[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

The Synthesis of Ketones of the Type $RCOCHR_2$ from α,α-Disubstituted β-Keto Esters. An Extension of the Acetoacetic Ester Type of Ketone Synthesis[1]

BY BOYD E. HUDSON, JR., AND CHARLES R. HAUSER

The classical acetoacetic ester synthesis of ketones, involving the mono- and di-alkylation of ethyl acetoacetate and the subsequent "ketonic" hydrolysis, gives only the methyl ketones, CH_3COCH_2R and CH_3COCHR_2. Higher acyl acetates, $RCOCH_2COOC_2H_5$, might be alkylated and then cleaved to give the ketones, $RCOCH_2R$ and $RCOCHR_2$, but most of these β-keto esters are rather difficult to prepare and their di-alkylation is sometimes difficult to effect. Symmetrical ketones of the type RCH_2COCH_2R have been prepared[2] by the self-condensation of the esters, $RCH_2COOC_2H_5$, and hydrolysis of the resulting β-keto esters, $RCH_2COCHRCOOC_2H_5$. The latter keto esters might be alkylated and then cleaved to give certain ketones of the type $RCOCHR_2$. A more convenient and more general method for the preparation of these ketones, however, is described in the present paper. The method consists in the acylation of the sodium enolates of disubstituted acetic acid esters (prepared by means of sodium triphenylmethyl) with acid chlorides, and the ketonic hydrolysis of the resulting α,α-disubstituted β-keto esters.

$$H{-}CR_2CO_2C_2H_5 + (C_6H_5)_3CNa \longrightarrow Na[CR_2CO_2C_2H_5] + (C_6H_5)_3CH$$

$$RC(=O)Cl + Na[CR_2CO_2C_2H_5] \longrightarrow RCOCR_2CO_2C_2H_5 + NaCl$$

$$RCOCR_2CO_2C_2H_5 \xrightarrow[\text{hydrolysis}]{\text{ketonic}} RCOCHR_2 + CO_2 + C_2H_5OH$$

The α,α-disubstituted β-keto esters used in this work were prepared according to the method previously described.[3] Generally a mixture of acetic and sulfuric acids was used to hydrolyze the keto esters,[4] but for more difficult cleavages hydriodic acid[5] was used. Hydrolyses were effected by boiling the esters with the acetic–sulfuric acid mixtures in a flask connected by a ground-glass joint to a reflux condenser equipped with a bubble counter. The cooled solution was diluted with 100 cc. of water, 100 cc. of ether was added, and the mixture made alkaline to phenolphthalein with cold 20% sodium hydroxide solution. The ether layer was separated and the aqueous layer extracted twice with ether. The combined ether solutions were dried with sodium sulfate followed by "Drierite," and the solvent distilled. The resi-

TABLE I

KETONIC HYDROLYSIS OF β-KETO ESTERS

β-Keto ester used, ethyl	Hydrolysis mixture, cc. g.	H_2SO_4	H_2O	CH_3CO_2H	50% HI	Time, hr.	Ketone	Yield g.	%	B. p., °C. (mm.)
Isobutyrylisobutyrate	14.8	10	10	30		4	Di-isopropyl[a]	7.0	78	121–125 (760) Mostly at 123–124[a]
n-Butyryldimethylacetate	21.0	5	10	55		3.5	*n*-Propyl isopropyl[b]	10.2	79	134–136 (760)[b]
Propionyldimethylacetate	14.2	4	4	40		8	Ethyl *s*-butyl	6.7	78	134–136 (760)[c]
Isovalerylmethylethylacetate	14	8	5	38		14	Isobutyl *s*-butyl[d]	7.0	75	165–167 (760)
Benzoyldimethylacetate	20	10	5	30		3	Phenyl isopropyl	13.4	81	102 (15) 218 (760)[e]
Benzoylmethylethylacetate	13			75	75	48	Phenyl *s*-butyl	6.0	69	109 (10)[f]
Benzoyldiethylacetate[h]	15			75	75	48	Diethylacetophenone[g]	8.0	75	117–118 (10) 247–249 (760)[g]

[a] M. p. of semicarbazone, 159–160°; Hauser and Renfrow, THIS JOURNAL, **59**, 1826 (1937). [b] M. p. of semicarbazone, 119°; Meerwein, *Ann.*, **419**, 139 (1919). [c] Hanriot and Bouveault, *Bull. soc. chim.*, [3] **1**, 550 (1889). [d] *Anal.* Calcd. for $C_9H_{18}O$: C, 76.0; H, 12.8. Found: C, 76.1; H, 12.8. The semicarbazone, which formed after 2–3 weeks, melted at 132.5° after recrystallization from ligroin. *Anal.* Calcd. for $C_{10}H_{21}ON_3$: N, 21.2. Found: N, 21.4. See Kopff, Nenitzescu, Isacescu and Cantuniari, *Ber.*, **69B**, 2249 (1936). [e] Schmidt, *ibid.*, **22**, 3250, note 2 (1889). [f] Dumesnil, *Ann. chim.* [9] **8**, 72 (1917). [g] M. p. of oxime, 90°; Haller and Bauer, *Compt. rend.*, **150**, 1477 (1910). [h] Attempts to hydrolyze ethyl benzoyldiethylacetate by the acetic–sulfuric acid method gave only small amounts of the ketone; prolonged refluxing with higher concentrations of sulfuric acid led to considerable charring. See Hope and Perkin, *J. Chem. Soc.*, **95**, 2044 (1909).

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(2) Briese and McElvain, THIS JOURNAL, **55**, 1697 (1933).

(3) Hudson and Hauser, *ibid.*, **63**, 3156 (1941).

(4) Previously, acetic acid (85%) alone has been used for the ketonic hydrolysis of certain β-keto esters; see Meincke and McElvain, *ibid.*, **57**, 1445 (1935); Dieckmann and Kron, *Ber.*, **41**, 1266 (1908). Also, sulfuric acid has been used; see Bouveault and Loquin, *Bull. soc. chim.*, [3] **31**, 1154 (1904).

(5) Leuchs, Heller and Hoffmann, *Ber.*, **62**, 875 (1929).

due on fractionation with a 6-inch Widmer column gave the ketone. In hydrolyses with hydriodic acid, the cooled mixture was extracted with benzene. The benzene solution was washed with water, decolorized with sodium thiosulfate, washed with water and sodium bicarbonate solution and dried. The solvent was distilled and the residue on fractionation gave the ketone.

The results of the experiments are summarized in Table I.[6] The yields of the ketones from the β-keto esters varies from 69 to 81%. The yields of the β-keto esters from disubstituted acetic acid esters and acid chlorides vary from 51 to 74%.[3] The over-all yields of the ketones from the esters and acid chlorides vary from 38–58%. The synthesis therefore offers a satisfactory preparation of the ketones. The method may be extended to the preparation of phenyl ketones with substituents in the ring.

(6) Boiling points and melting points are corrected. Microanalyses are by Saul Gottlieb, Columbia University, New York, N. Y.

Summary

A convenient general method is described for the preparation of ketones of the type $RCOCHR_2$. Esters of the type $HCR_2CO_2C_2H_5$, in the form of their sodium enolates, are condensed with acid chlorides[3] to give β-keto esters of the type $RCOCR_2CO_2C_2H_5$, which on hydrolysis give the ketones.

The method represents an extension of the acetoacetic ester type of ketone synthesis.

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The Preparation and Properties of Three Isomeric *n*-Hexyl Cresols and their Chlorinated Derivatives

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6-*n*-Hexyl-*m*-cresol (1-hydroxy-3-methyl-6-*n*-hexylbenzene) was reported by Lamson and Brown[1] to be an active ascaricide. Although its anthelmintic activity is less than that of *n*-hexylresorcinol, it possesses the advantage of being less irritating to the mucous membranes of the gastro-enteric tract. Its mono-chloro derivative, 4-chloro-6-*n*-hexyl-*m*-cresol (1-hydroxy-3-methyl-4-chloro-6-*n*-hexylbenzene) was recently reported by Hartman and Schelling[2] to be an effective bactericidal substance, especially against staphylocci, streptococci, pyocyaneus, and the gram-negative bacilli when solutions are acidified to *p*H of 3 with the addition of hydrochloric or other acids. The toxicity, both local and systemic, was said to be comparatively low. The anthelmintic property of this compound had not been studied.

In view of these reports, we deemed it worthwhile to prepare from the isomeric cresols the isomeric *n*-hexylcresols and their monochloro derivatives so that a study of their biologic properties might be made. The effect of orientation and of chlorination of *n*-hexylcresols on the toxicity as well as other biologic activities will be published elsewhere.

The starting material of this synthesis was Chinese castor oil.[3] This was pyrolyzed with sodium hydroxide in a copper flask; the soap was thus decomposed to secondary octyl alcohol (methyl-*n*-hexylcarbinol). The crude secondary alcohol formed was then oxidized with potassium dichromate and sulfuric acid, first to methyl *n*-hexyl ketone[3] and then to *n*-caproic acid.[4] The acid, after purification by fractional distillation, was treated with thionyl chloride to form *n*-caproyl chloride.[5]

To convert the three isomeric cresols to the *n*-hexylchlorocresols, two methods were used. For the first method, the cresols were esterified with *n*-caproyl chloride to tolyl caproates. These esters, when subjected to Fries rearrangement,[6] were converted to the corresponding phenolic ketones (*n*-hexoyl-cresols) which were then reduced by Clemmensen's method[7] to the corresponding

(1) Lamson and Brown, *J. Pharm. Expil. Therap.*, **53**, 227 (1935).

(2) Hartman and Schelling, *Am. J. Surgery*, **46**, 460 (1939).

(3) (a) Kao and Ma, *Science Reports*, National Tsing Hua University, *A1*, 129 (1932). (b) Kao and Yen, *J. Chinese Chem. Soc.*, **2**, 21 (1934).

(4) Tseng, "Laboratory Manual of Organic Chemistry," National Peking University Press, 1935, p. 79.

(5) (a) Meyer, *Monatsh.*, **22**, 48 (1901); (b) Beilstein, "Handbuch d. org. Chem.," Bd. II, 1920, p. 324.

(6) (a) Blatt, *Chem. Rev.*, **27**, 413 (1940); (b) Baltzly and Bass, THIS JOURNAL, **55**, 4292–4294 (1933).

(7) (a) Gattermann and Wieland, "Die Praxis des organischen Chemikers," 1933, p. 372. (b) Read and Wood, "Organic Syntheses," Vol. XX, 1940, pp. 57–59. (c) Clemmensen, *Ber.*, **46**, 1840 (1913).