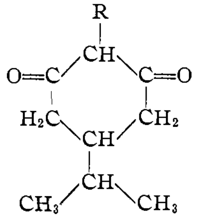
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

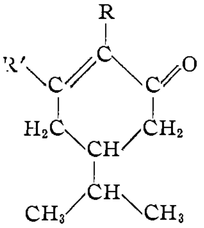
Monocyclic Terpenes from Cyclic 1,3-Diketones[1]

BY ROBERT L. FRANK AND HENRY K. HALL, JR.

The use of cyclic 1,3-diketones as key intermediates appears an attractive approach to the synthesis of monocyclic terpenes of the type represented by carvone and carvotanacetone (VII). In this paper are reported such syntheses of the racemic form of the naturally-occurring carvotanacetone and a number of its analogs.



I, R = H
II, R = CH_3
III, R = C_2H_5



IV, R = CH_3, R′ = Cl
V, R = H, R′ = OC_2H_5
VI, R = R′ = H
VII, R = CH_3, R′ = H
VIII, R = H, R′ = CH_3
IX, R = H, R′ = C_2H_5
X, R = R′ = CH_3

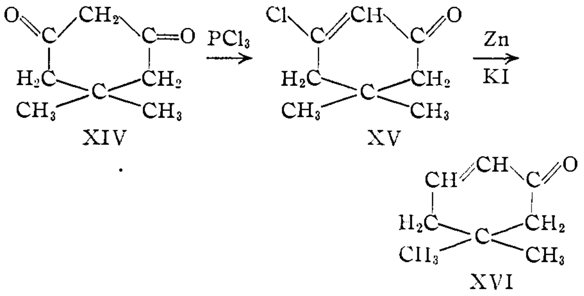
5-Isopropyl-1,3-cyclohexanedione (I) was prepared readily in 80% yield by a modification of the method of Crossley and Pratt[2] in which isobutylideneacetone (XI) is condensed with ethyl malonate. This diketone served as the starting material for all the carvotanacetone analogs. Similar direct preparation of the 2-alkyl derivatives (II and III) of the diketone was not convenient because the starting materials (XII and XIII) corresponding to isobutylideneacetone (XI) are obtained only in poor yield and in mixtures of isomers from isobutyraldehyde and unsymmetrical ketones of the type CH_3COCH_2R.[3]

$(CH_3)_2CHCH{=}CHCOCH_2R$ XI, R = H; XII, R = CH_3; XIII, R = C_2H_5

Methylation of the parent diketone I was accomplished readily by means of methyl iodide to give 5-isopropyl-2-methyl-1,3-cyclohexanedione (II) in 75% yield. Ethylation by means of ethyl bromide or iodide, however, occurred only at the oxygen atom to form the enol ether (V). This is in accord with the experience of Desai[4] with a number of cyclic 1,3-diketones and of Moore and Thorpe with α-cyano-β-hydrindone.[5]

Conversion of the diketones I and II to the corresponding cyclohexenones (VI and VII) involves reduction and dehydration. Direct reduction, either by catalytic hydrogenation or by chemical means, did not appear feasible. The method of Stutsman and Adkins,[6] using Raney nickel and limited amounts of hydrogen, is not easily controlled with cyclic diketones. The Meerwein–Ponndorf reduction is known to fail with 1,3-diketones.[7]

Indirect reduction of the diketones has been accomplished nicely by two means. The 3-chlorocyclohexenone (IV) was formed in 67% yield from the diketone II by means of phosphorus trichloride, and subsequent reductive dehalogenation with zinc dust and potassium iodide gave carvotanacetone (VII) in 72% yield. Model experiments with methone (XIV) gave somewhat lower yields.



XIV XV XVI

The use of potassium iodide is a controlling factor in the success of this reaction. The experiments of Crossley and Renouf[8] with 3-chloro-5,5-dimethyl-2-cyclohexenone (XV) using a zinc-copper couple but no potassium iodide provide evidence for the necessity of enhancing the reactivity of the halogen. Some further methods of dehalogenation which were less satisfactory are described briefly in the Experimental Part.

The other indirect method involves the intermediate formation of the diketone enol ethers. The preparation of such cyclic enol ethers has been studied by Crossley and Renouf[9] and more recently by Woods and Tucker.[10,11] In the present work an improved procedure was found, consisting of direct etherification by means of ethanol and *p*-toluenesulfonic acid, with removal of water

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[1] This is the third communication on the chemistry of terpenes. For the second, see THIS JOURNAL, **71**, 3889 (1949).

[2] Crossley, *J. Chem. Soc.*, **81**, 675 (1902); Crossley and Pratt, *ibid.*, **107**, 171 (1915).

[3] Haeussler and Dijkema, *Ber.*, **77B**, 601 (1944).

[4] Desai, *J. Chem. Soc.*, 1079 (1932).

[5] Moore and Thorpe, *ibid.*, **93**, 168 (1908).

[6] Stutsman and Adkins, THIS JOURNAL, **61**, 3303 (1939). Unpublished data in this Laboratory indicate that conditions which will accomplish hydrogenation of methone reduce it readily all the way to 5,5-dimethyl-1,3-cyclohexanediol.

[7] Unpublished results of Adkins and his students. See also Lund, *Ber.*, **70**, 1520 (1937). The use of potassium isopropoxide (Woodward, Wandler and Brutschy, THIS JOURNAL, **67**, 1425 (1945)) also failed to reduce methone.

[8] Crossley and Renouf, *J. Chem. Soc.*, **91**, 63 (1907).

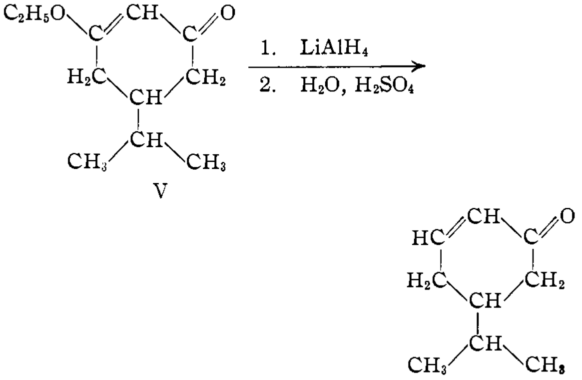
[9] Crossley and Renouf, *ibid.*, **93**, 629 (1908).

[10] Woods, THIS JOURNAL, **69**, 2549 (1947).

[11] Woods and Tucker, *ibid.*, **70**, 2174 (1948).

as soon as it formed. This gives high yields with methone (XIV) and 5-isopropyl-1,3-cyclohexanedione (I), but fails with the 2-substituted diketone II.

Reduction of the cyclic enol ethers by means of lithium aluminum hydride, followed by hydrolysis, gave 5,5-dimethyl-2-cyclohexenone (XVI) in 48% yield from 5,5-dimethyl-3-ethoxy-2-cyclohexenone and 5-isopropyl-2-cyclohexenone (VI) in 64% yield from 3-ethoxy-5-isopropyl-2-cyclohexenone (V).[12]



V

VI

To introduce alkyl groups into the 3-position we have investigated the use of Grignard reagents. Addition of phenylmagnesium bromide to cyclic 1,3-diketones or to their enol ethers has been shown by Woods and Tucker[10,11] to be a feasible synthesis of 3-phenylcyclohexenones. In our work methylmagnesium iodide reacted similarly with the ethyl enol ether of methone to give isophorone, but the yield was lower (31%) than with the phenyl Grignard reagent. Application to the enol ether V, using methyl and ethyl Grignard reagents, gave mixtures of products from which the desired cyclohexenones (VIII and IX) were isolated only in low yield through the intermediate formation of their semicarbazones. A low yield of 2,3-dimethyl-5-isopropyl-2-cyclohexenone (X) was also obtained by addition of excess methylmagnesium iodide to the diketone II. These results are in accord with recent experiments by Woods and co-workers.[13]

Ultraviolet absorption spectra of all the cyclohexenones prepared are in agreement with the predictions of Woodward.[14]

The odor of dill was noticeable, in order of diminishing similarity, in Compounds VII, X, IX and VIII. Compounds VI and XVI had no resemblance to dill in this respect.

Experimental

5-Isopropyl-1,3-cyclohexanedione (I).—The formation of an oily impurity which troubled Crossley and Pratt[2] in this preparation was eliminated by performing the condensation with a large volume of solvent to give a fluid reaction mixture rather than a thick paste. To a solution of sodium ethoxide prepared from 73.8 g. (3.20 gram-atoms) of sodium and 2000 ml. of absolute ethanol were added 546 g. (3.42 moles) of ethyl malonate and 360 g. (3.22 moles) of isobutylideneacetone (available by the method of Eccott and Linstead).[15] The mixture was refluxed for one hour, an additional 500 ml. of absolute ethanol was added, and refluxing was continued for two more hours. A solution of 400 g. (7.00 moles) of potassium hydroxide in 1850 ml. of water was then added and the mixture refluxed for six hours, then neutralized with 12% hydrochloric acid. The ethanol was distilled, and the residue treated with three 45-g. portions of activated charcoal. Strong acidification then yielded 597.5 g. of tan precipitate, m. p. 62–64°, a mixture of the monohydrate of the product with potassium chloride, sufficiently pure for further reactions. Recrystallization of a sample from water gave the diketone monohydrate in amount equivalent to a yield of 80%, m. p. 62° (lit.,[2] 67.5°).

5-Isopropyl-2-methyl-1,3-cyclohexanedione (II).—To a solution of 2.2 g. (0.096 gram-atom) of sodium in 45 ml. of absolute ethanol was added 15.0 g. (0.082 mole) of 5-isopropyl-1,3-cyclohexanedione monohydrate. The solution was chilled in an ice-bath and 7.3 ml. (16.6 g., 0.117 mole) of methyl iodide was added, after which the mixture was refluxed for three and one-half hours. The ethanol was then distilled to leave a red oil which solidified on cooling. This was dissolved in 30 ml. of ether and extracted with several portions of 10% aqueous sodium bicarbonate. The bicarbonate extracts were acidified with hydrochloric acid and the resulting precipitate recrystallized from aqueous acetone to give 11.4 g. (75%) of crystalline product, m. p. 178–181°.

The same procedure with corresponding amounts of 5-isopropyl-1,3-cyclohexanedione and ethyl bromide resulted in a 32% yield of 3-ethoxy-5-isopropyl-2-cyclohexenone, b. p. 111–116° (2 mm.); $n^{20}\mathrm{D}$ 1.4953. Similar alkylations with ethyl iodide, ethylene chloride and ethylene bromide gave only alkali-insoluble oils, presumably the O-alkyl derivatives.

3-Chloro-5,5-dimethyl-2-cyclohexenone (XV) **and 3-Chloro-5-isopropyl-2-methyl-2-cyclohexenone** (IV).—The method of Crossley and co-workers[8,16] with 17.0 g. (0.12 mole) of methone and 7.0 g. (0.051 mole) of phosphorus trichloride yielded 9.0 g. (47.5%) of colorless 3-chloro-5,5-dimethyl-2-cyclohexenone of camphoraceous odor, b. p. 105° (20 mm.); $n^{20}\mathrm{D}$ 1.4942. It gave no reaction with ethanolic silver nitrate, but gave a green flame in the Beilstein copper wire test. The same procedure with thionyl chloride instead of phosphorus trichloride failed to yield the desired product.

A similar procedure with 37.3 g. (0.222 mole) of 5-isopropyl-2-methyl-1,3-cyclohexanedione and 12.2 g. (0.089 mole) of phosphorus trichloride in 220 ml. of chloroform yielded 27.5 g. (67%) of colorless 3-chloro-5-isopropyl-2-methyl-2-cyclohexenone, b. p. 121.5–124.5° (11 mm.); $n^{20}\mathrm{D}$ 1.5037; sp. gr.$^{20}_{20}$ 1.079; *MR* calcd. (no exaltation), 50.8; *MR* found, 51.2. The compound had an odor similar to that of dill oil.

Anal.[17] Calcd. for $C_{10}H_{15}OCl$: C, 64.34; H, 8.10; Cl, 19.00. Found: C, 64.87; H, 8.09; Cl, 18.94.

5,5-Dimethyl-2-cyclohexenone (XVI).—Ten grams (0.153 gram-atom) of zinc dust (previously activated by washing with dilute hydrochloric acid), 6.0 g. (0.038 mole) of 3-chloro-5,5-dimethyl-2-cyclohexenone, 5.0 g. (0.03 mole) of potassium iodide and 30 ml. of methanol were stirred vigorously for seven hours in a 125-ml. flask equipped with

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[12] This constitutes a new synthetic application of lithium aluminum hydride. Preliminary investigations indicate that its scope cannot be widely extended, however. Reduction failed to occur with the O-methyl derivative of dibenzoylmethane and with the O-ethyl derivative of ethyl acetoacetate. Reaction with ethyl ethoxymethylenemalonate gave a low yield (*ca.* 5%) of ethyl methylenemalonate.

[13] Woods, Griswold, Armbrecht, Blumenthal and Plapinger, THIS JOURNAL, **71**, 2028 (1949).

[14] Woodward, *ibid.*, **63**, 1123 (1941); **64**, 76 (1942).

[15] Eccott and Linstead, *J. Chem. Soc.*, 905 (1930).

[16] Crossley and LeSueur, *ibid.*, **83**, 110 (1903).

[17] Microanalyses were carried out by Miss Emily Davis, Miss Rachel Kopel and the Clark Microanalytical Laboratory.

a Hershberg stirrer. The mixture was then filtered, and the filtrate evaporated. The residue was shaken vigorously (till it dissolved) with a mixture of 57 ml. of 5% hydrochloric acid and 50 ml. of ether. The ether layer was dried over magnesium sulfate and distilled in a modified Claisen flask to yield 2.6 g. (55%) of 5,5-dimethyl-2-cyclohexenone, b. p. 75° (15 mm.); $n^{20}\mathrm{D}$ 1.4710; sp. gr. $^{20}{}_{20}$ 0.927; *MR* calcd. (no exaltation), 36.8; *MR* found, 37.4. A semicarbazone melted at 191–192.5° after three crystallizations as shiny plates from ethanol (lit.,[8] 195°).

Other reductive dehalogenations of 3-chloro-5,5-dimethyl-2-cyclohexenone were tried as follows: Refluxing of 4.0 g. of chloro compound in 75 ml. of absolute ethanol with 50 g. of Raney nickel for twelve hours gave 3.2 g. of liquid, b. p. 74–82° (13 mm.); $n^{20}\mathrm{D}$ 1.4508, a mixture containing starting material, the desired cyclohexenone, and the further reduced cyclohexanone. Ultraviolet absorption[18] in ethanol solution showed a maximum at 238 mμ characteristic of the cyclohexenone. Similar reduction of the bromo analog gave a like mixture. Rosenmund reduction of the chloro compound, using the conditions described by Fieser and Hershberg for 1-acenaphthaldehyde,[19] gave a 78% recovery of the starting material. Use of lithium aluminum hydride in dry ether also resulted in recovery of the starting material.

5,5-Dimethyl-2-cyclohexenone was also prepared in 48% yield (20.0 g. from 56.7 g. of 5,5-dimethyl-3-ethoxy-2-cyclohexenone) by the exact procedure used for the lithium aluminum hydride reduction of 3-ethoxy-5-isopropyl-2-cyclohexenone described below.

***dl*-Carvotanacetone** (VII).—The preceding reduction with zinc was repeated with 26.9 g. (0.145 mole) of 3-chloro-5-isopropyl-2-methyl-2-cyclohexenone, 38.0 g. (0.582 gram-atom) of activated zinc dust, 19.1 g. (0.114 mole) of potassium iodide, and 115 ml. of ethanol to give 15.9 g. (72%) of colorless *dl*-carvotanacetone which smelled strongly of dill or caraway oil, b. p. 109° (14 mm.): $n^{20}\mathrm{D}$ 1.4813: sp. gr. $^{20}{}_{20}$ 0.9355 (lit.,[20] 1.4805 and 0.9351, respectively); *MR* calcd. (no exaltation), 45.8; *MR* found, 46.3. Its ultraviolet absorption spectrum showed a maximum at 237 mμ (log ϵ 4.19, 0.006 g. per liter of 95% ethanol solution). A semicarbazone melted at 173–174.5° after three crystallizations from ethanol (lit.,[21] 177–178°).

5,5-Dimethyl-3-ethoxy-2-cyclohexenone.—A mixture of 38.5 g. (0.275 mole) of methone, 50 ml. (39.4 g., 0.86 mole) of absolute ethanol, 300 ml. of benzene and 1 g. of *p*-toluenesulfonic acid was refluxed under a continuous water separator. When no more water appeared in the distillate, the mixture was fractionally distilled to yield 38.0 g. (83%) of colorless product, b. p. 93° (1 mm.); $n^{20}\mathrm{D}$ 1.4881. When immersed in a Dry Ice-bath, the liquid set to a glass, and crystallized on warming, m. p. 57–58°.

3-Ethoxy-5-isopropyl-2-cyclohexenone (V).—The above procedure with 444 g. (2.64 moles) of 5-isopropyl-1,3-cyclohexanedione monohydrate, 550 ml. (434 g., 9.45 moles) of absolute ethanol, 3 liters of benzene and 14.3 g. of *p*-toluenesulfonic acid gave 337.0 g. (72%) of slightly yellow 3-ethoxy-5-isopropyl-2-cyclohexenone, b. p. 124° (1 mm.); $n^{20}\mathrm{D}$ 1.4952. Ultraviolet absorption showed a maximum at 249.5 mμ (log ϵ 4.20, 0.006 g. per liter of 95% ethanol solution).

The structure of this product was confirmed by refluxing a sample with 12% aqueous sodium hydroxide. Acidification gave a precipitate of 5-isopropyl-1,3-cyclohexanedione monohydrate, m. p. 63–65°.

Application of this means of etherification to 5-isopropyl-2-methyl-1,3-cyclohexanedione (II) resulted in a nearly quantitative recovery of the diketone.

5-Isopropyl-2-cyclohexenone (VI).—To a solution of 19.4 g. (0.107 mole) of 3-ethoxy-5-isopropyl-2-cyclohexenone in 100 ml. of dry ether was added with stirring 1.0 g. (0.0263 mole) of lithium aluminum hydride over a period of three minutes. A vigorous reaction occurred. The mixture was stirred at 25° for one hour, poured into 200 ml. of water, acidified with dilute sulfuric acid, and the layers separated. The water layer was extracted once with 50 ml. of ether, and the ether solutions combined. Drying over magnesium sulfate and distillation in a modified Claisen flask gave 9.2 g. (64%) of product, b. p. 104–108° (13 mm.); $n^{20}\mathrm{D}$ 1.4795; sp. gr. $^{20}{}_{20}$ 0.936; *MR* calcd. (no exaltation), 41.2; *MR* found, 41.9. Ultraviolet absorption showed a peak at 226.5 mμ (log ϵ 3.95, 0.006 g. per liter of 95% ethanol solution).

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.98; H, 10.46.

A 2,4-dinitrophenylhydrazone melted at 126°.

Anal. Calcd. for $C_{15}H_{18}O_4N_4$: C, 56.59; H, 5.70. Found: C, 56.49; H, 5.82.

Isophorone from 5,5-Dimethyl-3-ethoxy-2-cyclohexenone.—A Grignard reagent was prepared from 5.1 g. (0.212 gram-atom) of magnesium, 33.2 g. (0.232 mole) of methyl iodide and 100 ml. of dry ether. To it was added with stirring at room temperature over a five-minute period a solution of 25.3 g. (0.151 mole) of 5,5-dimethyl-3-ethoxy-2-cyclohexenone in 100 ml. of dry ether. Spontaneous refluxing subsided after ten minutes. The mixture was poured onto ice and steam distilled, the distillate extracted with two 50-ml. portions of ether, and the ether extracts dried over magnesium sulfate and fractionally distilled to yield 6.0 g. (29%) of isophorone, b. p. 93–95° (13 mm.); $n^{20}\mathrm{D}$ 1.4768. Repetition of this experiment with reaction times of thirty minutes and twelve hours gave yields of 28 and 31%, respectively.

5-Isopropyl-3-methyl-2-cyclohexenone (VIII).—A Grignard reagent prepared from 3.2 g. (0.133 gram-atom) of magnesium, 20.8 g. (0.145 mole) of methyl iodide and 100 ml. of dry ether was transferred to a separatory funnel and added with stirring over a ten-minute period to a solution of 24.1 g. (0.133 mole) of 3-ethoxy-5-isopropyl-2-cyclohexenone in 50 ml. of dry ether. The solution was refluxed for one and one-half hours, after which time it no longer gave a positive Gilman test with Michler ketone. The mixture was poured into 100 ml. of water containing 20 g. of ammonium chloride, the layers separated, the water layer extracted once with ether, and the combined ether solutions dried over magnesium sulfate. Fractional distillation in an eight-inch helix-packed column gave 5.6 g. of impure product, b. p. 110–113° (13 mm.); $n^{20}\mathrm{D}$ 1.4748–1.4850. This yielded 14.3 g. of semicarbazone, m. p. 168–171°, when treated with 6.0 g. of semicarbazide hydrochloride, 9.0 g. of sodium acetate and 50 ml. of 95% ethanol.

The semicarbazone was placed in 100 ml. of 20% sulfuric acid and steam distilled. The distillate was saturated with sodium chloride, extracted with two 50-ml. portions of ether, and the extracts dried over magnesium sulfate and distilled. The product was 2.3 g. (11.4%) of 3-methyl-5-isopropyl-2-cyclohexenone, with a camphor-like odor only faintly like dill, b. p. 120–121° (12 mm.); $n^{20}\mathrm{D}$ 1.4865; sp. gr. $^{20}{}_{20}$ 0.928 (lit.,[22] 1.4890^{16} and 0.9390$^{15}{}_{15}$, respectively); *MR* calcd. (no exaltation), 45.8; *MR* found, 44.4. Ultraviolet absorption showed a maximum at 234.5 mμ (log ϵ 4.10, 0.006 g. per liter of 95% ethanol solution).

3-Ethyl-5-isopropyl-2-cyclohexenone (IX).—The procedure was that of the preceding experiment, using 5.2 g. (0.217 gram-atom) of magnesium, 26.0 g. (0.239 mole) of ethyl bromide and 100 ml. of dry ether for the Grignard reagent and 50.0 g. (0.274 mole) of 3-ethoxy-5-isopropyl-2-cyclohexenone. The impure product weighed 16.9 g. (47%), b. p. 113–115° (6 mm.); $n^{20}\mathrm{D}$ 1.4913. This yielded 16.9 g. of semicarbazone, tiny plates from ethanol, m. p. 147–149°.

Anal. Calcd. for $C_{12}H_{21}ON_3$: C, 64.54; H, 9.48. Found: C, 64.72; H, 9.70.

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(18) Ultraviolet absorption spectra were kindly determined by Mrs. J. C. Brantley using a Beckmann Model D spectrophotometer.

(19) Fieser and Hershberg, THIS JOURNAL, **62**, 49 (1940); see also "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 369.

(20) Brühl, *Ber.*, **32**, 1225 (1899).

(21) Kötz and Steinhorst, *Ann.*, **379**, 26 (1911).

(22) Knoevenagel, *Ann.*, **288**, 323 (1895).

Regeneration of the ketone as described above yielded 3.8 g. (10.5%) of colorless 3-ethyl-5-isopropyl-2-cyclohexenone, having a sweet odor faintly reminiscent of both camphor and dill, b. p. 123° (11 mm.); $n^{20}D$ 1.4862; sp. gr. $^{20}{}_{20}$ 0.927; *MR* calcd. (no exaltation), 50.5; *MR* found, 50.9. Ultraviolet absorption showed a maximum at 235 mμ (log ε 4.10, 0.006 g. per liter of 95% ethanol solution).

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.33; H, 11.18.

2,3-Dimethyl-5-isopropyl-2-cyclohexenone (X).—To a Grignard reagent prepared from 14.0 g. (0.61 gram-atom) of magnesium, 91.6 g. (0.63 mole) of methyl iodide and 200 ml. of dry ether was added with stirring over a period of thirty minutes 44.6 g. (0.29 mole) of 2-methyl-5-isopropyl-1,3-cyclohexanedione. Two hundred fifty milliliters of benzene was added, the ether distilled, and the mixture refluxed with stirring for five hours. It was then poured onto ice, acidified with hydrochloric acid, and filtered. The layers were separated, the water layer extracted with benzene, and the combined benzene solutions distilled in an eight-inch helix-packed column to give 11.5 g. of impure product, b. p. 80–111° (4 mm.). Reaction with 10 g. of semicarbazide hydrochloride yielded 6.7 g. of semicarbazone, rhombs from ethanol, m. p. 202–203°.

Anal. Calcd. for $C_{12}H_{21}ON_3$: C, 64.54; H, 9.48. Found: C, 64.83; H, 9.69.

Regeneration of the ketone as described above gave 2.1 g. (4.4%) of product, similar in odor to carvotanacetone but sweeter, b. p. 123° (12 mm.); $n^{20}D$ 1.4900; sp. gr. $^{20}{}_{20}$ 0.927; *MR* calcd. (no exaltation), 50.5; *MR* found, 51.8. Ultraviolet absorption showed a peak at 243.5 mμ (log ε 4.14, 0.006 g. per liter of 95% ethanol solution).

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.75; H, 11.14.

Summary

Cyclic 1,3-diketones such as 5-isopropyl-1,3-cyclohexanedione have been investigated as starting materials for the synthesis of monocyclic terpenes. It has been found that such diketones can be converted in good yields to 2-cyclohexenones by the intermediate formation of 3-chloro-2-cyclohexenones and subsequent reductive dehalogenation with zinc and potassium iodide or by reduction of their enol ethers by means of lithium aluminum hydride. *dl*-Carvotanacetone and a number of analogs of this natural terpene have been synthesized in the course of the investigation.

URBANA, ILLINOIS RECEIVED SEPTEMBER 6, 1949

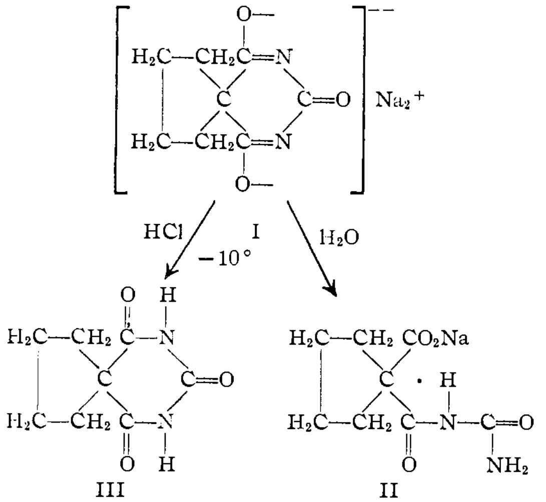
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF DELAWARE]

The Relative Instability of a C_5-Spirobarbituric Acid

BY GLENN S. SKINNER, GEORGE LIMPEROS AND RUSSELL H. PETTEBONE

The 1,1-dicarboxylic ester derivatives of cyclobutane and cyclohexane both yield stable spirocycloalkane-1,5'-barbituric acids.[1] The corresponding cyclopropane derivative, however, yields polymeric material.

It is significant that the esters having an even number of carbon atoms in the ring yielded barbituric acid derivatives which were stable under the vigorous conditions used in their preparation and the results suggest an alternation in the effect of the size of the ring. Accordingly, we condensed cyclopentane-1,1-dicarboxylic ester with urea under the mild conditions employed for the lactone esters.[2] A disodium salt (I) was formed with similar ease. The molecule of ethyl alcohol, however, did not remain when the sample was dried to constant weight under similar conditions. Moreover, in aqueous solution, the salt (I) decomposed rapidly into (II) with the cleavage of the barbituric acid ring. The barbituric ring remained intact while the other ring was opened when the condensation product from a lactone ester was treated similarly. By addition of the salt (I) to a freezing mixture of ice and hydrochloric acid the spirobarbituric acid (III) was obtained.



Δ³-Cyclopentene-1,1-dicarboxylic ester gave no monomeric barbituric acid and the ester itself underwent polymerization in the alkaline medium even in an atmosphere of hydrogen. The pure ester polymerized slowly. The following physical constants of a freshly distilled sample were determined for comparison with those of the saturated ester.

	$n^{25}D$	d^{25}
$(—CH_2CH_2—)_2C(CO_2C_2H_5)_2$	1.4390	1.0186
$(=CHCH_2—)_2C(CO_2C_2H_5)_2$	1.4500	1.0168

MR Calcd.	*MR* Found	$^a\eta^{25°}$	$^b\gamma^{25°}$	*P* Calcd.	*P* Found
54.93	54.70	0.03525	30.96	488.1	496.6
53.65	55.94	.04847	30.68	478.1	490.7

[a] Ostwald viscosimeter. [b] Capillary rise method.

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(1) Dox and Yoder, THIS JOURNAL, **43**, 677, 1366, 2097 (1921).

(2) Skinner, Stokes and Spiller, *ibid.*, **69**, 3083 (1947).