[Contribution from the Department of Chemistry, The Florida State University]

Hydrolysis of Certain ζ-Ketonitriles

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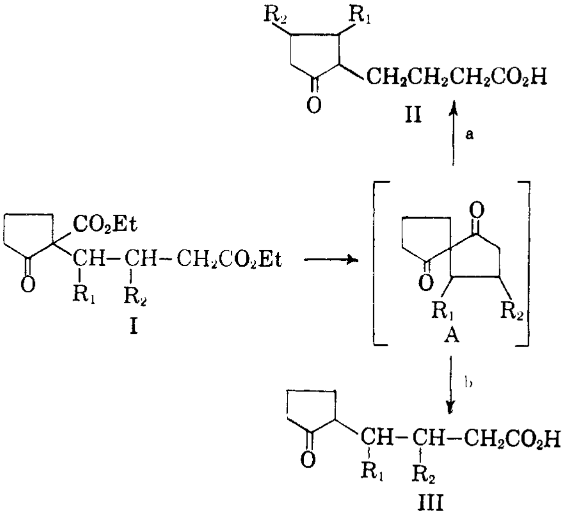
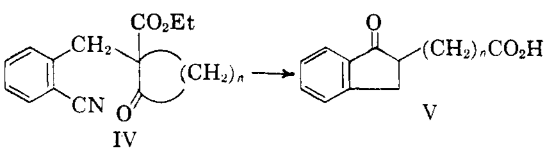
In contrast with their lower homologs, 5-(1-carbethoxy-2-oxocyclopentyl)valeronitrile and ethyl 2-keto-1-[β-(*o*-cyanophenyl)ethyl]cyclopentane carboxylate are hydrolyzed and decarboxylated by hydrochloric acid without rearrangement.

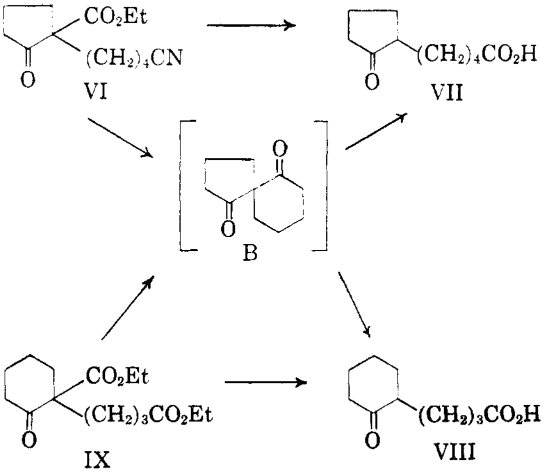
Earlier papers of this series[1,2] demonstrated that β-ketoesters of type I and IV on acid hydrolysis undergo rearrangement and furnish ε-ketoacids of type II and V respectively. The spirodiketone A was suggested as a possible intermediate for the first series of isomerizations; analogous diketones may be postulated for other such rearrangements.[3]

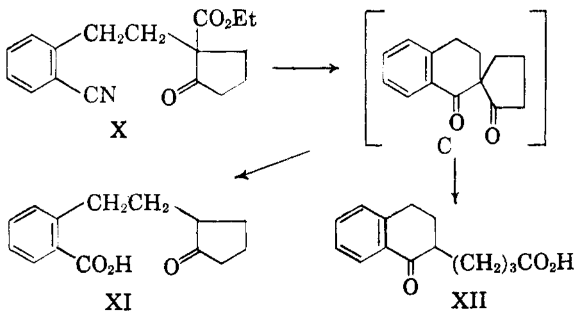
At first glance there appears to be no simple explanation for the implied assumption that the diketone A is cleaved preferentially by path *a* instead of *b*, unless the reaction is equilibrium rather than rate-controlled.[4] One must then ask why II should be favored over III. In the case of the aromatic ε-ketoacids obtained from IV, the increased stabilization which results when the carbonyl group is conjugated with the aromatic ring may conceivably be invoked as furnishing the driving force for the rearrangement.





In order to gain more information on the extent of the rearrangement it was decided to investigate the acid-catalyzed hydrolysis of two potential ζ-ketoacids, VI and X.[6] If the spirodiketones B and C are capable of formation under the conditions of the reaction, the possibility of isomerization is clearly indicated.





The results show that no rearrangement occurs when VI and X are refluxed with concentrated hydrochloric acid. The solid acid obtained by hydrolysis of VI melted at a temperature which corresponded to the melting point of the rearrangement product, 4-(2-oxocyclohexyl)butyric acid (VIII), but its infrared spectrum, a mixed melting point determination and the melting points of several derivatives clearly differentiated it from VIII and established its structure as VII. This was confirmed

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[1] W. Herz, *J. Am. Chem. Soc.*, **78**, 1485 (1956).

[2] W. Herz, *J. Am. Chem. Soc.*, **78**, 2529 (1956).

[3] F. Ramirez and A. P. Paul, *J. Am. Chem. Soc.*, **77**, 1035 (1955).

[4] But the alcoholysis of certain 1,3-diketones in the presence of hydrogen chloride which corresponds to the cleavage step above does not appear to be reversible.[5]

[5] H. Adkins, W. M. Kutz, and D. D. Coffman, *J. Am. Chem. Soc.*, **52**, 3212 (1930).

[6] The choice of these compounds was dictated by the relative ease of preparation as well as by the hope that any tendency to form the postulated intermediates (the spirodiketones or their imino analogs) would be enhanced if the carbethoxy group were replaced by the cyanide radical.

by Wolff-Kishner reduction of VII to the known 5-cyclopentylvaleric acid.

The structure of VIII would seem to be well authenticated since it has been prepared by three different methods.[7–9] In the course of the present work it was also prepared by acid hydrolysis of IX. This indicates that the spirodiketone B is not in equilibrium with VII or VIII under the conditions used since otherwise the same compound, or mixture of compounds, should have been obtained from VI *and* from IX.

The β-ketoester X was prepared in low yield by condensation of cyclopentanone carboxylic ester with β-*o*-cyanophenylethyl bromide which in turn was obtained from *o*-cyanohydrocinnamic acid by the Hunsdiecker reaction. Hydrolysis of X with concentrated hydrochloric acid resulted, as in an earlier instance,[2] in two products. The neutral fraction was identified as the nitrile corresponding to XI. The acidic fraction, a viscous oil, was not identical with 1-tetralone-2-butyric acid, m.p. 64–65°;[10] its infrared spectrum and the ultraviolet spectrum of its dinitrophenylhydrazone showed that the ketone group was not conjugated. The structure of the ketoacid must therefore be represented as XI which demonstrates that hydrolysis of X was not accompanied by rearrangement.

EXPERIMENTAL[11]

δ-(1-Carbethoxy-2-oxocyclopentyl)valeronitrile. To a suspension of 11.5 g. of powdered sodium in 400 ml. of toluene was added with heating and stirring 78 g. of ethyl cyclopentanone-2-carboxylate. After 2 hr. at reflux 81 g. of δ-bromovaleronitrile was added in one portion. The mixture was refluxed and stirred for an additional 18 hr., cooled, diluted with water and acidified with a little acetic acid. The toluene layer was separated and washed, dried and distilled. After a relatively large forerun containing starting material (mixture of nitrile and ester), the product was collected at 166–174° (2 mm.), wt. 43 g. (39%). The analytical sample boiled at 151–152° (0.5 mm.), n_D^{24} 1.4656.

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.37; H, 8.17; N, 5.94.

The semicarbazone, recrystallized several times from ethanol, melted at 154–156°.

Anal. Calcd. for $C_{14}H_{22}N_4O_3$: C, 57.12; H, 7.53. Found: C, 57.37; H, 7.51.

δ-(2-Oxocyclopentyl)valeric acid. A mixture of 40 g. of the preceding ester and 200 ml. of concentrated hydrochloric acid was refluxed for 20 hr., cooled, made basic, and extracted with ether. The aqueous layer was acidified and extracted with ether and the ether layer was dried and distilled. The product boiled at 163–168° (1.5 mm.), wt. 10.8 g. (35%). There was a considerable amount of high-boiling residue. The product crystallized on standing, After recrystallization from benzene-ligroin (b.p. 65–110°) it melted at 57–58°. The melting point of 4-(2-oxocyclohexyl)butyric acid is variously given as 57–58°,[7] 60–61°[8] and 56–57.5°.[9] The infrared spectrum, however, indicated that the compound was a cyclopentanone derivative (strong split carbonyl band with peaks at 1730 (cyclopentanone) and 1710 (carboxyl), and the derivatives melted generally higher than the corresponding derivatives of the cyclohexanone.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.25; H, 8.62.

The *semicarbazone* was recrystallized from ethanol in which it was rather insoluble, m.p. (capillary) 195–196° (dec.) with previous darkening, m.p. (Kofler) 207–208°.

Anal. Calcd. for $C_{11}H_{19}O_3N_3$: C, 54.75; H, 7.94; N, 17.42. Found: C, 54.84; H, 7.65; N, 16.9.

The *oxime* was recrystallized from ethanol-water and melted at 124–125.5.

Anal. Calcd. for $C_{10}H_7NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 59.79; H, 8.20; N, 6.64.

The *p-phenylphenacyl ester* was recrystallized from ethanol-water by taking up in a small amount of hot ethanol, allowing to cool, adding water to incipient cloudiness, adding a few drops of ethanol until the cloudiness had disappeared and allowing to stand. The colorless crystals melted at 71–72°.

Anal. Calcd. for $C_{24}H_{26}O_4$: C, 76.16; H, 6.93. Found: C, 76.37; H, 6.61.

δ-Cyclopentylvaleric acid. Reduction of 4 g. of the ketoacid by the procedure of Huang-Minlon[12] furnished 3.1 g. of an acid, b.p. 125–130° (2 mm.) [lit. 150–153 (9 mm.),[13] 149–150° (9 mm.)[14]], m.p. 9–10° (lit. 11°,[13] 12.5–14°[14], 14–15°[14]). The amide melted at 134–135° (lit. 138°,[13] 135–136°.[14]). The anilide melted at 78–79°, lit. 81°.[13] Mixed melting points with derivatives of authentic material prepared by the method of Coleman and coworkers[14] showed no depression.

Ethyl 4-(1-carbethoxy-2-oxocyclohexyl)crotonate. A suspension of 8.2 g. of potassium in 300 ml. of dry toluene was treated with 36 g. of cyclohexanone carboxylic ester and refluxed, with stirring, for 3 hr. A solution of 41 g. of ethyl γ-bromocrotonate in 50 ml. of toluene was then added dropwise. After 20 hr. at reflux, the mixture was worked up in the usual way and distilled, b.p. 166–174° (2.5 mm.), wt. 17.5 g. There was a considerable amount of high-boiling residue. The analytical specimen, b.p. 170–172° (2.5 mm.), n_D^{24} 1.4788, exhibited bands at 1730 and 1660 cm.$^{-1}$ in the double bond region of the infrared spectrum.

Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 64.29; H, 8.02.

The *semicarbazone* was recrystallized from ethanol-water (2:3) by seeding at room temperature and allowing to stand, m.p. 117–119°.

Anal. Calcd. for $C_{16}H_{25}O_5N_3$: C, 56.62; H, 7.43; N, 12.4. Found: C, 56.96; H, 7.59; N, 12.2.

Ethyl 4-(1-carbethoxy-2-oxocyclohexyl)butyrate. A solution of 14.5 g. of the unsaturated ester in 100 ml. of absolute ethanol was hydrogenated at 3 atm. (catalyst 5% palladium-on-charcoal) until hydrogen uptake ceased. The product was collected at 145–155° (1.5 mm.), wt. 11.2 g. The analytical sample boiled at 150–152° (1.5 mm.), n_D^{23} 1.4628.

Anal. Calcd. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.75; H, 8.58.

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(7) J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 817 (1937).

(8) W. Hückel and H. Naab, *Ann.*, **502**, 151 (1933).

(9) I. H. Nazarov and M. S. Burmistrova, *Zhur. Obshchei Khim.*, **20**, 1304 (1950).

(10) G. D. Johnson, W. B. Lindsey and B. R. Jones, *J. Am. Chem. Soc.*, **78**, 461 (1956). I am indebted to Dr. G. D. Johnson for furnishing me with an authentic sample of this compound.

(11) Melting and boiling points are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford, England. Infrared spectra were run by Miss Martha Brackett and Mr. Joseph Kovacic on a Perkin-Elmer Model 21 double beam instrument. Ultraviolet spectra were determined by Mrs. Shirley Ann Pinner and Dr. Enrico Clementi on a Beckman Model DK 1 recording spectrophotometer.

(12) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(13) M. M. Katsnelson and M. S. Kondakova, *Compt. rend. acad. sci.*, *URSS*, **17**, 367 (1937); *Chem. Abstr.* **32**, 7022 (1938).

(14) G. H. Coleman, J. E. Callen and C. A. Dornfeld, *J. Am. Chem. Soc.*, **68**, 1101 (1946).

The *semicarbazone*, m.p. 114–114.5°, was recrystallized from benzene-ligroin (b.p. 65–110°).

Anal. Calcd. for $C_{16}H_{27}N_3O_5$: C, 56.29; H, 7.97; N, 12.3. Found: C, 56.42; H, 7.72; H, 12.3.

4-(2-Oxocyclohexyl)butyric Acid. A mixture of 9.3 g. of the preceding ester and 75 ml. of concentrated hydrochloric acid was refluxed for 18 hr., cooled, made basic, extracted with ether, acidified, and again extracted with ether. The ether extract containing the acid fraction was dried and distilled; yield 4.1 g., b.p. 165–175° (3 mm.). The product solidified on standing and was recrystallized from petroleum ether (b.p. 30–60°) furnishing crystals of m.p. 57.5–59.5°, mixed m.p. with 5-(2-oxocyclopentyl)valeric acid 40–48°. The semicarbazone melted at 186–187° (lit. 185,[7] 189°,[8] 187–188°[9]). The oxime melted at 101–103° (lit. 101–103°,[8] 102–104°[7]). This ketoacid had only one strong band in the double bond region of the infrared spectrum (1710 cm.$^{-1}$, combination of carboxyl and cyclohexanone carbonyl).

β-o-Cyanophenylethyl bromide. o-Cyanocinnamic acid[15] was reduced catalytically (solvent absolute ethanol, catalyst 5% palladium-charcoal) to o-cyanodihydrocinnamic acid in 85–90% yield. The latter (16 g.) was converted to the silver salt by dissolving in the calculated amount of 1% sodium hydroxide solution and mixing with 170 g. (10% excess) of 10% silver nitrate solution. The precipitate was filtered, washed thoroughly with distilled water, ethanol, acetone, and ether, dried in a vacuum oven at 60° for one week and stored over phosphorus pentoxide; yield 23.5 g. (89%). The salt, wt. 40 g., was suspended in 150 ml. of dry carbon tetrachloride in a vessel protected from atmospheric moisture and a solution of 24 g. of dry bromine in 60 ml. of carbon tetrachloride was added with stirring and heating on the steam bath in the course of 3 hr. Stirring and heating was continued for an additional 4 hr. The mixture was cooled, filtered, washed with sodium bicarbonate solution, dried, and distilled; b.p. 111–116 (2 mm.), n_D^{23} 1.5719. The yields from several runs averaged 10 g. (34%); the bicarbonate washings yielded 1–3 g. of starting material.

Anal. Calcd. for C_9H_8BrN: C, 51.40; H, 3.84; N, 6.67. Found: C, 51.65; H, 3.92; N, 6.90.

Ethyl 2-keto-1-[β-(o-cyanophenyl)ethyl]cyclopentane carboxylate. To a suspension of 4.2 g. of potassium in 150 ml. of dry toluene was added 23.4 g. of cyclopentanonecarboxylic ester. After 5 hr. of stirring and heating a solution of 21 g. of β-o-cyanophenylethyl bromide in 75 ml. of toluene was added. Stirring and refluxing was continued for 3 days. The cooled mixture was diluted with water, acidified with acetic acid, the toluene layer washed with water, the aqueous washings were washed with ether, and the combined organic layers dried. The ether was removed and the residue was distilled in a short-path still. The first fraction, b.p. 75–120° (2 mm.), wt. 12.5 g. consisted primarily of cyclopentanonecarboxylic ester; the product, wt. 8.5 g. (30%), boiled unsharply in the range 190–195° because of pressure fluctuations arising from decomposition. Redistillation gave a colorless liquid, b.p. 180–185° (2 mm.), infrared bands at 2330 (CN) and 1730 cm.$^{-1}$ (shoulder at 1755 cm.$^{-1}$).

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.9. Found: C, 71.51; H, 6.65; N, 5.0.

The *semicarbazone* melted at 186.5–188° after three recrystallizations from aqueous ethanol.

Anal. Calcd. for $C_{18}H_{22}O_3N_4$: C, 63.14; H, 6.45; N, 16.4. Found: C, 62.95; H, 6.45; N, 16.4.

The above run represented the best of several similar condensations the yields from which varied widely but never exceeded 30%. Decomposition during the distillation was undoubtedly a factor, but the major reason for the low yields appeared to be dehydrohalogenation of the bromide under the influence of base. Thus an attempt to condense o-cyanophenylethyl bromide with the sodium derivative of cyclohexanonecarboxylic ester in t-butyl alcohol, a method which has been recommended for condensations with other phenylethyl bromides,[16,17] resulted in the isolation of a large fraction of b.p. 75–85° (2 mm.), which was a mixture of cyclohexanonecarboxylic ester and o-cyanostyrene (polymer formation on standing) as well as some high-boiling material which distilled over a wide range.

The condensation of o-cyanophenylethyl bromide with diethyl benzylmalonate was also investigated as the initial step in another projected synthesis. In addition to a 60% recovery of benzylmalonic ester and high-boiling residue, there was obtained a 55% yield of o-cyanostyrene, b.p. 95–102° (9 mm.), identified as the dibromide, m.p. 84.5–85.5° (lit. 86–86.5[18]).

2-β-(o-Cyanophenyl)ethylcyclopentanone. A mixture of 6.5 g. of the preceding β-ketoester and 30 g. of concentrated hydrochloric acid was refluxed for 12 hr., cooled, made basic, extracted with ether, acidified, and again extracted with ether. The neutral fraction was distilled to yield 2.4 g., b.p. 155–160° (2 mm.). The infrared spectrum had bands at 2230 (CN) and 1740 cm.$^{-1}$ (cyclopentanone).

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.59. Found: C, 78.94; H, 7.18; N, 6.80.

The *semicarbazone* was recrystallized from ethanol and melted at 204–205° (dec. slowly above 200°).

Anal. Calcd. for $C_{15}H_{18}N_4O$: C, 66.66; H, 6.71. Found: C, 66.36; H, 6.39.

The *2,4-dinitrophenylhydrazone*, orange-yellow crystals, (λ max 364 mμ), m.p. 151.5°, was recrystallized from benzene.

Anal. Calcd. for $C_{20}H_{19}N_5O_4$: C, 61.06; H, 4.87; N, 17.8. Found: C, 60.93; H, 4.94; N, 17.8.

2-β-(o-Carboxyphenyl)ethylcyclopentanone. The acid fraction from the preceding hydrolysis, crude wt. 1.8 g., could not be crystallized. It was distilled in a sublimator at a bath temperature of 190° (0.5 mm.). The infrared spectrum had bands at 1725 (cyclopentanone), 1695 (conjugated carboxyl) and 1408 cm.$^{-1}$  $(-CH_2-\underset{\underset{O}{\|}}{C}-)$ and differed considerably from the infrared spectrum of 1-tetralone-2-butyric acid, m.p. 64–65°, the possible rearrangement product which had bands at 1708 (carboxyl) and 1680 cm.$^{-1}$ (1-tetralone).

The analysis of the oil was low in carbon, but conversion to the 2,4-dinitrophenylhydrazone resulted in a satisfactory derivative.

The dinitrophenylhydrazone was chromatographed over alumina (solvent ethyl acetate). Ethyl acetate eluted a small amount of a yellow impurity; the major fraction was developed with 95% ethanol and eluted with 95% ethanol containing 2% acetic acid. Recrystallization from ethanol furnished golden-yellow needles m.p. 199–200° (dec.), whose ultraviolet spectrum (λ_{max} 364 mμ) showed that they were not derived from a conjugated ketone.

Anal. Calcd. for $C_{20}H_{20}N_4O_6$: C, 58.25; H, 4.89; N, 13.58. Found: C, 58.28; H, 4.79; N, 13.20.

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(18) C. S. Marvel and D. W. Hein, *J. Am. Chem. Soc.*, **70**, 1895 (1948).