[CONTRIBUTION FROM THE GEORGETOWN UNIVERSITY MEDICAL CENTER]

KETO-LACTOL TAUTOMERISM OF ALICYCLIC DELTA-KETO ACIDS[1, 2]

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We have previously noted that the Clemmensen reduction of 1-phenyl-4-ketocyclohexanecarboxylic acid (I) resulted in a high yield of the ester (IIa) (1).[3] The unexpected esterification in dilute solution of the sterically hindered carboxyl group was in such marked contrast to our experience with similarly constituted compounds that a further study of this and related substances was undertaken.

Since the reduced acid, (IIb) showed the expected resistance to esterification it seemed reasonable to assume that the unusual behavior of I resided in the relation of the *delta*-ketone and carboxyl groups. Although many examples of keto-lactol tautomerism of suitably constituted γ- and δ-keto aliphatic and aryl acids have been described, (2), similar relationships in purely alicyclic compounds are less well known. That the carbonyl and carboxyl groups in I partake in a keto-lactol tautomerism has been demonstrated in two ways. Reaction of I with acetyl chloride for two hours at room temperature resulted in the formation of the acetyllactol, (IIIa). Reaction of I with ethereal diazomethane gave two methyl esters, (IIIb) and (IV).[4] The lower-melting product, m.p. 77–78°, was found to be identical with the ester prepared by reaction of the sodium salt with methyl iodide or by esterification with methanol in the presence of an acid catalyst. It has accordingly been assigned the structure of a normal ester, (IV). The higher-melting ester, m.p. 110–111°, could also be prepared by reaction of I with thionyl chloride followed by treatment with methanol and pyridine. This procedure has been previously utilized for the preparation of pseudo esters (3). In agreement with the formulation of this product as the pseudo ester, (IIIb), it has been found to be readily convertible to the normal ester (IV) by acid catalysis. This conversion is characteristic of pseudo esters.

Esterification of I could be effected in 60% yield by a 60-hr. reflux in 30% methanol solution containing some hydrochloric acid.[4] In consideration of the fact that I has been shown capable of reacting in either the keto or the lactol form, two possibilities may be considered for the anomalous esterification in dilute alcohol solution. Acid-catalyzed reaction of the keto form (I) with meth-

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[1] Supported by the Geschickter Fund for Medical Research, Inc.

[2] Presented at the Chicago meeting, American Chemical Society, September 3–8, 1950, before the Division of Organic Chemistry.

[3] The Clemmensen reduction of fluorylpropionic acid in aqueous alcohol resulted in the formation of a neutral product which was "boiled with one liter of 5% sodium hydroxide until dissolved." The nature of the material and the implications of its formation do not seem to have been noted [Koelsch, *J. Am. Chem. Soc.*, **55**, 3885 (1933)].

[4] Newman and McCleary obtained only the normal ester upon reaction of 2-benzoylbenzoic acids with diazomethane (3).

anol to give the hemiketol, (V), with subsequent stabilization of this intermediate by lactonization has some analogy in the chemistry of the acetone sugar derivatives and in the ready lactonization in dilute acids of δ-hydroxy acids. Rearrangement of the pseudo ester (IIIb) to the normal ester (IV) has been demonstrated as we have indicated above.

The second possibility of direct etherification of the lactol form, (IIIc), to the pseudo ester, (IIIb), is considered to be a less likely reaction sequence.

A previously observed increase in the reactivity between a γ-ketone and carboxyl groups as a function of increasing hindrance around the carboxyl group (3) finds analogy in this work. In the series of hydrogen, methyl, and phenyl substitution adjacent to the carboxyl group the ease of esterification increases with the size of the substitution (Table I). γ-Carboxypimelic acid, required for the preparation of 4-ketocyclohexanecarboxylic acid, was readily obtained by acid hydrolysis of γ-cyano-γ-carbethoxypimelonitrile, the cyanoethylation product of ethyl cyanoacetate (4).

TABLE I

ESTERIFICATION OF SUBSTITUTED 4-KETOCYCLOHEXANECARBOXYLIC ACIDS,

ESTERIFICATION, %

R	C_6H_5	CH_3[a]	H[b]
30% MeOH, 6 hr. reflux	35	30	20
50% MeOH, 6 hr. reflux	50	43	28
30% MeOH, 60 hr. reflux	60		

[a] Rubin and Wishinsky, *J. Am. Chem. Soc.*, **68**, 338 (1946).

[b] Perkin, *J. Chem. Soc.*, **85**, 424 (1904).

EXPERIMENTAL

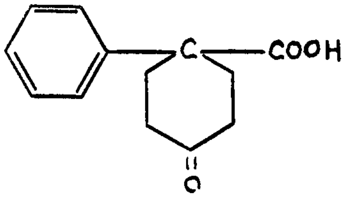
γ-Carboxypimelic acid. A mixture of 657 g. of γ-cyano-γ-carbethoxypimelonitrile (4) and 2.51 cc. of conc'd hydrochloric acid was refluxed for 12 hours. The solution was concentrated to dryness *in vacuo* and the residue extracted four times with ether. Concentration of the ethereal extract and recrystallization of the product from conc'd hydrochloric acid gave the tri-acid, m.p. 115–116° in 90% yield.

Reaction of 1-phenyl-4-ketocyclohexanecarboxylic acid (I) with acetyl chloride. On treatment of 1.0 g. of I with 5 cc. of acetyl chloride, hydrogen chloride was evolved and the acid went into solution. At the end of two hours the mixture was poured into ice, extracted with ether, and washed free of acidic material (0.3 g.) with sodium carbonate solution. Concentration of the neutral ether extract left a crystalline residue (0.5 g.) which melted at 149–150° on recrystallization from petroleum ether-ethyl acetate solution.

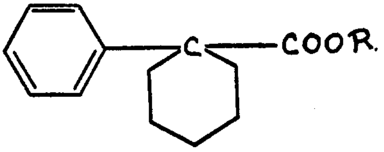
Anal. Calc'd for $C_{15}H_{16}O_4$: C, 69.23; H, 6.15; Sapon. equiv., 123.

Found: C, 69.31; H, 6.19; Sapon. equiv., 129.

Reaction of I with diazomethane. The reaction of 1 g. of I with excess ethereal diazomethane was vigorous and rapid. After standing for two hours at room temperature the excess diazomethane was removed by co-distillation with the ether. The product was taken up in ether, washed with bicarbonate solution and water, dried over magnesium sulfate, and concentrated to dryness.



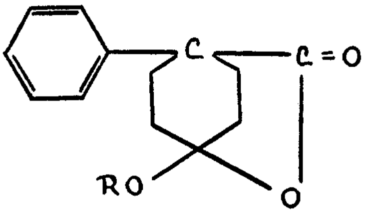
I



II

a) R = C_2H_5

b) R = H

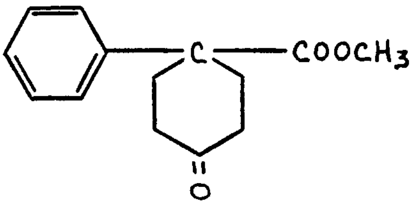


III

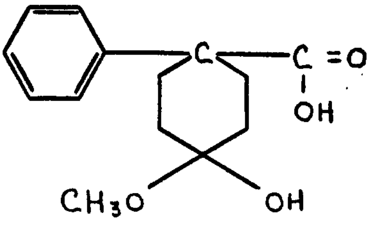
a) R = CH_3CO

b) R = CH_3

c) R = H



IV



V

Extraction of the residue with hot 60–90° petroleum ether gave a soluble fraction, m.p. 78–79°. This was the *normal* ester.

Anal. Calc'd for $C_{14}H_{16}O_3$: C, 72.4; H, 6.95.

Found: C, 72.4; H, 6.72.

The petroleum ether-insoluble fraction was recrystallized from ethyl acetate-pet. ether, m.p. 112–113°.

Anal. Calc'd for $C_{14}H_{16}O_3$; C, 72.4; H, 6.95.

Found: C, 72.4; H, 6.84.

Preparation of the normal ester (IV). *Methyl iodide on the sodium salt.* To a solution of 10 g. of I in 100 ml. of methanol was added a stoichiometric quantity of sodium methoxide. After 15 minutes an excess of methyl iodide was added and the mixture was refluxed until neutral. The alcohol and excess halide were removed by ditillation *in vacuo*, the residue was treated with water and extracted with ether. The extracts were washed with carbonate solution and water, dried over magnesium sulfate, and concentrated to dryness. The product, 8 g. (78%), m.p. 78–79°, showed no melting point depression on admixture with the low-melting product of the diazomethane reaction.

Psuedo ester formation (IIIb). To 5 g. of I in 20 ml. of dry benzene was added 10 ml. of purified thionyl chloride. After standing for several hours the mixture was refluxed for one hour and the excess thionyl chloride removed by distillation with the benzene *in vacuo*. The residue was treated dropwise with 30 ml. of a 50% mixture of methanol and pyridine. After reflux for one-half hour the mixture was poured into ice, extracted with ether, and the extracts washed with 3 *N* hydrochloric acid followed by sodium carbonate solution and water. Concentration of the ethereal solution gave an oil which crystallized slowly from ethyl acetate-petroleum ether. Recrystallization gave 2.0 g. of product, m.p. 110–111° (39%), which showed no mixed melting point depression with the high-melting fraction from the diazomethane reaction.

Rearrangement of the pseudo ester to the normal ester. A mixture of 1.0 g. of IIIb and 10 ml. of 10% hydrochloric acid was refluxed for four hours. Workup in the usual manner gave a quantitative yield of the normal ester, (IV), m.p. 78–79°.

Esterification studies. Weighed quantities (1 g.) of the crystalline acids were heated simultaneously, under reflux, with 10 cc. of methanolic solutions of the given strength containing 0.7 cc. of conc'd hydrochloric acid for the stated periods. The solutions were then poured into ice and sodium carbonate solution, the mixtures were extracted with ether, and the ethereal extracts were washed free of acidic material with sodium carbonate solution and concentrated on a water-bath. The residual oils were then heated for a short time at 0.1 mm. to remove traces of water. The percentage esterification was calculated from the weight of neutral material. In several instances the acidic fraction was recovered and weighed. Over-all recoveries were very nearly quantitative.

SUMMARY

1. Evidence for the existence of keto-lactol tautomerism in 1-phenyl-4-ketocyclohexanecarboxylic acid has been presented.

2. The normal and pseudo methyl esters have been prepared.

3. Some of the factors in the anomalous esterification in dilute alcohol of 4-ketocyclohexanecarboxylic acids have been studied and a reaction sequence suggested.

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