 30 ml. of water. To the combined aqueous layers there was added 50 ml. of 10% sodium hydroxide solution and 90 ml. of ether. After shaking vigorously for ten minutes, the organic layer was separated. The extraction was repeated four times, using an additional 50 ml. of 10% sodium hydroxide solution each time. The combined ether layers were washed once with 30 ml. of water and dried over magnesium sulfate. Upon evaporation of the solvent, there was obtained 1.31 g. (56%) of colorless oil with a non-floral (wood-like) odor; b. p. 152–155° (40 mm.).

Anal. Calcd. for C₁₂H₂₀O: C, 79.94; H, 11.18. Found: C, 79.97; H, 11.08.

The red 2,4-dinitrophenylhydrazone was recrystallized from methanol; m. p. 131–132°.

Anal. Calcd. for C₁₈H₂₄O₄N₄: C, 59.98; H, 6.71. Found: C, 60.40; H, 6.53.

Other Darzens Condensations.—A Darzens condensation was carried out with 18.9 g. of 2,3-dimethylcyclohexanone, 17.8 g. of methyl chloroacetate, and sodium methoxide from 3.8 g. of sodium. The crude glycidic ester was not distilled, but was hydrolyzed directly under alkaline conditions to yield 13.8 g. of crude glycidic acid. On pyrolysis in the usual way, a yield of 5.9 g. of 2,3-dimethylhexahydrobenzaldehyde was obtained. This material was not redistilled, but was condensed immediately with acetone.

From 22.0 g. of 2,2,3-trimethylcyclohexanone, 18.4 g. of methyl chloroacetate, and sodium methoxide from 3.9 g. of sodium there was obtained, after condensation and hydrolysis, 6.0 g. of crude glycidic acid. Pyrolysis of this acid yielded 1.9 g. of 2,2,3-trimethylhexahydrobenzaldehyde, which was condensed with acetone without preliminary purification by distillation. From the Darzens reaction, there was recovered 11.9 g. of 2,2,3-trimethylcyclohexanone.

An attempted Darzens condensation with 2,2,3,6-tetramethylcyclohexanone gave no glycidic acid after condensation and hydrolysis; the ketone was recovered unchanged. This observation is in agreement with Schäppi and Seidel.⁵

1-(2',3'-Dimethylcyclohexyl)-1-butenone-3.—From the condensation of 4.8 g. of 2,3-dimethylhexahydrobenzaldehyde with acetone there was obtained 4.2 g. of light yellow oil, evaporatively distilled at 150–165° (15 mm.). This material was dehydrated with hydrobromic acid in boiling toluene; from 1.94 g. of condensation product there was obtained 0.59 g. of 1-(2',3'-dimethylcyclohexyl)-1-butenone-3, evaporatively distilled at 110–120° (40 mm.). This material was a nearly colorless oil, with a strong but non-floral odor.

Anal. Calcd. for C₁₂H₂₀O: C, 79.94; H, 11.18. Found: C, 79.91; H, 10.99.

The red 2,4-dinitrophenylhydrazone was recrystallized from methanol; m. p. 136.5–138.5°.

Anal. Calcd. for C₁₈H₂₄O₄N₄: C, 59.98; H, 6.71. Found: C, 59.90; H, 6.58.

1-(2',2',3'-Trimethylcyclohexyl)-1-butenone-3.—The condensation of 1.50 g. of 2,2,3-trimethylhexahydrobenzaldehyde with acetone yielded 0.80 g. of condensation product. Without previous distillation, this was dehydrated with hydrobromic acid in toluene to provide 0.18 g. of crude 1-(2',2',3'-trimethylcyclohexyl)-1-butenone-3. This material was a nearly colorless oil with a strong odor; the odor was of a floral type, but did not resemble that of the ionones. For purposes of characterization, the oil was

(4) Horning, Horning and Walker, *THIS JOURNAL*, **70**, 3935 (1948).

(5) Schäppi and Seidel, *Helv. Chim. Acta*, **30**, 2199 (1947).

converted to the 2,4-dinitrophenylhydrazone; m. p. 133–134°, recrystallized from methanol.

Anal. Calcd. for $C_{19}H_{26}O_4N_4$: C, 60.94; H, 7.00. Found: C, 60.67; H, 6.90.

3-Methyl-4-carbethoxy-2-cyclohexen-1-one.—This material was prepared by a modification of the usual procedure for obtaining 3-methyl-5-alkyl-4-carbethoxy-2-cyclohexen-1-ones⁶ in 43% yield.

2,3-Dimethyl-4-carbethoxy-2-cyclohexen-1-one.—Sodamide was prepared as usual⁷ from 17.5 g. (0.74 mole) of sodium in 500 ml. of ammonia. There was added 130 g. (0.71 mole) of 3-methyl-4-carbethoxy-2-cyclohexen-1-one, and, after stirring for fifteen minutes, 250 ml. of dry ether was added. The ammonia was allowed to evaporate, and 110 g. (0.78 mole) of methyl iodide was added, along with enough ether to maintain the volume at about 500 ml. The mixture was heated under reflux with good stirring for one hour. Methanol (50 ml.) and water (200 ml.) were added; the aqueous layer was extracted with ether, and the combined ether solutions washed with 100-ml. portions of 5% sodium hydroxide solution, 5% hydrochloric acid, water, saturated sodium bicarbonate solution, and water. The solution was dried over magnesium sulfate and distilled under reduced pressure to yield 102 g. (73%) of the ester, b. p. 101–115° (0.5–1.0 mm.).

This ester has been prepared previously by alkylation with methyl iodide and sodium methoxide in methanol solution. Sodamide alkylation was used to avoid the extensive alcoholysis which occurs under these conditions.⁸

2,3-Dimethyl-2-cyclohexen-1-one.—Saponification of the ketoester was carried out by refluxing a mixture of 59 g. of the ketoester, 24 g. of sodium hydroxide, 150 ml. of water, and 50 ml. of alcohol for three hours. After acidification with 10% aqueous sulfuric acid, the solution was heated for one hour, cooled, and the product extracted with ether. The ether solution was washed with 100-ml. portions of 5% sodium hydroxide solution, water, 2% aqueous acetic acid, and saturated sodium bicarbonate solution and dried. Distillation yielded 27 g. (72%) of the ketone, b. p. 100–110° (16 mm.).

The 2,4-dinitrophenylhydrazone was recrystallized from ethanol; m. p. 195–197°.

Anal. Calcd. for $C_{14}H_{16}N_4O_4$: C, 55.25; H, 5.30. Found: C, 55.42; H, 5.21.

2,3-Dimethylcyclohexanone.—Catalytic reduction of 85 g. of the cyclohexenone was effected without a solvent, using 6 g. of 5% palladium-carbon catalyst, to yield 77 g. of the cyclohexanone, b. p. 180–182° (atm.).

Anal. Calcd. for $C_8H_{14}O$: C, 76.13; H, 11.18. Found: C, 76.07; H, 11.27.

The semicarbazone was recrystallized from methanol; m. p. 189–191°.

Anal. Calcd. for $C_8H_{17}N_3O$: C, 58.99; H, 9.35. Found: C, 58.77; H, 9.23.

6-Ethoxymethylene-2,3-dimethylcyclohexanone.—2,3-Dimethylcyclohexanone was formylated and converted into the enol ether according to the following procedure. A solution of 81 g. (1.1 mole) of ethyl formate in dry ether was chilled in an ice-bath, and powdered sodium methoxide from 20.2 g. (0.88 mole) of sodium was added. After complete reaction, an additional 300 ml. of dry ether and 55.0 g. (0.44 mole) of 2,3-dimethylcyclohexanone was added. After standing for twelve hours at room temperature, the mixture was treated with 300 ml. of water. The ether phase was separated and washed with 150 ml. of 10% sodium hydroxide solution. The combined water solutions were washed with ether, and acidified with 10% hydrochloric acid. The product, 6-hydroxymethylene-2,3-dimethylcyclohexanone, was extracted with ether.

(6) "Organic Syntheses," **27**, 24 (1948).

(7) "Organic Syntheses," **25**, 25 (1945).

(8) Hogg, *THIS JOURNAL*, **70**, 161 (1948).

After drying over magnesium sulfate, the ether was removed to yield 60.7 g. (89%) of crude material.

A mixture of the crude hydroxymethylene ketone in 450 ml. of dry acetone, with 121 g. of granular anhydrous potassium carbonate and 68.6 g. of ethyl iodide, was stirred at room temperature for three hours, and then allowed to stand for twelve hours. Pentane (800 ml.) was added, and the mixture filtered to remove inorganic salts. The solvents were removed by distillation, and the residue distilled under reduced pressure through a short Vigreux column; yield, 53.3 g. (67% over-all yield), b. p. 126–140° (15–17 mm.) of light yellow ethoxymethylene ether.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.57; H, 9.81.

2,2,3-Trimethylcyclohexanone.—Potassium amide was prepared from 12.4 g. (0.32 mole) of potassium in liquid ammonia. With the aid of a little dry ether, 53.0 g. (0.29 mole) of 6-ethoxymethylene-2,3-dimethylcyclohexanone was added; the solution was stirred for fifteen minutes and 300 ml. of dry ether was added. A nitrogen atmosphere was provided and, after evaporation of the ammonia, 45.3 g. (0.32 mole) of methyl iodide was added, and the mixture was heated under reflux with stirring for one hour. Methanol (50 ml.) and water (200 ml.) were added, and the aqueous layer separated. The ether solution was washed with 100 ml. of 5% aqueous acetic acid, and evaporated without drying. The residue was treated essentially as described by Johnson and Posvic.² The product was separated by ether extraction and was isolated by distillation under reduced pressure; yield, 22.0 g. (54%) of product, b. p. 90–100° (20 mm.).

Anal. Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.51. Found: C, 77.21; H, 11.60.

The 2,4-dinitrophenylhydrazone was recrystallized from ethanol; m. p. 134–136°.

Anal. Calcd. for $C_{15}H_{20}N_4O_4$: C, 56.24; H, 6.29. Found: C, 55.90; H, 6.00.

2,2,3,6-Tetramethylcyclohexanone.—To a solution of potassium amide from 3.04 g. of potassium in liquid ammonia there was added 10.0 g. of 2,2,3-trimethylcyclohexanone in a little dry ether. Approximately 200 ml. of dry ether was added, and the ammonia allowed to evaporate under a nitrogen atmosphere. Methyl iodide (11.1 g.) was added and the mixture was stirred under reflux for one hour. Methanol (15 ml.) and water (200 ml.) were added and the layers separated. The aqueous layer was extracted with ether, and the combined ether solutions washed with 100-ml. portions of 5% sodium hydroxide solution, 5% hydrochloric acid, water and saturated sodium bicarbonate solution. The product was isolated by distillation under reduced pressure; yield 9.0 g. (83%), b. p. 82–90° (17 mm.).

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 78.02; H, 11.55.

The work of Schäppi and Seidel,⁵ which appeared while this work was in progress, indicates that the product of this alkylation reaction (using sodamide-methyl iodide) may contain unreacted 2,2,3-trimethylcyclohexanone. Our product was used directly in a Darzens condensation with methyl chloroacetate, but no reaction was obtained, and the ketone was recovered unchanged. This is in accordance with the observations of the Swiss workers.

Summary

The application of the Darzens procedure to 3,5-dimethyl-, 2,3-dimethyl- and 2,2,3-trimethylcyclohexanone is described, together with the condensation of the resulting hexahydrobenzaldehydes with acetone to provide analogs of dihydroionone.