[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY,
POLYTECHNIC INSTITUTE OF BROOKLYN]

THE PREPARATION OF A SERIES OF 3-METHYL-5-SUBSTITUTED CYCLOHEXANONE-3-CARBOXYLIC ESTERS[1]

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In connection with certain other investigations it became desirable to prepare as intermediates a series of esters of alkyl substituted cyclohexanone-3-carboxylic acids. The present report describes the preparation and properties of these intermediates.

The method adopted for the synthesis of the cyclohexanone carboxylates was based upon observations of Knoevenagel (17) and Knoevenagel and Lange (18) to the effect that 3,5-dimethyl-2-cyclohexen-1-one readily undergoes addition of sodium bisulfite in aqueous solution with the formation of 3,5-dimethylcyclohexanone-3-sodium sulfonate. Furthermore, they reported that the latter readily exchanged the sulfonate group for a cyanide group upon interaction with sodium or potassium cyanide. The resulting cyanide could be hydrolyzed with aqueous mineral acid to the corresponding 3,5-dimethylcyclohexanone-3-carboxylic acid.

It has been our experience that the hydrolysis of the cyanide and esterification of the acid can be accomplished simultaneously in methyl alcoholic sulfuric acid solution.

The reactions involved in the preparation of the esters of cyclohexanone carboxylic acids may be outlined as on page 32.

The 3-methyl-5-alkyl-2-cyclohexen-1-ones listed in table I were prepared by Knoevenagel's technique (1, 2), and have all been previously described (1, 2, 3, 4, 5, 6, 7, 8). The mechanism of the formation of 2-cyclohexen-1-ones has been discussed by Hann and Lapworth (9) and Hammett (10).

The second step involved the preparation of the 3-cyano compounds from the corresponding 3-methyl-5-alkyl-2-cyclohexen-1-ones. In addition, the preparation of 3,5,5-trimethyl-3-cyanocyclohexanone from 3,5,5-trimethyl-2-cyclohexen-1-one, isophorone, was undertaken. Presumably, these cyano ketones could be prepared by direct addition of hydrogen cyanide to the α,β-unsaturated ketone (method A) or indirectly by treatment of the addition compounds of the α,β-unsaturated ketones and sodium bisulfite with sodium cyanide (method B).

Discussion of the mechanism of direct addition of hydrogen cyanide to α,β-unsaturated carbonyl compounds may be found in the literature (9, 11, 12, 13, 14, 15).

Experiments involving direct addition of hydrogen cyanide were carried out

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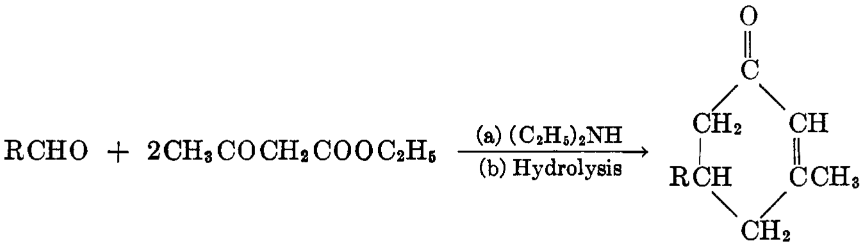
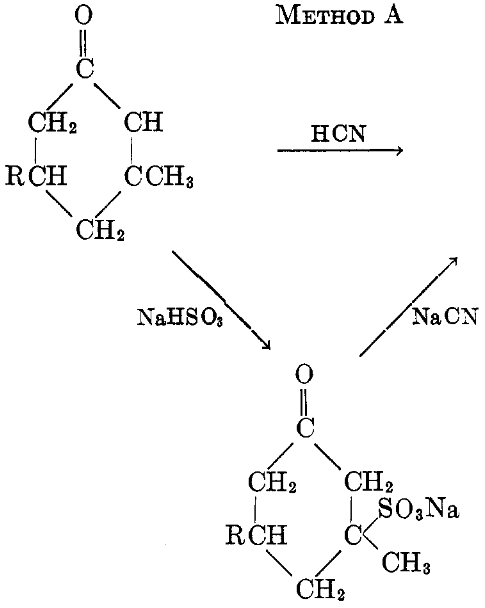
[1] Abstracted from a thesis presented by Carleton W. Roberts to the faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Master of Science.

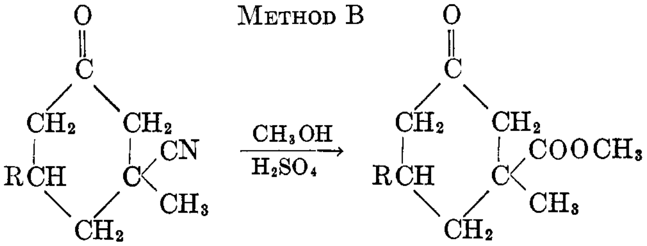
by treatment of a methanol-acetic acid solution of the α,β-unsaturated ketones with an aqueous solution of sodium cyanide. Satisfactory results were obtained only in the preparation of 3,5,5-trimethyl-3-cyanocyclohexanone. Repeated attempts to prepare 3,5-dimethyl-3-cyanocyclohexanone resulted only in the recovery of considerable amounts of unsaturated ketone, and isolation of small amounts of a mixture of the 3,5-dimethylcyclohexanone-3-carboxylic acid and amide. In the latter case it was evident that some 3-cyano compound must have been formed, but in no instance were satisfactory yields of the 3-cyano compound obtained.



METHOD A



METHOD B

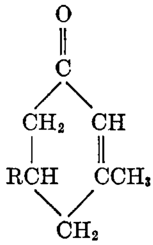


Since the direct addition of hydrogen cyanide to the 3,5-dimethyl-2-cyclohexen-1-one did not give good results, the indirect method, replacement of the sulfonic acid radical in the 3 position by the cyanide group, was investigated. The preparation was carried out by boiling a mixture of the α,β-unsaturated ketone and an aqueous solution of sodium bisulfite; the reaction was considered complete when the ketone had dissolved completely and the solution became homogeneous and clear. No attempt was made to isolate these bisulfite addition compounds. They were treated *in situ* with a concentrated solution of sodium cyanide to effect conversion to the 3-cyano derivatives.

Connor (16) reviewed generally the literature concerning the replacement of the sulfonic acid grouping by cyanide, and Knoevenagel (17) and Knoevenagel and Lange (18) prepared the 3,5-dimethyl-3-cyanocyclohexanone from the corresponding bisulfite addition compound. Except in the preparation of the 3,5,5-trimethyl-3-cyanocyclohexanone, satisfactory yields of 3-cyano compounds were obtained in all cases. Although the bisulfite addition product of isophorone apparently formed, since the ketone dissolved on refluxing in aqueous bisulfite solution, treatment of this solution with aqueous sodium cyanide resulted in almost quantitative recovery of the unsaturated ketone.

TABLE I

3-METHYL-5-SUBSTITUTED-2-CYCLOHEXEN-1-ONES



R	B.P. (°C.)	PRESSURE (MM.)	YIELD (%)	REF.
H	198–202	760	30	(3)
CH_3	208–211	760	40	(3)
C_2H_5	226–230	760	42	(4)
n-C_3H_7	120–122	12	45	(5)
i-C_3H_7	124–126	16		
	113–116	11.5		
	108–110	9	51	(5)
i-C_4H_9	111–112	5		
	133–135	11	41	(2)
C_6H_5	179–181	12	45.6	(2)

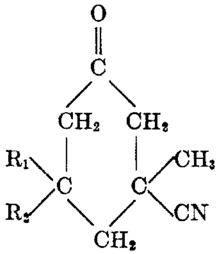
The third step in the preparation, the hydrolysis-esterification of the 3-cyano compounds to give the methyl esters of the corresponding carboxylic acids, was accomplished by refluxing a methyl alcohol-sulfuric acid solution of the cyanide for several hours and subsequent isolation and purification of the esters (19).

This procedure gave good yields except in the preparation of methyl 3-methylcyclohexanone-3-carboxylate. The keto esters were further characterized as 2,4-dinitrophenylhydrazones as indicated in Table III.

The authors wish to express their gratitude to Dr. Robert M. Herbst of E. Bilhuber Inc., Orange, New Jersey, for his suggestions, and interest in this work.

TABLE II

3-METHYL-5-SUBSTITUTED-3-CYANOCYCLOHEXANONES



R₁	R₂	FORMULA	B.P. (°C.)	PRESSURE (MM.)	M.P. (°C.)	YIELD (%)	ANAL., % N[b]	
							Calc'd	F'd
H	H	$C_8H_{11}NO$	92–93	2		32.1	10.2	10.1
			139–142	16				
			107–109	4				
CH_3	H	$C_9H_{13}NO$	145–146	12	93–94[a]	40.8	9.3	9.2
C_2H_5	H	$C_{10}H_{15}NO$	132–133	3		30.0	8.5	8.5
			142–143	8				
n-C_3H_7	H	$C_{11}H_{17}NO$	115–116	1		66.7	7.8	7.9
			154–156	11				
			163–166	15				
i-C_3H_7	H	$C_{11}H_{17}NO$	115–116	2		32.4	7.8	7.5
			147–149	9				
i-C_4H_9	H	$C_{12}H_{19}NO$	140–141	4		55.6	7.2	7.2
C_6H_5	H	$C_{14}H_{15}NO$	184–186	3–5	103–103.5	57.0	6.6	6.5
CH_3	CH_3	$C_{10}H_{15}NO$	144–145	12	69.5–70.5	60.0	8.5	8.5

[a] Knoevenagel and Lange (18) gave m.p. 92–94°.

[b] Kjeldahl Analysis done by Control Laboratory of E. Bilhuber, Inc., Orange, New Jersey.

Grateful acknowledgment is made also to E. Bilhuber, Inc., in whose laboratories this work was done.

EXPERIMENTAL[2]

Preparation of 3-methyl-5-alkyl-2-cyclohexen-1-ones. These compounds were prepared by Knoevenagel's method (1, 2) using six moles of acetoacetic ester, three moles of freshly distilled aldehyde, and 15 cc. of either diethylamine or piperidine.[3] The results of these preparations are summarized in Table I.

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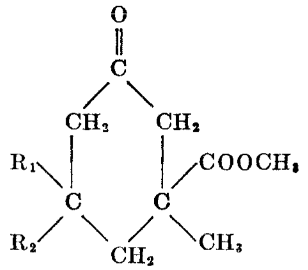
[2] All melting points and boiling points are uncorrected.

[3] The initial preparations of the 2-cyclohexen-1-ones were undertaken prior to the publication of an improved synthesis (5).

TABLE III

METHYL 3-METHYL-5-SUBSTITUTED-CYCLOHEXANONE-3-CARBOXYLATES



R₁	R₂	CYCLOHEXANONE CARBOXYLATES								2,4-DINITROPHENYLHYDRAZONES			
		FORMULA	B.P. (°C.)	PRESSURE (MM.)	YIELD (%)	ANAL.[a]				FORMULA	M.P. (°C.)	Anal., % N[a]	
						Calc'd		F'd				Calc'd	F'd
						C	H	C	H				
H	H	$C_9H_{14}O_3$	128.5–130.5	15	25.0	63.5	8.2	63.8	8.2	$C_{16}H_{18}N_4O_6$	130–131.5	16.0	16.0
CH_3	H	$C_{10}H_{16}O_3$	95.6–96	1	66.5	65.2	8.7	65.1	8.8	$C_{16}H_{20}N_4O_6$	159.5–161	15.4	15.5
C_2H_5	H	$C_{11}H_{18}O_3$	124–125	12	72.0	66.7	9.1	66.5	9.1	$C_{17}H_{22}N_4O_6$	128.5–129.5	14.8	14.7
			101.5–102	1									
n-C_3H_7	H	$C_{12}H_{20}O_3$	104–105	1	86.7	67.9	9.4	67.9	9.4	$C_{18}H_{24}N_4O_6$	145.0–145.5	14.3	14.1
			149–150.5	15									
i-C_3H_7	H	$C_{12}H_{20}O_3$	94–95	1	83.3	67.9	9.4	68.3	9.5	$C_{18}H_{24}N_4O_6$	144.5–145.0	14.3	14.1
i-C_4H_9	H	$C_{13}H_{22}O_3$	136–140	9–10	57.7	69.0	9.8	70.7	9.7	$C_{19}H_{26}N_4O_6$	152.5–154	13.8	13.8
			131–132	8									
C_6H_5	H	$C_{15}H_{18}O_3$	174–176	5–6	75.0	73.1	7.4	74.5	7.3	$C_{21}H_{22}N_4O_6$	160–161	13.1	13.3
CH_3	CH_3	$C_{11}H_{18}O_3$	108–109	1	65.4	66.7	9.1	67.8	9.1	$C_{17}H_{22}N_4O_6$	143–144.5	14.8	15.3
			131–134	12									
			136–137	13									

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[a] Microanalysis for Carbon Hydrogen and for Nitrogen by W. Saschek New York, New York.

3,5,5-Trimethyl-2-cyclohexen-1-one, obtained from the Carbide & Carbon Chemical Corporation, was redistilled, b.p. 212–214°.

Preparation of the 3-cyano compounds. Method A (Direct). One hundred thirty-eight grams (1 mole) of isophorone (b.p. 212–214°) was dissolved in a mixture of 950 cc. of methanol, 50 cc. of water, and 60 g. (57.2 cc., 1 mole) of glacial acetic acid. To this was added during 15 minutes, with constant stirring, 98 g. (2 moles) of powdered sodium cyanide dissolved in 375 cc. of water. The resulting warm solution was allowed to stand for one week at room temperature.

After removal of most of the methanol from the reaction mixture under reduced pressure (water-bath temperature between 50–60°), the residual solution was diluted with 500 cc. of water, and the oil taken up in 250 cc. of benzene. Since some solid separated on shaking with benzene, it was found helpful to filter the benzene layer and the interfacial layer after most of the clear aqueous layer had been drawn off. The aqueous layer was extracted with two 200-cc. portions of benzene, the benzene solutions combined, and dried over sodium sulfate.

Most of the benzene was removed by distillation at atmospheric pressure, and the residual material was distilled under reduced pressure. The fractions shown in Table IV were obtained.

TABLE IV

FRACTIONATION OF 3-CYANO COMPOUND

FRACTION	B.P. (°C)	BATH TEMP. (°C)	PRESSURE (MM.)	YIELD	PRODUCT
1	92–100	120–140	11–14	38 g.	isophorone
2	120–140	140–160	11	20 g.	mixed
3	144–150	174–178	11	71 g.	cyanide

The third fraction solidified on cooling and was practically pure cyanide.

A portion was recrystallized from 99% isopropyl alcohol, m.p. 69.5–70.5°.

Method B (Indirect). The cyclohexenone (0.25 mole) was suspended in a solution of 34.5 g. (0.31 mole) of sodium bisulfite and 75 cc. of water, and boiled under reflux until the ketone dissolved completely (20–30 minutes). The solution was cooled, and a warm solution of 15.2 g. (0.31 mole) of sodium cyanide in 35 cc. of water was added. While the reaction mixture was heated for an hour in a boiling water-bath, some solid material separated, and the cyano ketone appeared as an immiscible oil. The reaction mixture was cooled, the oil taken up in 50 cc. of benzene, and the aqueous solution and solid extracted with two 50-cc. portions of benzene. The benzene extracts were combined and dried over sodium sulfate.

After removal of most of the benzene at atmospheric pressure, the residual material was distilled under reduced pressure. Three fractions were collected. The first fraction was original ketone, the second fraction was a mixture of the ketone and cyano ketone, and the third fraction was practically pure cyano ketone. The yields, allowing for recovered unsaturated ketone, varied between 30% and 70% with the exception of the 3,5,5-trimethyl-2-cyclohexen-1-one which gave no cyano compound by this method. The cyano compounds were purified either by redistillation or, in the case of solids, by recrystallization from 99% isopropyl alcohol. The main cyanide fraction was generally employed in the next step without further purification. The results of methods A and B are summarized in Table II.

Hydrolysis and esterification of cyanides. One mole of the cyano ketone was suspended in a carefully prepared solution of two moles of concentrated sulfuric acid in an equal weight of 95% methyl alcohol. After standing overnight, the reaction mixture was boiled under reflux for about seven hours. After about three and one-half hours the reaction mixture separated into two phases and enough methanol (75–100 cc.) was added carefully to restore a homogenous solution. Finally the reaction mixture was cooled and poured into about a liter of cold water. The ester separated and was taken up in about 200 cc. of benzene. The aqueous portion was extracted with two 200-cc. portions of benzene. The benzene solutions were combined, washed with a 10% solution of potassium carbonate, and dried over anhydrous sodium sulfate.

After the solvent was removed from the benzene solution at atmospheric pressure, the ester was distilled under reduced pressure.

The yields varied between 25–86% of water-white oily products which usually turned darker on standing in the light or on storage. Analytical samples were purified by repeated redistillations; analytical results indicated that the products were the desired keto esters. The results are summarized in Table III.

Preparation of 2,4-dinitrophenylhydrazones of keto esters. The 2,4-dinitrophenylhydrazones were prepared in the usual manner (20) except that methyl alcohol was used in place of ethyl alcohol. Their properties are recorded in Table III.

SUMMARY

1. Using Knoevenagel's methods, a series of 3-methyl-5-R-2-cyclohexen-1-ones, where R was hydrogen, methyl, ethyl, *n*-propyl, isopropyl, isobutyl, or phenyl, has been prepared.

2. The 3-cyanocyclohexanones were prepared from these unsaturated ketones and isophorone and their properties described. It was found that the cyano compound could be prepared best in two stages, (a) the addition of sodium bisulfite to the unsaturated ketone, and (b) replacement of the sulfonate group by the cyanide group except in the case of 3,5,5-trimethyl-3-cyanocyclohexanone, which could be prepared only by direct addition of hydrogen cyanide to the unsaturated ketone.

3. The 3-methyl-5-R-3-cyanocyclohexanones were converted by one step hydrolysis-esterification to the corresponding methyl 3-methyl-5-R-cyclohexanone-3-carboxylates. The 2,4-dinitrophenylhydrazones of this series of methyl 3-methyl-5-R-cyclohexanone-3-carboxylates were prepared.

BROOKLYN, NEW YORK

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