[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

THE PREPARATION OF 4-CARBETHOXY-3-METHYL-5-ALKYL-2-CY-CLOHEXEN-1-ONES AND 3-METHYL-5-ALKYL-2-CYCLO-HEXEN-1-ONES

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In studying certain examples of alicyclic-aromatic isomerizations, it was necessary to prepare a series of 3-methyl-5-alkyl-2-cyclohexen-1-ones (IV). For their preparation Knoevenagel's methods were used, in which an aliphatic aldehyde is condensed with two moles of ethyl acetoacetate to yield a *bis*-ester (I), followed by cyclization to a keto diester (II) and removal of the two carbethoxyl groups to give the ketones (IV). The carbethoxyl groups of 4,6-dicarbethoxy-3-methyl-5-alkyl-2-cyclohexen-1-ones (II) have in some cases been removed one at a time, yielding successively 4-carbethoxy-3-methyl-5-alkyl-2cyclohexen-1-ones (III) and 3-methyl-5-alkyl-2-cyclohexen-1-ones (IV); it is also possible to carry out the reaction sequence in a single operation yielding ketones IV from *bis*-esters I.



It was found that Knoevenagel's procedures for preparing the ketones (IV) possessed several unsatisfactory features when alkyl groups higher than methyl were involved. In the course of developing an improved general method for obtaining the ketones (IV), we have found an improved general method for preparing the keto esters (III) from *bis*-esters (I), and have also modified the procedure for obtaining 4,6-dicarbethoxy-3,5-dimethyl-2-cyclohexen-1-one (II, $R = CH_3$) from the *bis*-ester (I, $R = CH_3$).

The ring closure of the *bis*-esters (I) occurs readily under both acid and alkaline conditions. To obtain 4,6-dicarbethoxy-3,5-dimethyl-2-cyclohexen-1-one (II, $R = CH_3$), Knoevenagel (2) found it best to carry out the cyclization of the *bis*-ester (I, $R = CH_3$) (obtained from acetaldehyde) by means of hydrogen chloride in ether, but he encountered extensive decomposition during distillation of the produce *in vacuo*. If hydrochloric acid is added to an ether-benzene suspension of recrystallized *bis*-ester, a smooth cyclization results and 4,6-dicarbethoxy-3,5-dimethyl-2-cyclohexen-1-one (II, $R = CH_3$) can be isolated readily and with little decomposition on distillation. It was found that when the crude *bis*-esters (I) were maintained under reflux in glacial acetic acid containing sulfuric acid that a copious evolution of carbon dioxide occurred and 4-carbethoxy-3-methyl-5-alkyl-2-cyclohexen-1-ones (III), in which the alkyl group was methyl, ethyl, *n*-propyl, isopropyl, and *n*-hexyl, were formed in 52-71% yields. Selective removal of the 6-carbethoxyl group has been accomplished previously in several instances by heating *bis*-esters (I) with water at 140°, or with one equivalent of sodium ethoxide in alcohol.



We believe this reaction in acetic acid-sulfuric acid involves first a ring closure to the keto diester II, followed by an ester-interchange with acetic acid to yield a keto ester acid (V) which then decarboxylates immediately to yield the keto ester III. No attempt, however, has been made to prove that the removal of the ester group occurs by ester-interchange rather than by hydrolysis. In either case the equilibrium (interchange or hydrolysis) is driven to completion as a result of the decarboxylation. Presumably the 4-carbethoxyl group could also be removed by the same type of reaction, but the rate at which this occurs appears to be extremely slow when compared to the rate at which the 6-carbethoxyl group may be removed.

The products from this reaction were used in crude form for the preparation of the ketones IV. Saponification with aqueous alcoholic sodium hydroxide served to hydrolyze the remaining carbethoxyl group, and decarboxylation resulted on acidification of the solution. Yields of 56% to 78% of 3-methyl-5alkyl-2-cyclohexen-1-ones (IV) were obtained, in which the alkyl group was methyl, ethyl, *n*-propyl, isopropyl, and *n*-hexyl. Knoevenagel's methods for preparing these ketones involved prolonged heating of the crude condensation products (*bis*-esters) with acid (20% sulfuric acid) or alkali (10-15% sodium or potassium hydroxide). When these methods were applied to higher homologs of acetaldehyde, the yields were low and subject to wide variation.

This procedure for removing a carbethoxyl group from a β -keto ester may be capable of extension; the effect of acetic acid-sulfuric acid on similar compounds derived from aromatic aldehydes is being investigated.

EXPERIMENTAL

Condensation of aldehydes with ethyl acetoacetate. The condensation of freshly distilled propionaldehyde, *n*-butyraldehyde, isobutyraldehyde, and *n*-heptaldehyde with ethyl acetoacetate was carried out with equivalent molar amounts in the fashion described for acetaldehyde. The condensation product from acetaldehyde was a solid; from higher aldehydes it was a viscous oil which was used as obtained. In each of three 500-cc. flasks was placed 210 cc. (210 g., 1.6 mole) of ethyl acetoacetate. The flasks were chilled in an ice-salt bath and 45 cc. (34 g., 0.77 mole) of acetaldehyde was added to each flask. The contents were cooled to 0° and there was added to each flask, with shaking, 2 cc. of piperidine in 5 cc. of ethanol. The flasks were kept in an ice-salt bath for six hours, and the contents then combined and placed in a refrigerator. The mixture was kept in a refrigerator for three days, and a piperidine-ethanol mixture (3 cc. of piperidine, 5 cc. of ethanol) was added each day during this time. Crystallization usually occurred near the end of this period, but to ensure completeness of the reaction the mixture was allowed to stand for one day longer at room temperature. The product was usually used in crude form, although a recrystallization was necessary to provide material for the preparation of 4,6-dicarbethoxy-3,5-dimethyl-2-cyclohexen-1-one. The crystallization was carried out as rapidly as possible from a water-alcohol mixture, using 450 cc. of ethyl alcohol (95% denatured) and 300 cc. of water. The crystallized material was washed with cold, diluted alcohol and then air dried. The product was a colorless powder, m.p. 75-77.5°; yield, 390-405 g. The reported m.p. is 79-80° (1), but no further purification was attempted.

4,6-Dicarbethoxy-3,5-dimethyl-2-cyclohexen-1-one. Ten cubic centimeters of conc'd hydrochloric acid was added to a suspension of 390 g. of recrystallized bis-ester (I, $R = CH_1$) in 400 cc. of ether and 100 cc. of benzene, and the mixture shaken well. An additional 50 cc. of benzene was added and the mixture was allowed to stand for fifteen hours at room temperature. The solvents were removed, and the residue distilled *in vacuo* after the addition of about 50 cc. of toluene to facilitate the removal of water; yield, 292 g.; b.p. 188-190° at 19 mm. [reported (2) b.p. 225-230° at 35 mm.].

The yellow-orange 2,4-dinitrophenylhydrazone was recrystallized from ethanol; m.p. 126.5-127.5°.

Anal. Calc'd for C20H24N4O8: C, 53.57; H, 5.39.

Found: C, 53.40; H, 5.48.

4-Carbethoxy-3-methyl-5-alkyl-2-cyclohexen-1-one (III). Crude bis-esters (I) from homologs of acetaldehyde were added to the acetic acid-sulfuric acid solution and the procedure described for the methyl analog was then followed. Yields, properties, and references are in Table I, together with the melting points of the 2,4-dinitrophenylhydrazones. The keto esters (III) all gave dark enol colors with ferric chloride in aqueous alcohol.

The yield of crude *bis*-ester (I, $R = CH_3$) obtained from acetaldehyde as described was was melted on a steam-cone and poured into a mixture of 600 cc. of acetic acid and 40 cc. of conc'd sulfuric acid. About 10 g. of clay boiling chips was added, and the mixture was refluxed for one hour; during this time there was a vigorous evolution of carbon dioxide. The mixture was poured with (mechanical) stirring into 2 l. of ice-water, and the layers separated with the aid of ether. The organic layer was stirred with 1200 cc. of water and neutralized by the slow addition of solid sodium carbonate, and the solutions again separated. The ethereal solution of the crude material was used for the preparation of 3,5dimethyl-2-cyclohexen-1-one. In order to isolate 4-carbethoxy-3,5-dimethyl-2-cyclohexen-1-one, the ether solution was washed with 5% sodium hydroxide solution, with 2% aqueous acetic acid, dried (anhydrous sodium sulfate), and distilled under reduced pressure through a short column. The fraction boiling at 135-155° at 10 mm. was fractionated through a Widmer column (12 inch); yield, 234 g. (52%); b.p. 137-138° at 9 mm.

3-Methyl-5-alkyl-2-cyclohexen-1-one (IV). The ethereal solution containing crude 4-carbethoxy-3,5-dimethyl-2-cyclohexen-1-one, obtained as described, was heated gently under reduced pressure until the ether was removed. There was added 1140 cc. of water, 60 cc. of alcohol (95%), and 130 g. of sodium hydroxide. The mixture was heated on a steamcone, with shaking, until the ester dissolved. The solution was heated under reflux for 15 minutes, and then acidified carefully with sulfuric acid, using a solution of 100 cc. of conc'd sulfuric acid in 200 cc. of water. This was carried out slowly while cooling the flask with a stream of water. The acid was added to the *hot* solution at a rate compatible with the ensuing vigorous evolution of carbon dioxide. The acidified mixture was boiled under reflux for 15 minutes, allowed to cool, and the layers separated. The crude product was diluted with ether, washed with two 100 cc. portions of 5% sodium hydroxide solution, and then with 100 cc. of 5% aqueous acetic acid. The ethereal solution was dried (anhydrous sodium sulfate) and distilled under reduced pressure. There was obtained 160 g. (56%) of 3,5-dimethyl-2-cyclohexen-1-one, b.p. $84-86^{\circ}$ at 9 mm. [reported, 23% (6), 83% (9), 63-83% (11), no yield given (12, 13)].

The procedure for the methyl analog was followed generally, but the amount of alcohol used during the saponification for higher homologs was increased by 60 cc. for each carbon atom in the side chain, with a corresponding decrease in the amount of water. The amount of sodium hydroxide was increased to 200 g. for the isopropyl compound.

When higher aldehydes were used the results were:

5-ethyl: 66%; b.p. 98-102° at 9 mm. (12, 14, 15).

5-n-propyl: 78%; b.p. 110-113° at 9 mm. (12, 16).

5-isopropyl: 71%; b.p. 120-122° at 15 mm. (10, 13, 17).

5-n-hexyl: 73%, b.p. 154-155° at 11 mm. (10, 13, 18).

TABLE I

4-Carbethoxy-3-methyl-5-alkyl-2-cyclohexen-1-one

5-ALKYL	в.р., °С	vield,	2, 4-DINITROPHENYLHYDRAZONES				
			м .р., °С	Calc'd, %		Found, % ¹	
				с	н	С	н
Methyl ^a	137-138 (9 mm.)	52	133 -134	54.25	5.36	54.16	5.43
$\operatorname{Ethyl}{}^{\mathfrak{d}}$	146–149 (10 mm.)	61	120 -121.5	55.37	5.68	54.99	5.87
n-Propyl ^c	144-148 (10 mm.)	64	110.5-111.5	56.43	5.98	56.63	6.18
i-Propyl ^d	148–151 (10 mm.)	61	109 -110.5	56.43	5.98	56.19	6.13
n-Hexyl ^e	183-186 (10 mm.)	71	109 -110	59.17	6.77	59.00	6.84

^a (3, 4, 5, 6). ^bAnalytical data indicated less than analytical purity, not improved on further fractionation. Cale'd for C₁₂H₁₈O₈: C, 68.54; H, 8.63. Found: C, 67.37; H, 8.66. ^cAnal. Cale'd for C₁₂H₂₀O₈: C, 69.61; H, 8.99. Found: C, 69.36; H, 9.12. ^d(7). ^c(8). [']By a semimicro method following Elving and McElroy [Ind. Eng. Chem., Anal. Ed., 13, 660 (1941)].

SUMMARY

Improved preparative methods for obtaining 4-carbethoxy-3-methyl-5-alkyl-2-cyclohexen-1-ones and 3-methyl-5-alkyl-2-cyclohexen-1-ones from aliphatic aldehydes and ethyl acetoacetate by way of Knoevenagel's condensation have been developed.

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