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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF DUKE UNIVERSITY AND WAKE FOREST COLLEGE]

Influence of Ring Size and 2-Methyl Substituent on Two Modes of Alkaline Cleavage of 2-Acylcyclanones. Acylations of Cycloheptanone and Cyclooctanone[1]

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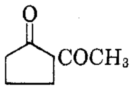
Received November 17, 1958

A semiquantitative study was made of the two possible modes of alkaline cleavage of the 2-acetyl derivatives of cyclopentanone, cyclohexanone, cycloheptanone, and cyclooctanone. 2-Acetylcyclopentanone underwent largely ring opening and 2-acetylcyclohexanone, mainly ring opening. However, only side chain cleavage was realized with 2-acetylcycloheptanone and 2-acetylcyclooctanone. Also, only side chain cleavage was observed with 2-benzoylcycloheptanone and 2-benzoylcyclooctanone. The 2-methyl derivatives of 2-acetylcyclopentanone and 2-acetylcyclohexanone underwent relatively less ring opening than the corresponding unsubstituted 2-acetylcyclanones. The boron fluoride–acid anhydride and the sodium amide–acid chloride methods of acylation of ketones were extended to cycloheptanone and cyclooctanone.

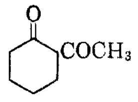
An earlier study[3] has indicated that 2-acetylcyclopentanone (I) undergoes ring opening with alkali to form keto acid II to a relatively greater extent than does 2-acetylcyclohexanone (III), to give keto acid IV.



I

$CH_3CO(CH_2)_4COOH$

II

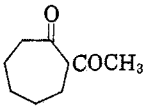


III

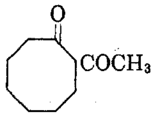
$CH_3CO(CH_2)_5COOH$

IV

This indicated influence of ring size on the two possible modes of alkaline cleavage has now been confirmed and extended employing not only the 2-acylcyclanones I and III but also 2-acetylcycloheptanone (V) and 2-acetylcyclooctanone (VI).



V



VI

In Table I are summarized the yields of the keto acids and of the ketones obtained on cleaving the β-diketones I, III, V, and VI with hot 10% sodium hydroxide. The ketones were isolated as their 2,4-dinitrophenylhydrazones from duplicate experiments carried out on the 0.1-mole scale. Blank experiments indicated that the yields were reproducible within ± 2%. The keto acids were isolated by distillation from experiments carried out on the 0.5-mole scale. The yields of keto acids II and IV given in Table I were obtained in three runs and two runs, respectively.

It can be seen from Table I that ring opening occurred in 85–90% yield with 2-acetylcyclopentanone and in 60–64% yield with 2-acetylcyclohexanone, but that only side chain cleavage was observed with 2-acetylcycloheptanone and 2-acetylcyclooctanone. Thus, the relative extent of the alkaline cleavage at *a* in VII decreased progressively and that at *b* increased as the size of the ring was increased from five to six carbon atoms and from six to seven or eight carbon atoms. Moreover there was a sharp

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[1] Supported in part by the National Science Foundation.

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[3] C. R. Hauser, F. W. Swamer, and B. I. Ringler, *J. Am. Chem. Soc.*, **70**, 4023 (1948).

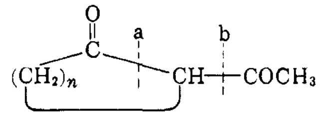
TABLE I

YIELDS OF KETO ACIDS AND KETONES FROM ALKALINE CLEAVAGES OF 2-ACETYLCYCLANONES

2-Acetyl-cyclanones	Keto Acid	Yield, %	Ketone	Yield, %	DNPH[a] M.P., °C.	Lit.[b] M.P.
I	II	85–90	Cyclopentanone	2–5	144–145	142
III	IV	60–64	Cyclohexanone	30–32	158–161	162
V			Cycloheptanone	95–98	148–150	148
VI			Cyclooctanone	96–99	174–176[c]	

[a] 2,4-Dinitrophenylhydrazone on which the yield of ketone is based. [b] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 316. [c] A sample melting at 176–177° was analyzed. *Anal.* Calcd. for $C_{14}H_{18}N_4O_4$; C, 54.89; H, 5.92; N, 18.29. Found: C, 54.79; H, 6.31, N, 18.42.

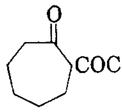
break in the mode of cleavage in passing from the six atom ring to the seven atom ring.



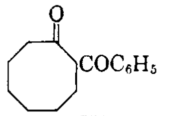
VII

These results are in line with what might be anticipated on the assumption that the mode of cleavage is dependent on the relative reactivity in each case of the ring carbonyl group *versus* that of the side chain carbonyl group towards the hydroxyl ion. The reactivity of the former group might be expected to be relatively decreased by a shielding effect due to puckering as the ring size is increased. An examination of molecular models appeared to be in agreement with this.

Similarly 2-benzoylcycloheptanone (VIII) and 2-benzoylcyclooctanone (IX) underwent cleavate at the side chain to form benzoic acid in yields of 94% and 96%, respectively. Presumably the corresponding ketones were also produced.

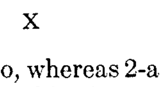


VIII

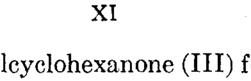


IX

It was further found that the 2-methyl derivatives of 2-acetylcyclopentanone and 2-acetylcyclohexanone undergo relatively less ring opening on alkaline cleavage than the corresponding unsubstituted 2-acylcyclanones. Thus, whereas 2-acetylcyclopentanone (I) gave keto acid II in 85–90% yield, the 2-methyl derivative X produced the keto acid XI in 65% yield under similar conditions.



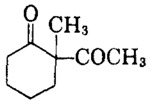
X



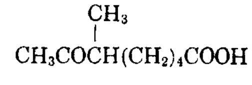
$$CH_3CO\overset{CH_3}{\overset{|}{C}}H(CH_2)_3COOH$$

XI

Also, whereas 2-acetylcyclohexanone (III) formed keto acid IV in 60–64% yield, the 2-methyl derivative XII afforded keto acid XIII in only 25% yield under similar conditions, and a 54% yield of 2-methylcyclohexanone was obtained.



XII



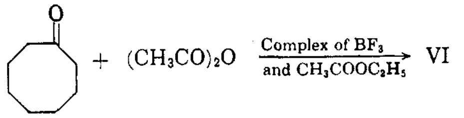
$$CH_3CO\overset{CH_3}{\overset{|}{C}}H(CH_2)_4COOH$$

XIII

These results indicate that the 2-methyl group presents a greater shielding effect at the ring carbonyl group than at the side chain carbonyl group.

Acylations of cycloheptanone and cyclooctanone. In connection with the alkaline cleavages considered above, several new acylations of cyclanones were effected.

Cycloheptanone and cyclooctanone were acylated with aliphatic anhydrides by means of the boron fluoride–ethyl acetate complex that has previously been found particularly suitable for cyclopentanone and cyclohexanone.[4,5] The reaction may be illustrated by the acetylation of cyclooctanone (Equation 1).



(1)

In Table II are summarized the yields and other data for these acylations. Also in this table is given a new result with cyclopentanone. It can be seen that the yields are quite satisfactory (50–75%). One of the products, 2-acetylcycloheptanone (V), has recently been prepared[6] in 62% yield by the original boron fluoride method of Meerwein and Vossen.[7]

Cycloheptanone and cyclooctanone were benzoylated by the sodium amide–acid chloride method which has recently been developed[8] for the benzoylation of cyclopentanone and for certain other acylations that have been difficult to effect by the more common procedures. The reaction may be illustrated with cyclooctanone (Equation 2).

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(4) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, VIII, 106, 131 (1954).

(5) R. M. Manyik, F. C. Frostick, J. J. Sanderson, and C. R. Hauser, *J. Am. Chem. Soc.*, **75**, 5030 (1953).

(6) E. Buchta and J. Kronz, *Angew. Chem.*, **67**, 77 (1955).

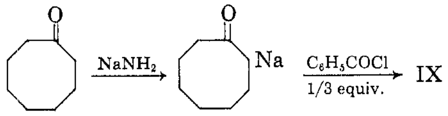
(7) H. Meerwein and D. Vossen, *J. prakt. Chem.*, **141**, 149 (1934).

(8) B. O. Linn and C. R. Hauser, *J. Am. Chem. Soc.*, **78**, 6066 (1956).

TABLE II

PREPARATION OF 2-ACYLCYCLANONES FROM CYCLANONES AND ALIPHATIC ANHYDRIDES BY BORON FLUORIDE–ETHYL ACETATE COMPLEX

2-Acylcyclanones	Yield, %	B.P., °C.	Mm.	n_D^{25}	Calcd C	Calcd H	Found C	Found H
2-Acetylcycloheptanone (V)	74	90–92	5	1.5050	70.10	9.15	70.44	9.31
2-Propionylcycloheptanone	58	102–105	5	1.4962	71.39	9.59	71.42	9.66
2-(2-Ethylbutyryl)cycloheptanone	50	102–104	2	1.4908	74.24	10.54	74.45	10.39
2-Acetylcyclooctanone (VI)	75	102–105	5	1.5113	71.39	9.59	71.55	9.64
2-Propionylcyclooctanone	62	113–114	5	1.5063	72.49	9.95	72.49	9.95
2-(2-Ethylbutyryl)cyclopentanone	55	80–83	2	1.4798	72.49	9.95	72.72	10.06



(2)

Most of the excess ketone employed in this method was recovered. It is possible that the benzoylations of cycloheptanone and cyclooctanone could also be effected satisfactorily with phenyl benzoate or methyl benzoate by the more common sodium amide or sodium hydride procedures, since such methods are suitable with cyclohexanone.[9]

EXPERIMENTAL[10]

Preparation of 2-acylcyclanones by boron fluoride method. 2-Acetylcyclopentanone (I) and 2-acetylcyclohexanone (III) were prepared by acetylating cyclopentanone and cyclohexanone with acetic anhydride by means of the boron fluoride–ethyl acetate complex essentially as described previously.[4,5]

In a similar manner, 2-acetylcycloheptanone (V), 2-acetylcyclooctanone (VI) and certain other 2-acylcyclanones were synthesized employing the appropriate cyclanone and aliphatic anhydride. The results are summarized in Table II.

Alkaline cleavage of 2-acylcyclanones. Table I. A. Determination of ketones. A 0.1-mole sample of the ketone was weighed into a glass-stoppered flask and dissolved in 50 ml. of 10% sodium hydroxide solution. The flask was stoppered and warmed on the steam bath for 2 hr. The flask was then fitted to a continuous extraction apparatus and extracted with ether overnight. The ether extract was evaporated to leave the free ketone. After dissolving in 50 ml. of 95% ethanol the solution was treated with 125 ml. of 2,4-dinitrophenylhydrazine reagent containing 0.12 mole of the carbonyl reagent. After standing in the refrigerator overnight the solid was collected on a sintered glass funnel which had been previously weighed. After washing with ice cold water the solid was dried in a desiccator to constant weight. A series of blanks indicated that the ketones could be estimated to within ±2% by this method.

B. Determination of keto acids II *and* IV. The β-diketone (0.5 mole) was dissolved in excess 10% sodium hydroxide solution and the solution was refluxed for 2 hr. The mixture was acidified with 10% sulfuric acid and continuously extracted with ether overnight. The ether extracts were evaporated and the residue distilled to give δ-acetylvaleric acid in 85–90% yield in 3 runs. The acid boiled at 147–150° at 3 mm., reported[3] b.p. 147–149° at 3 mm. Similarly, 60–64% yields of ε-acetylcaproic acid were obtained from two runs, b.p. 159–162° at 5 mm., reported[3] 160–162° at 4 mm.

2-Benzoylcycloheptanone (VIII) *and 2-benzoylcyclooctanone* (IX). These β-diketones were prepared by treating three molecular equivalents each of sodio cycloheptanone and sodio cyclooctanone in ether with one equivalent of benzoyl chloride in this solvent essentially as described previously[8] for certain other acylations, except that no nitrogen was employed.

2-Benzoylcycloheptanone (VIII), obtained in 40% yield (crude), melted at 55–56° after several recrystallizations from petroleum ether.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.69; H, 7.54.

Most (81%) of the 2 extra equivalents of the cycloheptanone was recovered.

The product gave a positive enol test with methanolic ferric chloride and slowly formed a copper chelate with saturated aqueous cupric acetate solution.

2-Benzoylcyclooctanone (IX) was obtained in 45% yield melting at 54–57°. After recrystallization from methanol-water, the product melted at 59–61°.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.87. Found: C, 78.15; H, 7.60.

Most (85%) of the 2 extra equivalents of the cyclooctanone was recovered.

The product gave a deep violet enol test with methanolic ferric chloride and formed a copper chelate with saturated aqueous cupric acetate solution.

Alkaline cleavage of β-diketones VIII *and* IX. Five-gram samples of the β-diketones VIII and IX were cleaved by 10% sodium hydroxide solution and the solution was acidified with dilute sulfuric acid to precipitate benzoic acid. From the cleavage of 2-benzoylcycloheptanone (VIII) there was obtained 2.63 g. of benzoic acid, m.p. 119–121° and mixed m.p. 119–121°, corresponding to 94% side chain cleavage. Similarly, 2-benzoylcyclooctanone (IX) gave 2.52 g. of benzoic acid, m.p. 120–121°, corresponding to a 96% side chain cleavage. A mixed m.p. showed no depression.

2-Acetyl-2-methyclyclopentanone (X) *and 2-acetyl-2-methylcyclohexanone* (XII). Potassium metal (21.45 g.; 0.5 g.-atom + 10%) was dissolved in hot *tert*-butyl alcohol (200 ml.). When solution was complete the mixture was cooled and 0.1 mole of 2-acetylcyclopentanone or 2-acetylcyclohexanone was dissolved in the solution. Methyl iodide (78.1 g.; 0.5 mole + 10%) was then added and the mixture stirred while cooling in an ice bath. Potassium iodide separated and the solution was allowed to come to room temperature. After 8 hr. the salt was filtered from the mixture and the alcohol evaporated under reduced pressure. The residue was distilled *in vacuo*.

There was obtained from 2-acetylcyclopentanone an 87% yield of the 2-methyl derivative (X), b.p. 82–86° at 10 mm.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.53; H, 8.63. Found: C, 68.76; H, 8.84.

The product failed to give an enol test with ferric chloride solution indicating the absence of the unalkylated starting material.

There was obtained from 2-acetylcyclohexanone a 79% yield of the 2-methyl derivative (XII), b.p. 95–98° at 10 mm.

Anal. Calcd. for $C_9H_{14}O_2$: C, 78.22; H, 7.87. Found: C, 77.95; H, 7.67.

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(9) See ref. 4, pp. 77–78 and 147.

(10) Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn. The melting points and boiling points are uncorrected.

The product failed to give an enol test with ferric chloride solution indicating the absence of the unalkylated starting material.

This compound (b.p. 130–133° at 48 mm.) has previously been prepared in unreported yield by methylating 2-acetylcyclohexanone by means of sodium in benzene.[11]

Alkaline cleavages of β-diketones X *and* XII. Samples of these β-diketones were cleaved by alkali according to the procedure for the unalkylated β-diketones.

There was obtained from 2-acetyl-2-methylcyclopentanone a 65% yield of δ-acetylcaproic acid, b.p. 127–128° at 1.5 mm. Neut. equiv. Calcd. 158. Found: 159. The ethyl ester, prepared in 92% yield by the Fisher method, boiled at 77–79° at 0.6 mm.

Anal. Calcd. for $C_{10}H_{18}O_3$; C, 64.47; H, 9.74; Found: C, 64.23; H, 9.72.

There was obtained from 2-acetyl-2-methylcyclohexanone a 25% yield of ε-acetylheptylic acid, b.p. 128–129° at 0.7 mm. Neut. equiv. Calcd. 172. Found: 173. The ethyl ester, prepared in 93% yield by the Fisher method, boiled at 84–85° at 0.6 mm.

Anal. Calcd. for $C_{11}H_{20}O_3$; C, 65.96; H, 10.06. Found: C, 65.82; H, 10.06.

Also there was obtained from the cleavage of 2-acetyl-2-methylcyclohexanone a 54% yield of 2-methylcyclohexanone boiling at 165–167°; reported b.p. 166°.[12]

DURHAM AND WINSTON-SALEM, N. C.

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(11) H. K. Sen and U. Bose, *J. Indian Chem. Soc.*, **4**, 62 (1927).

(12) A. Skita, *Ber.*, **56**, 1016 (1923).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

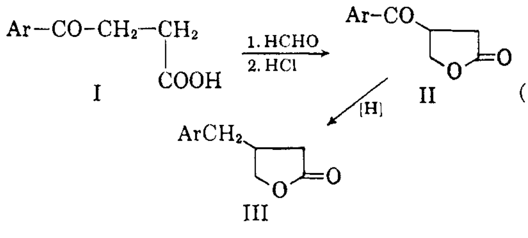
Substituted γ-Lactones. III. A General Route to β-Substituted γ-Butyrolactones[1]

JOHANNES ROTHE[2a] AND HANS ZIMMER[2b]

Received November 7, 1958

The reaction of β-aroylpropionic acids I with equimolecular amounts of formaldehyde in alkaline solution leads to β-aroylbutyrolactones II. This reaction appears to be a general one; with acetaldehyde, the corresponding β-aroyl-γ-valerolactones are obtained. A small yield of β-acetylbutyrolactone is formed from levulinic acid and formaldehyde. Catalytic hydrogenations and Meerwein-Ponndorf reductions of the II are described.

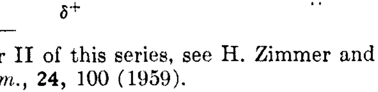
We were interested in preparing substituted β-benzylbutyrolactones as starting materials for further synthetic work. The hydroxymethylation of β-benzoylpropionic acid (Ia) or substituted β-benzoylpropionic acids, respectively, followed by lactonization and reduction of the carbonyl group, seemed to be a possible way:



(1)

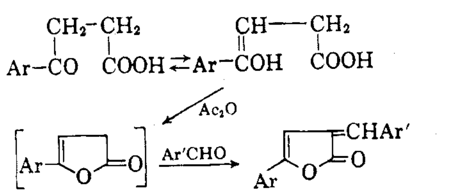
a: Ar = C_6H_5 *b*: Ar = $3,4\text{-}(CH_3O)_2C_6H_3$

According to theoretical considerations, the β-methylene group in I should be more reactive than the α-methylene group:



$$\mathrm{Ar}-\overset{\delta^-:\ddot{O}}{\underset{\delta^+}{\overset{\|}{C}}}\overset{\beta}{-}CH_2\overset{\alpha}{-}CH_2-\overset{:\ddot{O}\ \delta^-}{\overset{\|}{C}}-\overset{\delta^+}{\ddot{O}H}$$

It is a well known fact that the nucleophilic character of a keto-carbonyl-C-atom is stronger than that of a carboxyl-C-atom. Hence aldol-like condensations of aldehydes with I should preferably occur in the β-position. The reaction[3] of β-aroylpropionic acids with aldehydes under the influence of acetic anhydride to give α-arylidene-γ-arylcrotonolactones provides no argument against this assumption because, under the reaction conditions, enolization and lactonization seem to occur first, followed by condensation with the aldehyde:



(2)

In fact, reaction of ethyl β-benzoylpropionate and benzaldehyde with sodium ethylate in ethanolic solution yields up to 90% of β-benzylidene-β-benzoylpropionic acid.[3b]

There are two classic examples for the preparation of lactones based on the principle of an aldol-like condensation of a carbonyl compound

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(1) Paper II of this series, see H. Zimmer and J. Rothe, *J. Org. Chem.*, **24**, 100 (1959).

(2) (a) Chattanooga Medicine Company Post-doctorate Research Fellow 1956–58. Recipient of a Fulbright Travel Grant. Present address: Department of Chemistry, Harvard University, Cambridge, Mass. (b) To whom inquiries concerning this paper should be directed.

(3) (a) *e.g.*, J. Thiele, *Ann.*, **306**, 145 (1899); W. Borsche, P. Hofmann, and H. Kuhn, *Ann.*, **554**, 23 (1943); F. W. Schueler and C. Hanna, *J. Am. Chem. Soc.*, **73**, 3528 (1951); C. Hanna and F. W. Schueler, *J. Am. Chem. Soc.*, **75**, 741 (1953). (b) W. Borsche, *Ber.*, **47**, 1108 (1914).