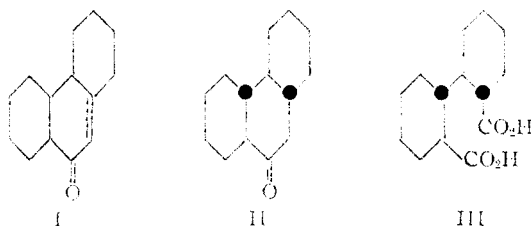


[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

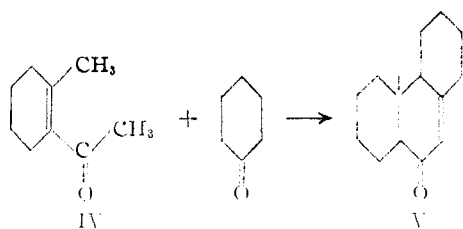
The Reaction of 1-Acetyl-2-methylcyclohexene with Cyclohexanone¹

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In 1935 Rapson and Robinson² condensed 1-acetyl- Δ^1 -cyclohexene with cyclohexanone in the presence of sodamide and obtained a tricyclic, unsaturated ketone, to which structure I was assigned. The correctness of this formulation was subsequently established by Linstead and co-workers³ by ultraviolet absorption measurements (λ_{\max} , 238 $m\mu$, $\log \epsilon$ 4.14) and by catalytic hydrogenation of the condensation product to a satu-



rated ketone (II), which furnished *trans-anti-trans* perhydrodiphenic acid (III) on nitric acid oxidation. With the object of incorporating an angular methyl group in the perhydrophenanthrene nucleus, Huber⁴ undertook extension of the Rapson-Robinson synthesis to 1-acetyl-2-methyl- Δ^1 -cyclohexene (IV), which was condensed with cyclohexanone in an ether-pyridine solution of potassium isopropoxide. The product, obtained as an oil (b. p. 81° (10⁻⁴ mm.)) in 29% yield, furnished a 2,4-dinitrophenylhydrazone, m. p. 103-104°, and a semicarbazone, m. p. 116-118°, in unspecified amounts and showed maximum absorption in *ether* at 238 $m\mu$. In view of the analogy to



the earlier work, and because phenanthrene was obtained by selenium dehydrogenation, structure V was proposed for the new substance by Huber. Similar condensations of acetylmethylcyclohexene with α -tetralone,⁵ with α -decalone⁵ and with 8-

methylhydrindanone-4⁶ have also been explored, but when these experiments were carried out, the structures of the various products were not adequately investigated and were based for the most part on Huber's results.⁷ Since substances related to V are of obvious interest in connection with steroid synthesis, we have re-examined the reaction of acetylmethylcyclohexene with cyclohexanone.

The acetylmethylcyclohexene employed by Huber was prepared from acetyl chloride and methylcyclohexene, which apparently was obtained by dehydration of commercial 2-methylcyclohexanol as described by Ruzicka, Koolhaas and Wind.⁸ Since methylcyclohexene derived from this source contains, in addition to the Δ^1 -isomer, as much as 53-65% of the Δ^2 -modification,⁹ it must be presumed that Huber's acetylmethylcyclohexene consisted of a complex mixture of isomers. Dehydration of 1-methylcyclohexanol, on the other hand, affords pure 1-methyl- Δ^1 -cyclohexene,⁵ which on reaction with acetyl chloride yields 1-acetyl-2-methylcyclohexene, $\lambda_{\max}^{\text{alc.}}$ 250 $m\mu$ (ϵ 4500), as an equilibrium mixture of α,β - and β,γ -unsaturated forms.⁹

We have condensed this material with cyclohexanone according to the procedure of Huber,⁴ except that potassium *t*-butoxide and *t*-butyl alcohol were substituted for potassium isopropoxide-isopropyl alcohol in order to avoid the possibility of ketone reduction.¹⁰ The reaction product was isolated in 56% yield as a light oil (b. p. 96-98° (10⁻³ mm.)) and exhibited maximum absorption in *alcohol* at 250 $m\mu$ (ϵ 5360). The substance was chromatographically homogeneous; analyses and a molecular weight determination corresponded to the formula C₁₅H₂₂O. The appearance of two bands in the carbonyl region of the infrared (Fig. 1), one at 5.96 μ and the other at 5.86 μ , indicated the presence of both conjugated and unconjugated carbonyl functions, which of necessity are associated with the same keto group and must therefore be attributed to α,β - and to β,γ -unsaturation, respectively. The product did not form a semicarbazone, dinitrophenylhydrazone, nor oxime.

(1) The work reported in this paper was supported by funds provided by the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council, and by the Eli Lilly Co., Indianapolis.

(2) Rapson and Robinson, *J. Chem. Soc.*, 1285 (1935).

(3) Linstead and Walpole, *J. Chem. Soc.*, 842, 850 (1939); Linstead and Doering, *This Journal*, **64**, 2003 (1942); Linstead, Davis and Whetstone, *ibid.*, **64**, 2009 (1942).

(4) Huber, *Ber.*, **71**, 725 (1938).

(5) Luderitz, Dissertation, Göttingen, 1944; Dimroth, *Angew. Chem.*, **59**, 23, 215 (1947). A copy of the Luderitz dissertation was made available to us through the courtesy of Dr. Karl Dimroth.

(6) Bagchi and Banerjee, *J. Ind. Chem. Soc.*, **23**, 397 (1946).

(7) The work of W. S. Johnson, Szpuszkowicz and Miller, *This Journal*, **72**, 3736 (1950), on the structures of some of these substances has recently come to our attention. We are indebted to Dr. Johnson for communicating his results to us.

(8) Ruzicka, Koolhaas and Wind, *Helv. Chim. Acta*, **14**, 1151 (1931).

(9) Dimroth and Luderitz, *Ber.*, **81**, 242 (1948); Braude and co-workers, *J. Chem. Soc.*, 1890 (1949); Turner and Voitte, *This Journal*, in press.

(10) Cf. Doering, Cortes and Knox, *This Journal*, **69**, 1700 (1947).

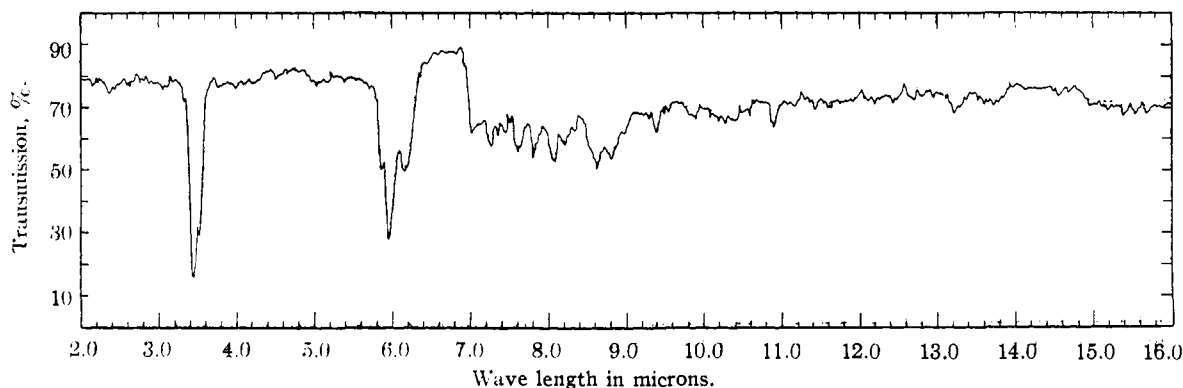
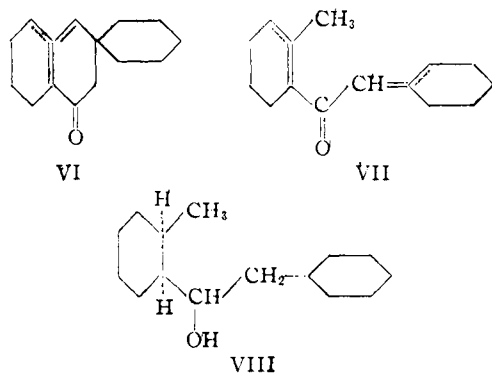


Fig. 1.—Infrared absorption spectrum of condensation product (VII) in carbon disulfide.

The ultraviolet absorption data noted previously are incompatible with a compound of structure V, which should absorb maximally at about $240\text{ m}\mu$.¹¹ Moreover, oxidation of the condensation product with potassium permanganate furnished considerable amounts of adipic acid, which cannot be derived in a simple way from V. Our attention was therefore directed to two alternative formulations, VI and VII, either of which could account for the observed properties.

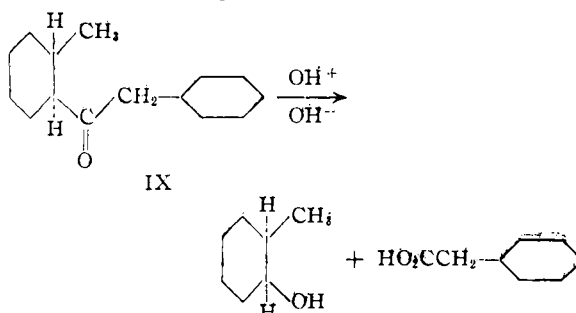


In order to distinguish these possibilities the condensation product was hydrogenated over platinum in acetic acid solution. Reduction ceased after the absorption of 3.02 molar equivalents of hydrogen, and a crystalline alcohol, $\text{C}_{16}\text{H}_{28}\text{O}$, melting at $65.5\text{--}66.5^\circ$ was isolated by slow crystallization from petroleum ether. This result excludes formula VI, for the absorption of three moles of hydrogen by a substance of this constitution would furnish a hydrocarbon. Structures VII and VIII may therefore be assigned, respectively, to the condensation product and to the derived saturated alcohol.

Unambiguous evidence supporting this conclusion was obtained in the following way. Oxidation of VIII with chromic acid gave an oily ketone (IX), which failed to yield a semicarbazone, but

(11) The value reported by Huber ($238\text{ m}\mu$) was obtained in ether. Correction for solvent effect (Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 184), gives a value in alcohol of $245\text{ m}\mu$.

which was characterized by intense absorption at $5.80\text{ }\mu$ in the infrared. No attempt was made to purify this material, and it was oxidized directly with a solution of perbenzoic acid in chloroform.¹²



Hydrolysis of the oxidation product afforded *cis*-2-methylcyclohexanol, isolated as the acid phthalate and identified by comparison with an authentic sample. There was also obtained an acidic compound that yielded an amide, m. p. $167\text{--}168^\circ$, identical in all respects with cyclohexylacetamide.

Although our results establish that the main product of the condensation of acetylmethylcyclohexene with cyclohexanone is VII, the presence of isomeric contaminants in amounts sufficiently small to escape detection cannot, of course, be excluded.

Attempts to obtain V by acid- or base-catalyzed cyclization of 1-(cyclohexylideneacetyl)-2-methylcyclohexene (VII) under forcing conditions were unsuccessful. The substance was unaffected by prolonged refluxing with sodium hydride in benzene, and whereas treatment with concentrated sulfuric acid produced some increase in the intensity of absorption of ultraviolet light ($\epsilon\ 8640$), the position of the absorption maximum ($250\text{ m}\mu$) was unchanged.

Experimental¹³

Condensation of 1-Acetyl-2-methyl- Δ^1 (and Δ^5)-cyclohexene with Cyclohexanone.—Fourteen grams of potassium under 200 ml. of anhydrous ether (protected by an atmosphere of nitrogen) was dissolved by the slow addi-

(12) C. J. Turner, THIS JOURNAL, **73**, 878 (1950).

(13) All melting points are corrected. Analyses were performed by Mr. S. M. Nagy, M. I. T.

tion of 125 ml. of dry *t*-butyl alcohol. The resulting slurry of potassium *t*-butoxide was then treated with a solution of 39.2 g. of 1-acetyl-2-methylcyclohexene¹⁴ and 28.0 g. of cyclohexanone in 100 ml. of anhydrous pyridine. The pyridine solution was added slowly with stirring and gave a clear orange solution, from which a heavy precipitate separated after about two hours. After one week, water was added, and the layers were separated. The aqueous phase was cooled, acidified with hydrochloric acid and thoroughly extracted with ether. The ether extracts were combined with the organic fraction obtained above and washed successively with water, dilute hydrochloric acid, water, dilute sodium hydroxide solution, and a saturated solution of sodium chloride. After filtration through anhydrous sodium sulfate, the solvent was removed, and the residue was fractionated at diminished pressure. The yield of material boiling at 85–105° at 10⁻³ mm. was 42.0 g.

Redistillation furnished 34.8 g. (56%) of product, b. p. 96–98° (10⁻³) mm., $\lambda_{\text{max}}^{\text{alc}}$, 250 m μ , ϵ 5360.

Anal. Calcd. for C₁₅H₂₂O: C, 82.51; H, 10.16; mol. wt., 218. Found: C, 82.63; H, 10.34; mol. wt. (Rast), 218.

Permanganate Oxidation of 1-(Cyclohexylideneacetyl)-2-methylcyclohexene (VII).—The ketonic condensation product (5.00 g.) obtained above was dissolved in 30 ml. of pyridine and added slowly to a cooled solution of 40.0 g. of potassium permanganate and 4.00 g. of potassium hydroxide in 300 ml. of 30% aqueous pyridine. The temperature of the reaction mixture was not allowed to rise above 40°.

After standing overnight at room temperature, the permanganate color had completely disappeared. The manganese dioxide was removed by filtration and washed thoroughly with hot water. Filtrate and washings were combined and concentrated to dryness under reduced pressure; the residue, after washing with ether, was dissolved in a small volume of water and acidified with hydrochloric acid. The resulting solution was then extracted repeatedly with ether, ethyl acetate and chloroform. The organic extracts were finally combined, treated with charcoal, filtered and concentrated to dryness.

Trituration with ether gave 1.08 g. of a crystalline solid (m. p. 139–146°), which on recrystallization from acetone melted at 150–152° and did not depress the melting point of adipic acid. No other crystalline component could be isolated from the mother liquors.

Hydrogenation of 1-(Cyclohexylideneacetyl)-2-methylcyclohexene.—Hydrogenation of VII (2.64 g., 12.1 mmoles) was carried out in 10 ml. of glacial acetic acid in the presence of 500 mg. of preduced platinum oxide. After twenty-two hours 881 ml. of hydrogen (3.02 molar equivalents) had been absorbed and no further reaction was observed.

The catalyst was removed by filtration, and the filtrate was diluted with ether, washed with water, dilute alkali, and saturated sodium chloride. After drying over anhydrous sodium sulfate, the ether was removed on the steam-bath, and the product was crystallized from a small volume of petroleum ether. The yield of material melting at 61.5–63.5° was 600 mg. The substance was difficult to handle in that it was quite soluble in the common organic solvents and could not be satisfactorily recovered from aqueous media. Recrystallization from a small amount of petroleum ether furnished a pure sample (prisms), possessing a pleasant odor and melting at 65.5–66.5°. The presence of a hydroxyl group was established by a sharp band at 2.80 μ in the infrared.

Anal. Calcd. for C₁₅H₂₄O: C, 80.29; H, 12.58. Found: C, 80.36; H, 12.63.

The mother liquors were not investigated for other isomers.

(14) The acetylmethylcyclohexene was obtained by the procedure of Ruzicka, Koolhaas and Wind (ref. 8) as modified by Dimroth and Lilderitz (refs. 5 and 9).

Oxidative Degradation.—In a separate experiment the total crude hydrogenation product from 10.0 g. of 1-(cyclohexylideneacetyl)-2-methylcyclohexene (VII) was dissolved in 50 ml. of acetic acid and cooled to 15°. A solution of 3.20 g. (1.05 equivalents) of chromic oxide in 100 ml. of 85% acetic acid was then added at a rate such that the temperature of the reaction mixture did not rise above 25°. After standing overnight at room temperature, the solution was diluted with a large volume of water and extracted with ether. The ether extracts were combined, washed successively with water, dilute hydrochloric acid, dilute sodium hydroxide, and saturated sodium chloride, filtered through anhydrous sodium sulfate, and concentrated to dryness under reduced pressure.

Five grams of crude ketone obtained in this way was treated with 48 ml. of 0.55 molar perbenzoic acid in chloroform solution. After standing for seven days at room temperature, ether was added, and the mixture was washed thoroughly with dilute sodium hydroxide solution, filtered through anhydrous sodium sulfate and concentrated to dryness. The residue was then hydrolyzed by refluxing overnight with a solution of 3.0 g. of sodium hydroxide in 70 ml. of 50% aqueous methanol. Dilution with water and ether extraction effected the separation of neutral and acidic fractions.

The neutral material (3.4 g.) was refluxed with 4.5 g. of phthalic anhydride in 15 ml. of dry pyridine for three and one-half hours, at the end of which time the mixture was cooled, diluted with water, acidified with hydrochloric acid, and extracted with ether. The product was then separated from considerable amounts of unchanged ketone (IX) by extraction with cold, dilute alkali, from which it was recovered by acidification and ether extraction. The resulting ethereal solution was concentrated, and on dilution with petroleum ether, furnished 2.23 g. of *cis*-2-methylcyclohexanyl acid phthalate, m. p. 101–103°. A mixed melting point with an authentic sample showed no depression.

The acidic fraction (1.0 g.) obtained on hydrolysis of the peracid oxidation product was dissolved in 10 ml. of anhydrous ether and treated with 2 ml. of purified thionyl chloride.¹⁵ After standing overnight at room temperature, the ether was removed, and benzene was added and evaporated three times in succession to eliminate the last traces of thionyl chloride. The crude acid chloride was then taken up in dry ether, cooled in ice, and saturated with dry ammonia gas. Removal of the ether and excess ammonia left a solid residue, which was dissolved in water and chloroform. The chloroform layer was washed with water and saturated sodium chloride, filtered through anhydrous sodium sulfate, and concentrated to dryness. Crystallization from chloroform-petroleum ether gave 890 mg. of crude material melting at 161–165°. Two recrystallizations from ethanol afforded a pure sample, m. p. 167–168°, that did not depress the melting point of a specimen of cyclohexylacetamide, prepared for comparison by hydrogenation (Ni) of phenylacetic acid and conversion of the resulting cyclohexylacetic acid into the corresponding amide.

Summary

Condensation of 1-acetyl-2-methyl- Δ^1 (and Δ^2)-cyclohexene with cyclohexanone under the influence of potassium *t*-butoxide affords 1-(cyclohexylideneacetyl)-2-methylcyclohexene as the principle product. This substance was previously formulated as a 10-keto-12-methyldodecahydrophenanthrene. Infrared absorption data suggest that the dienone consists of a mixture of α,β - and β,γ -unsaturated isomers.

CAMBRIDGE, MASS.

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(15) Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, Mass., 1941, p. 381.