[CONTRIBUTION FROM THE DEPARTMBNT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

Hydrolysis and Rearrangement of 2-Carbethoxy-2-(*o*-cyanobenzyl)-cycloalkanones

BY WERNER HERZ

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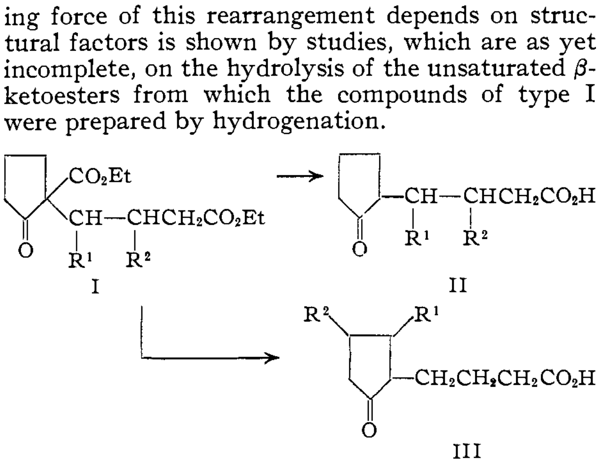
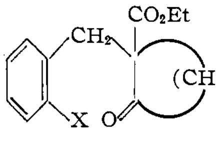
In an attempt to extend the scope of the rearrangement which occurs during the hydrolysis of certain β-keto-esters, 2-carbethoxy-2-(*o*-cyanobenzyl)-cyclopentanone and -cyclohexanone were subjected to acid hydrolysis. The products were derivatives of 1-indanone, presumably formed by rearrangement of the expected 2-*o*-carboxybenzylcycloalkanones.

An earlier article[1] described the discovery, incidental to our work on azulenes, that β-ketoesters of type I on acid hydrolysis undergo rearrangement and yield, not the expected ε-ketoacids II, but the isomeric ε-ketoacids III. That the driving force of this rearrangement depends on structural factors is shown by studies, which are as yet incomplete, on the hydrolysis of the unsaturated β-ketoesters from which the compounds of type I were prepared by hydrogenation.

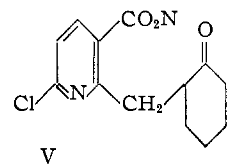


I II III

Because the demonstration of the rearrangement in the above series involved considerable difficulties, a simpler system was looked for. The hydrolysis of β-ketoesters of type IV where X is a potential carboxyl group was expected to provide compounds whose structure could be elucidated in a fairly simple manner and verified by synthesis. Indeed when Ramirez and Paul[2] subjected the closely related 2-(2′-oxocyclohexyl)-methyl-6-chloronicotinic acid (V) to treatment with acid, they became the first workers to observe such a rearrangement. The present paper describes the rearrangement which occurs when 2-carbethoxy-2-(*o*-cyanobenzyl)-cyclopentanone (VI) and 2-carbethoxy-2-(*o*-cyanobenzyl)-cyclohexanone (X) are hydrolyzed with mineral acids.



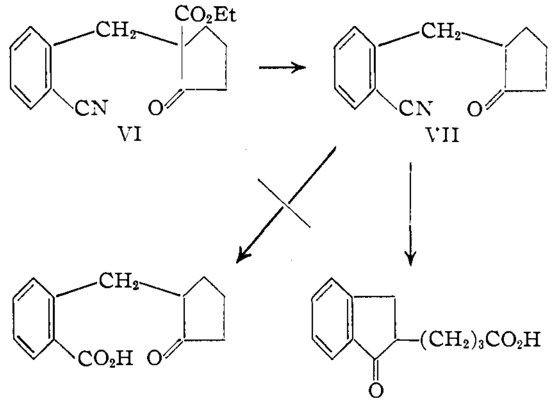
IV



V

The required compounds were synthesized in good to excellent yield by the condensation of α-bromo-*o*-tolunitrile with the appropriate 2-carbethoxycycloalkanone. When VI was hydrolyzed with concentrated hydrochloric acid, two products were isolated, a neutral compound $C_{13}H_{13}NO$ and an acid of the expected formula $C_{13}H_{14}O_3$. The neutral substance retained the cyano group, as evidenced by its infrared spectrum (C≡N frequency at 2210 cm.$^{-1}$)[3] and evolution of ammonia on boiling with base, as well as the cyclopentanone moiety (five-membered ring ketone at 1740 cm.$^{-1}$).[4] It is therefore 2-(*o*-cyanobenzyl)-cyclopentanone (VII). The acid was assigned the structure of γ-2-(1-indanone)-butyric acid (VIII), a rearrangement product, for the following reasons: (1) its infrared spectrum had only one strong carbonyl band centered at 1710 cm.$^{-1}$ and no band at 1400–1410 cm.$^{-1}$, whereas the "normal" product, 2-(*o*-carboxybenzyl)-cyclopentanone (IX), would be expected to exhibit a carbonyl doublet at 1740 and 1710 cm.$^{-1}$ and a band near 1400 cm.$^{-1}$ characteristic of $—CH_2—\underset{\underset{O}{\|}}{C}—$,[5] (2) its ultraviolet spectrum (λ_{max} 245, 288, 294) was typical of an indanone[6] and the *red* dinitrophenylhydrazone had λ_{max} 386 mμ typical of the absorption spectrum to be expected of the dinitrophenylhydrazone of an α,β-unsaturated ketone,[2,6] (3) cyclization of α-benzyladipic acid furnished, albeit in small yield, authentic γ-2-(1-indanone)-butyric acid whose properties were in all respects identical with the properties of the substance obtained by hydrolysis.

Further hydrolysis of VII by acid *and* by base yielded VIII, thus establishing the position of VII as a true intermediate in the conversion of VI to VIII. Attempts to isolate IX by hydrolysis of VI or VII with a limited amount of base failed, presumably because the isomerization of IX to VIII proceeds more readily than the hydrolysis of VII to IX.



VI VII IX VIII

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(1) W. Herz, THIS JOURNAL, **78**, 1485 (1956).

(2) F. Ramirez and A. P. Paul, *ibid.*, **77**, 1035 (1955).

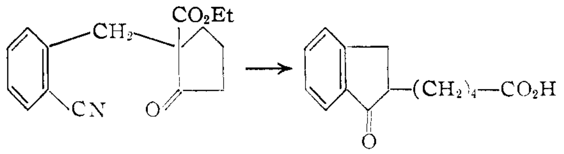
(3) D. G. F. Felton and S. F. D. Orr, *J. Chem. Soc.*, 2170 (1955).

(4) J. F. Grove and H. A. Willis, *ibid.*, 877 (1951).

(5) R. N. Jones and A. R. H. Cole, THIS JOURNAL, **74**, 5648 (1952).

(6) R. Huisgen and W. Rapp, *Chem. Ber.*, **85**, 826 (1952); D. Bisquard, *Bull. Soc. Chim. France*, (5) **8**, 55 (1941).

Hydrolysis of the homologous compound X with concentrated hydrochloric acid proceeded considerably more slowly than the hydrolysis of VI. Even prolonged boiling resulted in the recovery of much starting material. No neutral substance corresponding to VII was isolated. The only hydrolysis product, which was obtained in almost quantitative yield by using a mixture of hydrochloric and acetic acids, was identified as δ-2-(1-indanone)-valeric acid (XI).[7] The infrared spectrum had only one strong carbonyl band at 1700 cm.$^{-1}$ [8] and no band near 1400–1410 cm.$^{-1}$, the ultraviolet spectrum was entirely analogous to that of VIII (λ_{max} 247, 287, 295 mμ) and the *red* dinitrophenylhydrazone had a maximum at 384 mμ. Cyclization of α-benzylpimelic acid gave a 99% yield of authentic XI, identical in all respects with the hydrolysis product.



X XI

On the basis of these results it may be concluded that the rearrangement of ε-ketoacids is strongly favored when the formation of an indanone ring is possible.

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Experimental[9]

Ethyl *o*-Cyanobenzylcyclopentanone Carboxylate (VI).—To a dispersion of 6 g. of sodium sand in 400 ml. of dry toluene was added 39 g. of 2-carbethoxycyclopentanone. After 3 hr. of stirring and refluxing a solution of 49 g. of α-bromo-*o*-tolunitrile[10] in 200 ml. of dry toluene was added. The mixture was refluxed with stirring for 20 hr., cooled and diluted with water. The organic layer was washed, dried and distilled. The product was collected at 168–175° (1 mm.); yield 42 g. (62%). A middle cut, b.p. 170–171°, n^{23}D 1.5269, was reserved for analysis.

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32. Found: C, 70.51; H, 6.52.

The infrared spectrum (carbon tetrachloride solution) had peaks at 2210 cm.$^{-1}$ (conjugated C≡N), 1750 and 1730 cm.$^{-1}$ (carbethoxy group and five-membered ring ketone).

The semicarbazone melted at 178–179° after several crystallizations from ethanol.

Anal. Calcd. for $C_{17}H_{20}N_4O_3$: C, 62.18; H, 6.14. Found: C, 62.44; H, 5.97.

Acid Hydrolysis of VI.—A mixture of 42 g. of VI and 220 ml. of concentrated hydrochloric acid was refluxed for 12 hr., cooled, made basic and extracted with ether. Acidification of the aqueous layer gave an oil which solidified on standing, wt. 12.5 g (37%). The solid was taken up in ethanol, treated with charcoal, filtered, cooled, diluted with water until saturated at room temperature and chilled. The plates which separated were recrystallized twice more in a similar manner and then melted at 73–73.5°. The infrared spectrum (CCl_4 solution) exhibited typical carboxyl-OH absorption in the 3000–3600 cm.$^{-1}$ region and a strong asymmetrical carbonyl band near 1710 cm.$^{-1}$. There was no $-CH_2-\underset{\underset{O}{\|}}{C}-$ band at 1400–1410 cm.$^{-1}$. The ultraviolet spectrum (95% ethanol) had maxima at 245 mμ (ε 11700), 288 and 294 mμ.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.47; H, 6.26.

The semicarbazone was prepared by mixing a solution of 1.0 g. of VIII in 5 ml. of water and 0.4 g. of potassium carbonate with 0.8 g. of semicarbazide hydrochloride in 2 ml. of water. The oil which separated solidified on standing. Several recrystallizations from ethanol furnished crystals which decomposed at 238–239° with previous darkening.

Anal. Calcd. for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22. Found: C, 61.21; H, 6.07.

The dinitrophenylhydrazone, prepared by the method of Shriner and Fuson,[11] melted unsharply and was separated into two distinct fractions by chromatographing over alumina. The ethyl acetate used as solvent eluted a component melting at 142.5–144° after repeated crystallization from ethanol. The color varied from orange-red to scarlet depending on the conditions of crystallization. The ultraviolet spectrum had λ_{max} 382 mμ (ε 32100), indicating the presence of an α,β-unsaturated ketone chromophore.[12] Analysis showed that the substance was the ethyl ester of the expected derivative.

Anal. Calcd. for $C_{21}H_{22}N_4O_6$: C, 59.15; H, 5.20; N, 13.14. Found: C, 59.65; H, 5.00; N, 13.00.

The more strongly adsorbed component was developed with ethanol and eluted with ethanol containing 3% glacial acetic acid. Several recrystallizations from ethanol furnished crystals of m.p. 210–211° whose color varied from ochre to scarlet depending on the conditions of crystallization. The ultraviolet spectrum (λ_{max} 386 mμ, ϵ_{max} 25600) indicated that it was derived from an α,β-unsaturated ketone.[12]

Anal. Calcd. for $C_{19}H_{18}N_4O_6$: C, 57.28; H, 4.55. Found: C, 57.26; H, 4.62.

The phenylphenacyl ester melted at 97–98.5° after crystallization from ethanol.

Anal. Calcd. for $C_{27}H_{24}O_4$: C, 78.62; H, 5.86. Found: C. 78.31; H, 5.71.

2-(*o*-Cyanobenzyl)-cyclopentanone (VII).—The neutral ether extract from the acid hydrolysis of VI was dried and distilled, furnishing 16.6 g. (54%) of a fraction, b.p. 140–145° (0.8 mm.). The analytical sample boiled at 140–142° (0.8 mm.), n^{23}D 1.5482. The infrared spectrum exhibited bands at 2210 cm.$^{-1}$ (aromatic C≡N), 1740 cm.$^{-1}$ (cyclopentanone) and, *inter alia*, a relatively strong band at 1408 which may be ascribed to $-CH_2\underset{\underset{O}{\|}}{C}-$.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.53; N, 7.0. Found: C, 78.13; H, 6.53; N, 6.7.

In subsequent runs the relative proportions of VII and VIII varied somewhat, depending on the reflux period and the amount of acid used, but the total yield of acidic and neutral products remained at 80–85%.

Basic Hydrolysis of VII.—Three grams of VII was refluxed with 1.2 g. of sodium hydroxide in 22 ml. of water until the solution became clear and ammonia evolution ceased. The basic solution was extracted with ether, neutralized cautiously to *p*H 6 and allowed to stand. During this period the heavy oil which had separated on acidification gradually crystallized, wt. 2.9 g. Repeated slow crystallization from a benzene–ligroin mixture furnished crystals which sintered at 78–80° and melted at 83–84°. Subsequent runs gave

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(7) The increase in yield seems to be due entirely to greater solubility in the mixed solvent since acetic acid alone had no effect on VI.

(8) The location of this band does not permit a decision between the "normal" structure and XI since the former, 2-(*o*-carboxybenzyl)-cyclohexanone, would also be expected to show only one carbonyl band near 1700 cm.$^{-1}$ (composite of carboxyl and 6-membered ring ketone).

(9) Melting points and boiling points are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford. Infrared spectra were run by Mr. Dean S. Keeley and Miss Martha Brackett on a Perkin-Elmer Model 21 instrument. Ultraviolet spectra were run by Mrs. Shirley Ann Pinner on a Beckman Model DK automatic recording spectrophotometer.

(10) Fa-Ki Tcheou, Yu-Tsun Shih and Kwan-Liang Lee, *J. Chinese Chem. Soc.*, **17**, 150 (1950).

(11) R. L. Shriner and R. C. Fuson, "Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

(12) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold, Ltd., London, 1954, p. 106.

material which melted variously at 73–76°, 81–83° and 80–82° depending on the speed of crystallization which could not be duplicated accurately. Mixed m.p. determinations of the various products with each other and with the acid hydrolysis product resulted in a m.p. at or just below the m.p. of the higher melting component. Infrared spectra of all fractions were identical and each product gave the two dinitrophenylhydrazones described earlier in approximately the same amounts, the same semicarbazone and the same *p*-phenylphenacyl ester.

Cyclization of α-Benzyladipic Acid.—A mixture of 11.8 g. of α-benzyladipic acid[13] and 50 ml. of thionyl chloride was heated on the steam-bath for several hours. Excess thionyl chloride was removed *in vacuo*, the acid chloride was dissolved in 200 ml. of nitrobenzene and mixed with 13.4 g. of anhydrous aluminum chloride. The mixture was decomposed with ice and steam distilled. The material remaining in the flask was chilled. This resulted in the separation of 11 g. of black viscous gum mixed with a few crystals. It was extracted with dilute base, the base was extracted with ether, acidified and chilled. A blackish semi-solid mixed with crystalline material separated. It was taken up in hot benzene, filtered, treated with charcoal, filtered, allowed to cool and diluted with high-boiling petroleum ether. A brown gum separated. The solution was decanted, diluted with more petroleum ether (b.p. 65–110°) and allowed to stand. As the benzene evaporated, crystalline material separated.

Another crystallization, carried out in the same manner, furnished 0.85 g. of crystals, m.p. 73–74°, whose infrared spectrum was identical with that of VIII. A mixed m.p. was not depressed. Treatment with dinitrophenylhydrazine gave the two derivatives of m.p. 142.5–144° and 210–211° which did not depress the m.p. of the dinitrophenylhydrazones of the hydrolysis product.

The use of polyphosphoric acid for this cyclization[14] resulted in the formation of acidic gums from which we were unable to isolate VIII.

Ethyl *o*-Cyanobenzylcyclohexanone Carboxylate (X).—Condensation of 49 g. of α-bromotolunitrile with the sodio derivative prepared by refluxing 43 g. of 2-carbethoxycyclohexanone and 6 g. of sodium in toluene in the manner described for 2-carbethoxycyclopentanone furnished 61.5 g. (86%) of a fraction, b.p. 190–195° (2.5 mm.) which solidified on standing. Recrystallization from a benzene–ligroin mixture furnished rhombohedral crystals, m.p. 77.5–79°. The infrared spectrum exhibited a band at 2230 cm.$^{-1}$ (C≡N) and a broad band centered at 1715 cm.$^{-1}$ (composite of keto and ester groups).

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 72.57; H, 6.81. Found: C, 72.38; H, 6.41.

The semicarbazone was recrystallized from ethanol and melted at 207.5–208°.

Anal. Calcd. for $C_{18}H_{22}N_4O_2$: C, 63.14; H, 6.48. Found: C, 63.05; H, 6.46.

Hydrolysis of X.—A solution of 3.5 g. of X, 30 ml. of acetic acid and 30 ml. of concentrated hydrochloric acid was refluxed for 18 hr. The solvent was removed *in vacuo*, the residue was diluted with water, made basic and extracted with ether. The ether layer on evaporation yielded a very small amount of residue. Acidification of the aqueous layer precipitated 3.3 g. of a solid which was recrystallized repeatedly from ethanol. The large plates melted at 92.5–94.5°.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.11; H, 6.85.

The infrared spectrum (chloroform solution) exhibited a strong, somewhat asymmetric band at 1700 cm.$^{-1}$ (composite of conjugated cyclopentenone and carboxyl). The ultraviolet spectrum (95% ethanol) was typical of an indanone (λ_{max} 244, 287, 295, ϵ_{max} 11900, 2210, 2200).

The dinitrophenylhydrazone was purified by passing it through an alumina column (solvent and eluent ethyl acetate). Only one zone was observed. Recrystallization from ethyl acetate furnished crystals, m.p. 140.5–142°, whose ultraviolet spectrum in 95% ethanol (λ_{max} 384 mμ, ϵ 29600) was typical of an indanone dinitrophenylhydrazone. Analysis showed that the substance was the ethyl ester of the expected derivative, as in the case of the lower homolog.

Anal. Calcd. for $C_{22}H_{24}N_4O_6$: C, 59.99; H, 5.49; N, 12.7. Found: C, 59.76; H, 5.47; N, 12.9.

The semicarbazone was recrystallized from absolute ethanol. It melted at 223–224° (gas evolution) with previous darkening.

Anal. Calcd. for $C_{15}H_{19}N_3O_3$: C, 62.26; H, 6.62. Found: C, 61.99; H, 6.34.

The *p*-phenylphenacyl ester melted at 92.5–94° after crystallization from ethanol, mixed m.p. with XI 82–90°.

Anal. Calcd. for $C_{28}H_{26}O_4$: C, 78.85; H, 6.14. Found: C, 78.55; H, 5.89.

Hydrolysis of X with concentrated HCl alone usually resulted in recovery of much starting material. In a typical experiment, 9.6 g. of X was refluxed with 100 ml. of concd. hydrochloric acid for 20 hr. At intervals of 5 hr., 25-ml. portions of fresh hydrochloric acid were added. Separation of the organic product into neutral and basic fractions yielded 5.5 g. of starting material and 1.8 g. of δ-2-(1-indanone)-valeric acid. Attempted hydrolysis of X with glacial acetic or 50% acetic acid resulted in quantitative recovery of starting material.

Cyclization of α-Benzylpimelic Acid.—Benzylpimelic acid,[15] wt. 8.7 g., was converted to the acid chloride and cyclized with aluminum chloride as described previously. The brown material, wt. 8.0 g. (99%) which remained after steam distillation of the reaction mixture crystallized on chilling. Recrystallization from ethanol–water furnished plates melting at 92–94°, mixed m.p. with hydrolysis product 92–94°. Dinitrophenylhydrazones, semicarbazones and phenylphenacyl esters also were identical.

TALLAHASSEE, FLORIDA

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[13] D. A. Duff and C. K. Ingold, *J. Chem. Soc.*, 87 (1934); R. Cornubert, P. Anziani and G. Morelle, *Bull. soc. chim.*, [5] **11**, 299 (1944).

[14] J. Koo, THIS JOURNAL, **75**, 1891 (1953).

[15] J. W. Cook and C. L. Hewett, *J. Chem. Soc.*, 62 (1936).