[Contribution from the Avery Laboratory, University of Nebraska]

A NEW SYNTHESIS OF 3,4-DIMETHYL-2-CYCLOHEXENONE AND 3,4-DIMETHYLCYCLOHEXANONE

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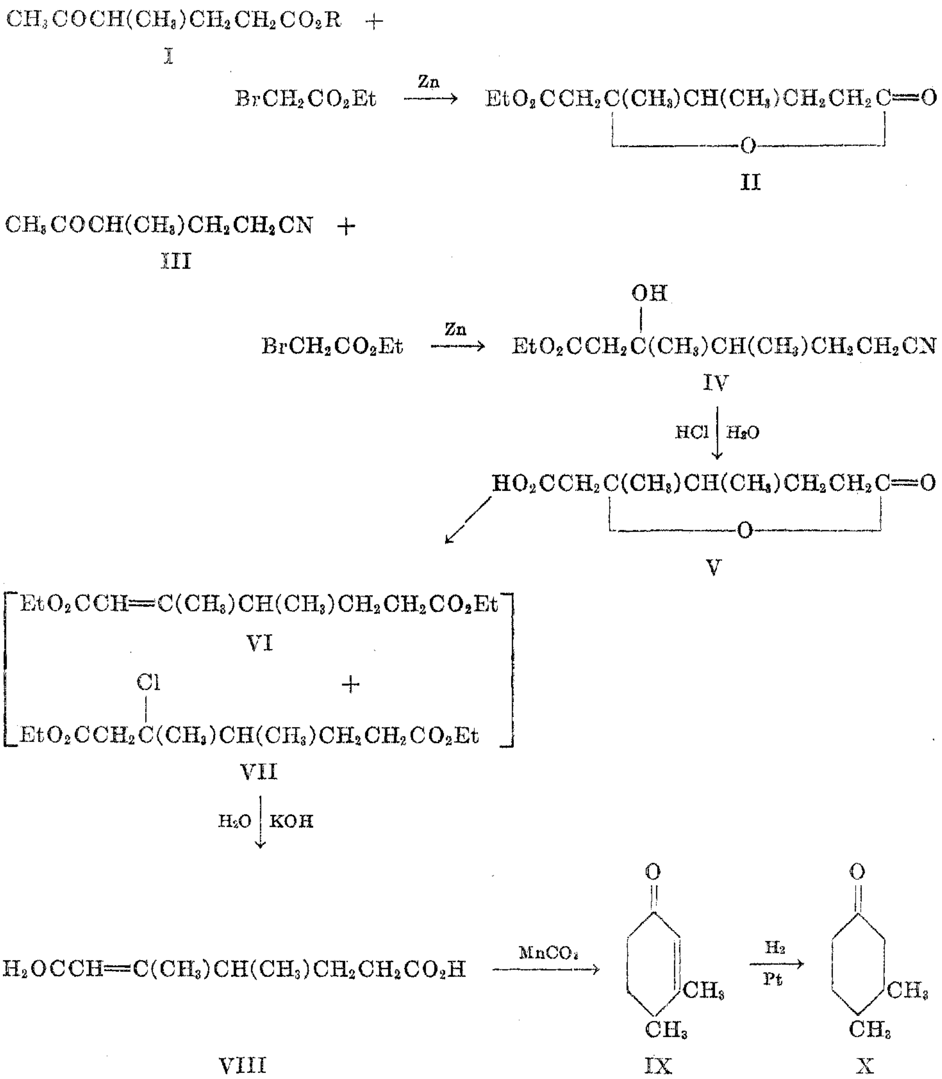
Of the eleven most reasonable possibilities for the structure of a ketone, $C_8H_{14}O$ isolated by von Braun and coworkers (1–3) from the degradation products of a naphthenic acid, $C_{10}H_{18}O_2$, only three may exist in *cis-trans* isomeric forms. One of these, 3,5-dimethylcyclohexanone, has been characterized in both the *cis* and *trans* forms (4, 5); the other two, 3-methyl-4-ethylcyclopentanone (2, 6) and 3,4-dimethylcyclohexanone (X) (7–11), apparently have been prepared in only one configuration.

All earlier syntheses of X have involved hydrogenation of 3,4-dimethylphenol to 3,4-dimethylcyclohexanol and oxidation of the latter to X (4). Apparently the reduction step is essentially stereospecific leading to only one arrangement of the methyl groups (probably *cis*) on the cyclohexane ring. This communication reports our first attempt to prepare the *cis-trans* isomers of X through a modification and extension of a procedure used previously (12) in this laboratory for the synthesis of 3,3,4-trimethylcyclopentanone. The sequence followed is outlined on the flow sheet.

At first an attempt was made to follow closely the earlier work (12) by preparing ϵ-carbethoxy-β,γ-dimethyl-δ-caprolactone (II) from the Reformatsky reaction between methyl or ethyl γ-acetylvalerate (I, R = CH_3 or C_2H_5) and ethyl bromoacetate. However, the yield of II was at best only 18%, so this sequence was abandoned. The Reformatsky reaction between γ-acetylvaleronitrile (III) (13) and ethyl bromoacetate gave ethyl ϵ-cyano-β-hydroxy-β,γ-dimethylcaproate (IV) in 35% yield. Hydrolysis of IV with concentrated hydrochloric acid gave a crude product (in 98% yield) assumed to be the lactone V. Attempts to cleave the crude lactone by successive treatment with thionyl chloride and ethanolic hydrogen chloride followed by thermal dehydrohalogenation (12) to the unsaturated ester VI were not entirely successful. The properties of the resulting compound agreed more with those of the chloro ester VII than with those of VI. The yield of crude VII was about 71%. Alkaline hydrolysis of VII gave 96% of 3,4-dimethyl-2-heptenedioic acid (VIII) as a noncrystallizable oil. Even after treatment with Raney nickel to remove any catalyst poisons, attempts to hydrogenate VIII over platinum oxide were unsuccessful. Subsequent development of an alternative, independent route (to be reported later) for the synthesis of the saturated analog of VIII obviated the necessity for accomplishing the hydrogenation of VIII, and, in connection with other studies in this laboratory (14), attention was directed toward the possibility of cyclizing VIII to the cyclohexenone. Cyclization of VIII by distillation with a small amount of manganous carbonate at 280–290° gave 3,4-dimethyl-2-cyclohexenone (IX) in 63%



yield. This result was somewhat surprising in view of the poor yields obtained from the cyclizations of α-hydromuconic acids to cyclopentenones under similar conditions, decarboxylation being the principal reaction in that series (14), and the low yields of cyclohexenones obtained by Ruzicka (15) from the distillation of the anhydrides of 2-heptenedioic acids.

Frank, Armstrong, Kwiatek, and Price (16) have reported that the reaction of γ,δ-dimethyl-γ-caprolactone with phosphorus pentoxide gave 2,2,3-trimethyl-4-cyclopentanone and a second ketone tentatively identified as IX. Comparison of the physical constants and of the semicarbazones of the ketones prepared in this and in the earlier (11) work indicates that the two were the same (IX).

The hydrogenation of IX in the presence of platinum oxide proceeded rapidly to form X in essentially quantitative yield. The properties of X and its semicarbazone (Table I) agreed very well with those reported previously by Ungnade and McLaren (9) and Nickels and Heintzelman (11) but only fairly well with other reported values (14). As pointed out in the Experimental section, the very low melting point reported by von Auwers (8) for the semicarbazone of X is probably accounted for by a slow rate of heating. Repeated fractional distillation of X and repeated recrystallization of its semicarbazone yielded no evidence to indicate the presence of more than one isomer. Apparently the hydrogenation of IX proceeded in a stereospecific manner to give a single isomer of X. Cornubert, Andre, and Hartmann (5) have reported that hydrogenation of 3,5-dimethyl-2-cyclohexenone under a variety of conditions gave only *cis*-3,5-dimethylcyclohexanone. Presumably by analogy the hydrogenation of IX gave *cis*-X, although a definite assignment of configuration must await further study.

TABLE I

PROPERTIES OF 3,4-DIMETHYLCYCLOHEXANONE (X)

SOURCE	B.P., °C.	SEMICARBAZONE M.P., °C.	n_D^{20}
Sebatier and Mailhe (7)	187 (corr.)	175	—
von Auwers (8)	187	189	1.4476
Ungnade and McLaren (9)	186.4–188	184–185	1.4513
Décombe (10)	186–189	189–190	—
Nickels and Heintzelman (11)	—	—	1.4520
Baumgarten and Eifert	187–189 (731.5)	184–185[a] 172.5–173[b]	1.4512

[a] Placed in bath at 180°. [b] Placed in cold bath.

EXPERIMENTAL

Ethyl γ-acetylvalerate (I, R = C_2H_5). α-Methylacetoacetic ester was prepared in 66% yield according to the method of Lucas and Young (17), b.p. 75–76° (15 mm.). From the sodium salt of the keto ester and ethyl β-bromopropionate, diethyl α-methyl-α-acetylglutarate was prepared in 27% yield by the procedure of Clemo and Welch (18), b.p. 158–160° (16 mm.). Hydrolysis of the latter with concentrated hydrochloric acid gave γ-acetylvaleric acid (13, 19) in 76% yield, b.p. 160° (15 mm.).

A mixture of 68 g. (0.47 mole) of γ-acetylvaleric acid, 28 g. (0.61 mole) of ethanol, 50 ml. of benzene, and 0.5 g. of sulfosalicylic acid was heated under reflux in an apparatus equipped with a Barrett-type water separator until no more water was collected (two hours). The excess ethanol and benzene were distilled off and the residue was washed with water, dried over sodium sulfate, and distilled, giving 57 g. (71%) of ethyl γ-acetylvalerate, b.p. 114° (15 mm.), n_D^{25} 1.4282.

Methyl γ,γ-diacetylbutyrate. To a cooled solution of 120 g. (5.2 moles) of sodium in 2 l. of absolute ethanol was added 500 g. (5.0 moles) of acetylacetone with stirring over a period of 1.5 hours. After addition was complete the mixture was stirred one hour and the resulting solid was filtered off, washed with cold ethanol, and dried *in vacuo*, giving 576 g. (95%) of sodium acetylacetone. A mixture of 78 g. (0.64 mole) of sodium acetylacetone and 115 g. (0.94 mole) of methyl β-chloropropionate was heated to 120°. At this point a vigorous reaction commenced and the mixture refluxed rapidly for several minutes. After the initial reaction subsided, heating was continued for seven hours at 110–120°. The mixture was cooled, the minimum amount of water was added to dissolve the sodium chloride, and the organic layer was taken up in 100 ml. of ether. The ethereal solution was dried over sodium sulfate and distilled, giving 67 g. (57%) of methyl γ,γ-diacetylbutyrate, b.p. 144–148° (15 mm.), n_D^{20} 1.4536. This procedure was adapted from that of March (20).

Methyl γ-acetylvalerate (I, R = CH_3). To a cooled solution of 13.8 g. (0.7 mole) of sodium in 500 ml. of ethanol was added 107 g. of methyl γ,γ-diacetylbutyrate. The mixture was heated on the water bath and 50 g. (0.7 mole) of methyl iodide was added slowly. Heating was continued for nine hours. The minimum amount of water was added to the cooled mixture to dissolve the precipitated salts and the solution was extracted with six 100-ml. portions of ether. The ethereal solution was dried over sodium sulfate and distilled, giving 81 g. (90%) of methyl γ-acetylvalerate, b.p. 113–117° (16 mm.), n_D^{20} 1.4288, d_4^{20} 0.988.

Anal. Calc'd for $C_8H_{14}O_3$: C, 60.73; H, 8.92.

Found: C, 60.51; H, 8.99.

This procedure was adapted from the procedure of March (20) for the preparation of ethyl γ-acetylvalerate.

ϵ-Carboethoxy-γ, δ-dimethyl-δ-caprolactone (II). To 86.5 g. (1.3 moles) of freshly sandpapered zinc foil in a three-necked flask fitted with a stirrer, dropping-funnel, and reflux condenser was added 150 ml. of a solution of 73 g. (0.42 mole) of ethyl γ-acetylvalerate, 117.2 g. (0.74 mole) of methyl γ-acetylvalerate, 234 (1.4 moles) of ethyl bromoacetate, 350 ml. of toluene, and 400 ml. of benzene. The reaction started vigorously, and the remainder of the solution of reactants was added at such a rate that refluxing was maintained. The mixture was heated for one hour after addition was complete, poured on crushed ice, and decomposed with an excess of 10% sulfuric acid. The benzene-toluene layer was separated and the water layer was extracted with two 100-ml. portions of benzene. The combined organic layers were distilled, giving 63 g. (*ca.* 30%) of recovered methyl and ethyl γ-acetylvalerate, b.p. 100–120° (15 mm.) and 24 g. (10%; 18% based on recovered starting material) of ϵ-carboethoxy-γ, δ-dimethyl-δ-caprolactone, b.p. 139–144° (1 mm.).

Anal. Calc'd for $C_{11}H_{18}O_4$: C, 61.65; H, 8.47.

Found: C, 61.22; H, 8.31.

Ethyl ϵ-cyano-β-hydroxy-β, γ-dimethylcaproate (IV). γ-Acetylvaleronitrile was prepared in 24–30% yield by the monocyanoethylation of methyl ethyl ketone (13). To a 3-l. flask fitted with a stirrer, reflux condenser, and dropping-funnel was added 71.5 g. (1.1 moles) of freshly sandpapered zinc foil and 50 ml. of benzene. The benzene was distilled from the apparatus to dry it, and while the flask was still warm 150 ml. of a solution of 125 g. (1.0 mole) of γ-acetylvaleronitrile, 200 g. (1.2 moles) of ethyl bromoacetate, 300 ml. of benzene, and 200 ml. of toluene was added along with a few crystals of iodine. An immediate reaction took place and the remainder of the solution of reactants was added at such a rate that the reaction mixture refluxed vigorously. Toward the end of the addition and for 45 minutes afterward heat was applied to maintain reflux. The reaction mixture was poured on ice, excess 10% sulfuric acid was added, the layers were separated, and the water layer was extracted with four 100-ml. portions of benzene. The organic layer was washed twice with dilute sodium bicarbonate solution and twice with water. The benzene was removed at atmospheric pressure and the residue was distilled under reduced pressure, giving 75 g. (35%) of ethyl ϵ-cyano-β-hydroxy-β,γ-dimethylcaproate, b.p. 148° (2 mm.).

Anal. Calc'd for $C_{11}H_{19}NO_2$: C, 66.96; H, 9.71; N, 7.10.

Found: C, 67.12; H, 9.54; N, 7.33.

Hydrolysis of ethyl ϵ-cyano-β-hydroxy-β,γ-dimethylcaproate. A mixture of 54 g. (0.25 mole) of ethyl ϵ-cyano-β-hydroxy-β,γ-dimethylcaproate and 81 ml. of concentrated hydrochloric acid was heated under reflux for four hours. The mixture was evaporated under reduced pressure and the resultant mixture of oils and solid was extracted with two 50-ml. portions of ether. The ether was evaporated and 25 ml. of benzene was added to the residue and distilled to remove the last traces of water. The resulting brown oil weighed 46 g. (98%), based on the formation of the lactone, $C_9H_{14}O_4$ (V).

3,4-Dimethyl-2-heptenedioic acid (VIII). A mixture of 46 g. (0.25 mole) of the lactone V above and 92 ml. (1.28 moles) of thionyl chloride was heated for three hours on the water-bath. The cooled mixture was added slowly to 250 ml. of absolute ethanol which had been saturated with hydrogen chloride at 0°. The ethanol was distilled over at atmospheric pressure until the temperature of the vapor reached 80° and the residue was distilled at 15 mm. (water pump) until the temperature rose to 100°. The remaining liquid was distilled using an oil pump and the fraction boiling up to 144° (3 mm.) was collected. Redistillation gave 49 g. (71%) of a product that was probably largely diethyl β-chloro-β,γ-dimethylpimelate (VII), b.p. 128–132° (3 mm.). The product gave a strong positive test for halogen and negative tests for carbon-carbon unsaturation.

Without further purification the crude chloro ester (49 g., 0.18 mole) was heated under reflux with a solution of 38 g. (0.67 mole) of potassium hydroxide in 100 ml. of 95% ethanol for four hours. The alcohol was evaporated and the residue made acid to Congo Red with cold dilute sulfuric acid. The resulting mixture was extracted with three 50-ml. portions of ether. The ether was dried over sodium sulfate and evaporated, leaving 31.5 g. (96%) of crude 3,4-dimethyl-2-heptenedioic acid, a brown oil. Attempts to cause the product to crystallize in various freezing mixtures were unsuccessful. Attempts to hydrogenate the material over platinum oxide at 45 p.s.i. pressure were likewise unsuccessful (even after treatment with Raney nickel to remove catalyst poisons).

3,4-Dimethyl-2-cyclohexenone (IX). An intimate mixture of 13 g. (0.07 mole) of the crude unsaturated acid (VIII) and 1.5 g. (0.013 mole) of manganous carbonate in a small distilling flask was heated in an air-bath at 280–290° until no more liquid distilled. The distillate was saturated with potassium carbonate and was extracted with two 25-ml. portions of ether. The ether was dried over potassium carbonate and evaporated. Distillation of the residue gave 5 g. (63%) of 3,4-dimethyl-2-cyclohexenone, b.p. 190–192° (729 mm.), 102–104° (17 mm.), n_D^{20} 1.4702, ultraviolet absorption maximum (in absolute ethanol) 235 mμ, log ε 3.74 [Frank, *et al.* (16) reported b.p. 100–101° (18 mm.), n_D^{20} 1.4779, ultraviolet absorption maximum 231 mμ, log ε 3.02].

The semicarbazone of the ketone, recrystallized from dilute ethanol, melted at 182–183° (dec., placed in bath at 180°).

Anal. Calc'd for $C_9H_{16}N_3O$: C, 59.59; H, 8.34; N, 23.19.

Found: C, 59.40; H, 9.02; N, 23.12.

3,4-Dimethylcyclohexanone (X). Hydrogenation of 5.0 g. (0.043 mole) of 3,4-dimethylcyclohexenone in 50 ml. of absolute ethanol in the presence of 0.1 g. of platinum oxide was complete in 30 minutes. The alcohol was evaporated and the residue distilled, giving a quantitative yield of 3,4-dimethylcyclohexanone, b.p. 187–189° (731.5 mm.), n_D^{20} 1.4512.

The *semicarbazone*, recrystallized from dilute ethanol, melted at 172.5–173° (dec., placed in cold bath) and at 184–185° (dec., placed in bath at 180°).

Anal. Calc'd for $C_9H_{17}N_3O$: C, 58.99; H, 9.35; N, 22.93.

Found: C, 59.22; H, 9.25; N, 22.52.

Repeated recrystallization of the semicarbazone yielded no substance different from that described above. The melting point of the semicarbazone showed a considerable dependence on the mode of determination. When placed in a cold bath and heated, slow browning was observed with a surprisingly sharp *apparent* liquefaction at the temperature indicated. When placed in the bath at 180° and held there long enough to establish equilibrium, the semicarbazone did not melt until the temperature was raised to 182–183°. We believe the higher temperature to be more acceptable as the "melting point", for at that temperature there is less decomposition accompanying melting and the substance resolidifies on cooling, whereas decomposition is more extensive when the slow rate of heating is employed and the substance does not resolidify on cooling.

SUMMARY

γ-Acetylacrylonitrile undergoes the Reformatsky reaction with ethyl bromoacetate to form ethyl ε-cyano-β-hydroxy-β,γ-dimethylcaproate. The latter is

converted by successive acid hydrolysis, treatment with thionyl chloride and alcoholic hydrogen chloride, and alkaline hydrolysis and dehydrohalogenation to 3,4-dimethyl-2-heptenedioic acid. Cyclization of the latter affords a new synthetic route to 3,4-dimethyl-2-cyclohexenone and catalytic hydrogenation of the cyclohexenone gives a new route to 3,4-dimethylcyclohexanone.

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