Synthesis of Resin Acid Intermediates. 8α,10β-Dimethyl-8β-carbomethoxy-$\Delta^{1,9;3,4}$-hexahydronaphthalone-2 and 8α,10β-Dimethyl-8β-carbomethoxy-$\Delta^{1,9}$-octalone-2

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Condensation of 2,6-dimethyl-2-carbomethoxy-6-formylcyclohexanone with acetone gives a small yield of dienone from which pure 8α,10β-dimethyl-8β-carbomethoxy-$\Delta^{1,9;3,4}$-hexahydronaphthalone-2 (XI) has been isolated. Condensation of 2,6-dimethyl-2-carbomethoxycyclohexanone with N,N-diethylaminobutanone-3 methiodide afforded a mixture of bicyclic unsaturated ketones from which pure 8α,10β-dimethyl-8β-carbomethoxy-$\Delta^{1,9}$-octalone-2 (XVI) has been isolated, converted to XI, and shown to have stereochemistry as designated.

As part of a research program directed toward synthesis of diterpene resin acids *via* bicyclic intermediates possessing the difficultly accessible *gem*-methylcarboxyl grouping and suitable functionality for elaboration to a variety of natural substances, we have investigated ring extension from a "preformed ring A" unit, such as 2,6-dimethyl-2-carbomethoxycyclohexanone (I).[2] Bicyclic material of potentially useful structure was obtained both by condensation of I with methyl vinyl ketone and by condensation of 2,6-dimethyl-2-carbomethoxy-6-formylcyclohexanone (II) with acetone, and it is these results which are described in this paper. However, in view of the better yields obtained in other preparations of similar bicyclic intermediates,[3] no further pursuit of these two routes is planned.

The condensation of II with acetone was investigated first. 2-Methyl-2-carbomethoxycyclohexanone[4] was converted to its hydroxymethylene derivative[5] (III), m.p. 36–40°, in 68% yield with methyl formate and sodium methoxide in methanol under conditions which permitted precipitation of the enolate salt of III, thereby preventing alkoxide cleavage of the fully substituted β-keto ester moiety.

Methylation of 2-methyl-6-hydroxymethylenecyclohexanone (IV) yields a product suitable for subsequent condensation with acetone, only about 20% of the enol ether being formed.[6] In the present case, however, methylation of III with methyl iodide in acetone using potassium carbonate as catalyst always afforded at least 50% enol ether V. The amount of this O-alkylation product could be determined easily by comparing the ultraviolet absorption of the crude product with that of pure V, $\lambda_{\max}^{\text{EtOH}}$ 280 mμ (ε 7500). The amount of desired C-alkylation product (II)[7] present was very difficult to ascertain, for attempted isolation afforded only V and I, presumably produced by decarbonylation of II. Therefore, the crude methylation product was used directly in the next step.

The reason for the difference in the C- *vs.* O-alkylation ratio between IV[6] and III can be seen from a conformational consideration of the respective anions undergoing alkylation, if one assumes that C-alkylation occurs more readily with an axially approaching electrophilic center.[8] Such approach of methyl iodide to the π-cloud of the anion of 2-methyl-2-carbomethoxy-6-hydroxymethylenecyclohexanone (VI) will necessarily generate a 1,3-diaxial interaction with either the methyl or carbomethoxyl group. In the anion of 2-methyl-6-hydroxymethylenecyclohexanone (VII), on the other hand, a hydrogen can be in the 1,3-diaxial relationship to the incipient C-methyl group. Thus, C-methylation will be less favored with the larger axial group of VI and O-methylation becomes the more likely reaction path.

The condensation of the crude methylation mixture with acetone was conducted, as is the custom,[9] in two steps: first, refluxing with piperidine and acetic acid to effect condensation at the aldehyde, and, second, treatment with stronger base to effect ring closure to the dienone. The first step afforded a crude product which had ultraviolet absorption at 220–225 mμ (ε 2000), corresponding to a yield of *ca.* 8% from III of α,β-un-

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(1) (a) Recipient of support under the terms of an institutional research training grant from the U. S. Public Health Service, 1960–1962; Dartmouth College Senior Fellow, 1961–1962. (b) National Science Foundation Undergraduate Research Participant during the 1961–1962 and 1962–1963 academic years.

(2) Similar and essentially identical ring A units have been used as starting materials for an A → A–C phenylethylcyclohexanol → A–B–C (by acid-catalyzed ring closure) approach to resin acids and related compounds [see, *e.g.*, R. D. Haworth and R. L. Barker, *J. Chem. Soc.*, 1299 (1939); R. D. Haworth and B. P. Moore, *ibid.*, 633 (1946); B. K. Bhattacharyya, *J. Indian Chem. Soc.*, **22**, 165 (1945); F. E. King, T. J. King, and J. G. Topliss, *Chem. Ind.* (London), 113 (1956), and *J. Chem. Soc.*, 573 (1957); J. A. Barltrop and N. A. J. Rogers, *ibid.*, 2566 (1958); U. R. Ghatak, *Tetrahedron Letters*, 19 (1959); U. R. Ghatak, D. K. Datta, and S. C. Ray, *J. Am. Chem. Soc.*, **82**, 1728 (1960)].

(3) T. A. Spencer, T. D. Weaver, M. A. Schwartz, W. J. Greco, Jr., and J. L. Smith, to be published.

(4) W. E. Bachmann and A. S. Dreiding, *J. Org. Chem.*, **13**, 317 (1948).

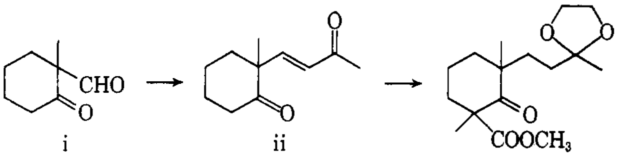
(5) E. W. Garbisch, Jr. [*J. Am. Chem. Soc.*, **85**, 1696 (1963)], has presented evidence that enolized β-keto aldehydes may exist to a significant or even preponderant degree at equilibrium in the "aldo enol" form rather than in the "hydroxymethylene ketone" form. The β-keto aldehyde species described in this paper are shown in the customary hydroxymethylene ketone form; obviously, no inference can be drawn about the actual equilibrium composition from the reactions of the species.

(6) W. S. Johnson and H. Posvic, *ibid.*, **69**, 1361 (1947).

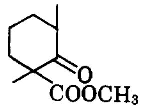
(7) The C-methylation of VI can, of course, generate a pair of diastereoisomers, with the 2- and 6-methyl groups *cis* and *trans*. Structure II is an expression for this mixture.

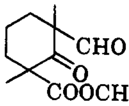
(8) Ample precedent exists for the assumption of stereoelectronic control of enolate methylation [see, *e.g.*, R. E. Ireland and R. C. Kierstead, *J. Org. Chem.*, **27**, 703 (1962)].

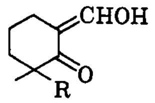
(9) A. L. Wilds and C. Djerassi, *J. Am. Chem. Soc.*, **68**, 1716 (1946); R. B. Woodward and T. Singh, *ibid.*, **72**, 494 (1950); see also ref. 11. While exploring an approach to diterpene intermediates outlined below (i → ii → iii) we found that piperidine and acetic acid, under the conditions of Woodward and Singh (*op. cit.*), actually cause cyclization of ii to 10-methyl-$\Delta^{1,9;3,4}$-hexahydronaphthalone-2, for the product absorbed at 240 mμ, and its hydrogenation product gave a 2,4-dinitrophenylhydrazone with m.p. 125–127°, (lit. m.p. 125–127°). However, in cases where the ring-closing aldol condensation is at a more hindered carbonyl (as in VIII–IX → XI–XII), the separate strong base step is necessary.

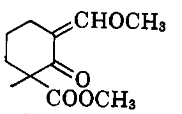


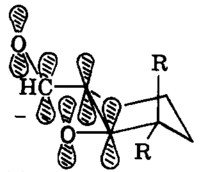
i ii iii


I


II


III, R = $COOCH_3$
IV, R = H

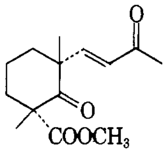

V

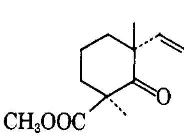


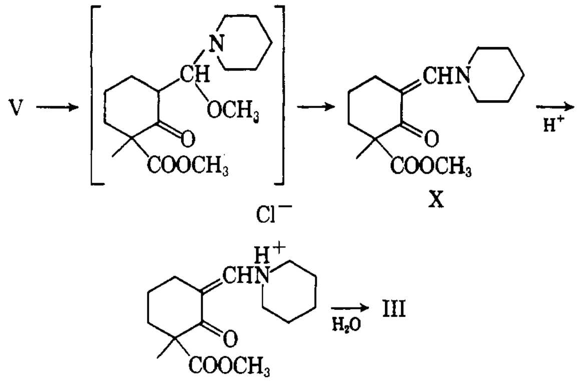
VI, R,R = CH_3,$COOCH_3$
VII, R,R = CH_3,H

saturated ketones VIII and IX, based on an assumed ϵ of 10,000 for pure material.[10] Chromatography effected concentration of the chromophoric material (maximum ϵ attained was 8100), separating it from an easily eluted, mobile oil which was fractionally distilled to afford a small amount of mesityl oxide (undoubtedly formed by self-condensation of acetone during the 90-hr. treatment with piperidine and acetic acid) and higher-boiling material, judged by boiling point, refractive index, and infrared spectrum to be composed predominantly of I and 2-methyl-2-carbomethoxycyclohexanone.

The major portion of enol ether V had been assumed to have been removed from the product during work-up by acid hydrolysis to III, followed by extraction of this substance with base. However, another path of removal of V came to light when it was observed that the aqueous acid wash layer, initially homogeneous, deposited upon standing an oil which proved to be essentially pure III. This "recovered" material undoubtedly found its way into the aqueous acid *via* the enamine X, as shown below.

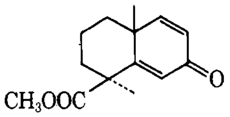

VIII

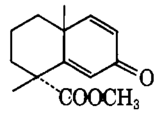

IX

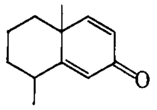


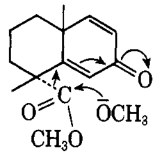
Treatment of the mixture containing VIII and IX with strong basic catalysts afforded material with absorption at 243 mμ, as expected for dienones XI and XII. The yield in the cyclization was never good; using purified starting material (ϵ 8100), the crude product (*ca.* 65%) had λ_{max} 243 mμ with ϵ 4000 to 4500 depending on conditions. The over-all yield of crude dienone from III thus may be estimated at 2%. Chromatography of the product from potassium *t*-butoxide-catalyzed cyclization afforded a very small amount of crystalline dienone, m.p. 90–91°, which was subsequently shown (*vide infra*) to be the isomer with the axial carbomethoxyl group (XI). The epimeric dienone XII was never obtained pure.

When the cyclization catalyst was sodium methoxide, there was isolated, in addition to XI, 8,10-dimethyl-$\Delta^{1,9;3,4}$-hexahydronaphthalone-2 (XIII), the dienone prepared by Bloom[11] by condensation of 2,6-dimethyl-2-formylcyclohexanone[6] with acetone. This dienone could arise by decarbomethoxylation as depicted in XIV, and its isolation can be taken as a possible indication of the presence of XII in the cyclization product, since nucleophilic attack (as in XIV) at the axial carbomethoxyl group of XI is unlikely (*vide infra*).[12] In view of the low yield in all the steps from III to the crude mixture of XI and XII, further conversions of these substances were not attempted, and attention was turned to the alternate approach, the Robinson annelation reaction of I.


XI


XII


XIII


XIV

In order to test the feasibility of Michael addition of I, we first tried the excellent acceptor acrylonitrile in the presence of potassium *t*-butoxide and obtained 51% of purified cyanoethylated product. This consisted of the two diastereoisomers of XV, one of which solidified, m.p. 64–65°. No attempt was made to identify the stereochemistry of these isomers[13] nor to use them for formation of the B ring *via* modification of the nitrile group.

That the reaction of I with methyl vinyl ketone did not proceed equally as smoothly was not unexpected. The Robinson annelation reaction applied to 2-methylcyclohexanone affords at best about 30% of 10-methyl-$\Delta^{1,9}$-octalone-2,[14] and in the case of I there is additional steric hindrance to both initial Michael addition and cyclization, plus the presence of a base-sensitive β-keto

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[10] 3-Penten-2-one shows λ_{max}^{EtOH} 224 mμ (ϵ 9700); K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

[11] S. M. Bloom, *J. Am. Chem. Soc.*, **80**, 6280 (1958). We wish to thank Dr. Bloom for kindly sending us a copy of the infrared spectrum of XIII and a sample of its 2,4-dinitrophenylhydrazone.

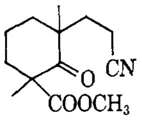
[12] Dienone XIII could arise by other pathways, *e.g.*, decarbomethoxylation of VIII and/or IX followed by cyclization, so that its isolation alone is by no means conclusive evidence for the presence of XII.

[13] By analogy to the Michael addition to I of methyl vinyl ketone, which afforded predominantly XVI, the predominant, crystalline cyanoethylation product would have the 2- and 6-methyl groups *trans*. If XVI arises by axial attack of the Michael acceptor, reaction occurs preferentially with methyl rather than carbomethoxyl in the "3-axial" position.

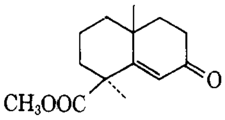
[14] A. S. Hussey, H. P. Liao, and R. H. Baker, *J. Am. Chem. Soc.*, **75**, 4727 (1953); A. L. Wilds, C. H. Hoffman, and T. H. Pearson, *ibid.*, **77**, 647 (1955).

ester moiety.[15] With N,N-diethylaminobutanone-3 methiodide under conditions similar to those of Cornforth and Robinson[16] there was obtained from I a yield of 11% (on the basis of ultraviolet absorption) of bicyclic unsaturated ketone, presumably a mixture of XVI and XVII.

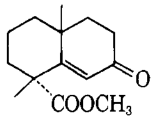
Extensive column chromatography effected considerable concentration but very incomplete separation of XVI and XVII, for only a small amount of one crystalline isomer, m.p. 89.5–90.5°, was obtained. Vapor phase chromatography showed that there were two major components in the chromophoric fractions, and that the preponderant one was the crystalline isomer. Since this isomer was adsorbed less strongly (elution or v.p.c.), it was very tentatively assigned structure XVI, with the carbomethoxyl group axial. Selenium dioxide oxidation of this crystalline isomer yielded the previously isolated crystalline dienone, suggesting that the latter was XI.



XV



XVI

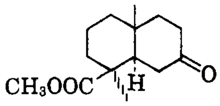


XVII

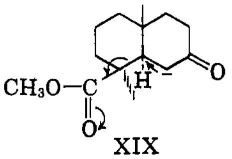
Confirmation of these stereochemical assignments was sought in the resistance which a tertiary carboalkoxyl in a 1,3-diaxial relationship to a methyl should exhibit to basic hydrolysis, as found in the cases of podocarpic[17] and agathic[18] esters and in a similar bicyclic system.[19] To this end, XVI was hydrogenated over palladium on carbon to yield a dihydro compound, m.p. 77.0–77.5°, which was assigned the *trans* structure XVIII by analogy to results of hydrogenation of similar systems.[20]

The saponification resistance of this keto ester was tested, but it was found that XVIII was converted by refluxing aqueous base to oily material whose infrared spectrum was consistent with products resulting from cleavage (reverse Michael reaction) as shown in XIX. When the ketone group of XVIII was first reduced with sodium borohydride (to give presumably largely XX) and the product then subjected to refluxing 3 *N* sodium hydroxide solution for 24 hr., no ester hydrolysis occurred; neutral material identical in the infrared with the starting hydroxy ester was recovered in 95% yield.

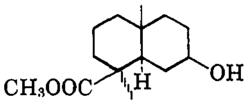
On the other hand, when some of the oil containing primarily the isomeric unsaturated ketone XVII was subjected to the same sequence—hydrogenation, sodium borohydride reduction, and basic hydrolysis—saponification occurred; *ca.* 60% of acidic material was obtained which solidified to afford a substance, m.p. 201–203°, possessing an elemental analysis consistent with the expected principal product of this sequence, XXI.



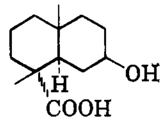
XVIII



XIX



XX



XXI

The n.m.r. spectra of XVI and XVIII[21] also confirmed the axial nature of the carbomethoxyl group in these substances, since the angular methyl resonance appeared at a higher field than expected for an epimeric substance like XVII, owing to transannular shielding by the axial carbomethoxyl.[22] The details of the argument will be deferred until a future publication when the n.m.r. spectra of similar intermediates[3] will be discussed.

Experimental

Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Melting points were taken either in an open capillary or on a micro hot stage; those of analytical samples are corrected. Boiling points are uncorrected. Ultraviolet spectra were determined in 95% ethanol on a Bausch and Lomb Spectronic 505 recording spectrophotometer. Infrared spectra were determined on a Perkin-Elmer Model 21 recording spectrophotometer.

2-Methyl-2-carbomethoxycyclohexanone.—2-Carbomethoxycyclohexanone was prepared in 40–45% yield by condensation of cyclohexanone with diethyl oxalate in methanol containing sodium methoxide, followed by pyrolysis of the intermediate glyoxylate, in a modification of the procedure of Snyder.[23] Methylation was performed by the method of Bachmann[4] in *ca.* 90% yield.

2-Methyl-2-carbomethoxy-6-hydroxymethylenecyclohexanone (III).—To a mixture of 173 g. (1.02 moles) of 2-methyl-2-carbomethoxycyclohexanone, b.p. 77–80° (0.8 mm.) (possibly contaminated with a small amount of the corresponding ethyl ester), and 300 g. (5 moles) of methyl formate (Brothers Chemical Co.) in a 2-l., three-necked flask equipped with mechanical stirrer, reflux condenser, and thermometer, and cooled to −8° in an ice–acetone bath was added dropwise over a 45-min. period a solution of 23 g. (1 mole) of sodium in 200 ml. of anhydrous methanol. Another 300 g. of methyl formate was added to the yellow-orange mixture which was then stirred with cooling for 3

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(15) Evolution of gas upon acidification of the reactions of I in the presence of potassium *t*-butoxide suggested that either β-keto acids or *t*-butyl esters may have been formed; *cf.* H. O. House, *et al.*, *J. Am. Chem. Soc.*, **84**, 2614 (1962).

(16) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949).

(17) I. R. Sherwood and W. F. Short, *ibid.*, 1006 (1938).

(18) L. Ruzicka and J. R. Hosking, *Helv. Chim. Acta*, **14** 203 (1931).

(19) C. L. Graham, F. J. McQuillin, and P. L. Simpson, *Proc. Chem. Soc.*, 136 (1963), and references cited therein.

(20) See, *e.g.*, G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **78**, 250 (1956); F. Sondheimer and D. Elad, *ibid.*, **79**, 5542 (1957); B. Gaspert, T. G. Halsall, and D. Willis, *J. Chem. Soc.*, 624 (1958); and, particularly, W. L. Meyer and A. S. Levinson, *J. Org. Chem.*, **28**, 2184 (1963). Some caution is necessary, however, in making the assumption that, in the words of E. Wenkert and B. G. Jackson [*J. Am. Chem. Soc.*, **80**, 211 (1958)], "... for obvious steric reasons hydrogenation of a $\Delta^{5,6}$ linkage in the presence of an axial angular methyl group and an axial C-4 substituent results in an A/B *trans* system," because in certain cases *cis* fusion has been obtained [see S. N. Mahapatra and R. M. Dodson, *Chem. Ind.* (London), 253 (1963); T. G. Halsall, W. J. Rodewald, and D. Willis, *J. Chem. Soc.*, 2798 (1959); N. B. Haynes and C. J. Timmons, *Proc. Chem. Soc.*, 345 (1958)]. Even if reduction of XVI unexpectedly did afford *cis* fusion, the combination of saponification and n.m.r. evidence (*vide infra*) still serves as proof of the structure of XVI.

(21) We wish to thank Professor Walter L. Meyer of Indiana University for determining these spectra and providing valuable interpretative discussion concerning them.

(22) R. W. J. Carney, Ph.D. thesis, Iowa State University, 1962, provides numerous examples of such an effect in resin acid derivatives; it also has been observed in resin acids and bicyclic substances in this laboratory.

(23) H. R. Snyder, L. A. Brooks, and S. H. Shapiro, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 531.

hr. and at room temperature for 15 hr. A voluminous white precipitate formed during the first hours of reaction.

The reaction was cooled to −8° in an ice–acetone bath again and 500 ml. of water was added slowly through a dropping funnel, with the temperature kept below 0°. The mixture, which at this point consisted of a yellow solution covered by an oily layer, was extracted twice with chloroform to remove neutral organic material. The aqueous layer was acidified carefully to *ca.* pH 5 by the addition of solid sodium dihydrogenphosphate and dilute hydrochloric acid, with stirring. Then the mixture was extracted thoroughly with benzene (some emulsion trouble), which was washed with water and saturated sodium chloride solution. The benzene was removed on the steam bath under reduced pressure, and the residue was distilled under nitrogen. 2-Methyl-2-carbomethoxy-6-hydroxymethylenecyclohexanone was obtained as a slightly yellow oil, b.p. 103–107° (1.4 mm.); the yield was 136.5 g. (68%). This product gave an immediate deep purple color with ferric chloride solution and solidified on standing to give crystals which melted, after washing with ether, at 36–40°. Redistillation afforded colorless material, b.p. 79° (0.25 mm.); $n^{25}\mathrm{D}$ 1.4992; $\lambda_{\max}^{\mathrm{EtOH}}$ 289 mμ (ϵ 8000); $\lambda_{\max}$ 5.73, 6.05, and 6.26 μ.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.64; H, 7.04.

When the condensation with methyl formate was conducted in a larger amount of methanol, so that the enolate salt of the product did not precipitate, the yield was reduced to 15–20%. Sodium hydride and potassium *t*-butoxide as catalysts gave only poor yields of hydroxymethylene compound.

Methylation of 2-Methyl-2-carbomethoxy-6-hydroxymethylenecyclohexanone.—The procedure used was a modification of that of Johnson and Posvic.[6] To a 2-l., three-necked flask were added 95 g. (0.69 mole) of potassium carbonate (reagent grade, anhydrous), 870 ml. of acetone (reagent grade, previously dried over potassium carbonate), 136 g. (0.69 mole) of 2-methyl-2-carbomethoxy-6-hydroxymethylenecyclohexanone (b.p. 103–107° at 1.4 mm.), and 65 ml. (148 g., 1.04 mole) of methyl iodide (Brothers Chemical Co.). The mixture was mechanically stirred at room temperature for a total of 45 hr. After 19 hr. an additional 30 ml. of methyl iodide was added. The yellow mixture was diluted with 700 ml. of anhydrous ether, allowed to stand for a few hours, and filtered. The filtrate was reduced in volume under reduced pressure to afford 141 g. of orange oil which had $\lambda_{\max}^{\mathrm{EtOH}}$ 278 mμ (ϵ 3600), indicating that it contained *ca.* 48% O-methylated product, and $\lambda_{\max}$ 3.68 μ, indicating presence of an aldehyde proton. This oil was customarily used directly in the next step; attempted isolation or concentration of the desired 2,6-dimethyl-2-carbomethoxy-6-formylcyclohexanone failed. When the methylation was run at reflux, the per cent of O-methylated material in the isolated product was higher, and no 3.68-μ band could be detected.

Fractionation of one methylation product prepared as described above afforded two distinct fractions. The first, b.p. 59–61° (0.2 mm.), had an infrared spectrum ($\lambda_{\max}$ 5.73 and 5.82 μ), a refractive index ($n^{25}\mathrm{D}$ 1.4570, lit.[24] $n^{24}\mathrm{D}$ 1.4571), and an elemental analysis (Found: C, 65.91; H, 8.79.) that showed it to be I. The second (and principal) fraction was redistilled to give colorless material with b.p. 100–101° (0.2 mm.) which was pure **2-methyl-2-carbomethoxy-6-methoxymethylenecyclohexanone** (V) which had $\lambda_{\max}^{\mathrm{EtOH}}$ 280 mμ (ϵ 7500); $\lambda_{\max}$ 5.73, 5.93, and 6.24 μ.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60; OCH_3, 29.24. Found: C, 62.19; H, 7.67; OCH_3, 28.96.

Condensation of the Methylation Mixture with Acetone.—To 141 g. of crude neutral oil obtained from the methylation procedure was added 675 ml. of acetone, 45 g. (0.53 mole) of piperidine, b.p. 105–106°, and 31.8 g. (0.53 mole) of glacial acetic acid. The light yellow solution was refluxed for a total of 87.5 hr. During this time, at *ca.* 20-hr. intervals, aliquots were removed, worked up as described below, and examined for ultraviolet absorption: the ϵ at 220–225 mμ was *ca.* 2000 at each interval, and there also was present a peak of unknown origin at 300 mμ (ϵ 1000). The reaction mixture was concentrated under reduced pressure and partitioned between water and ether. The ether layer was washed with dilute hydrochloric acid, water, dilute sodium bicarbonate solution, water, and saturated sodium chloride solution, was dried over sodium sulfate, and evaporated, leaving 95 g. of red oil.

The hydrochloric acid wash deposited upon standing an oil which proved to be III, $\lambda_{\max}$ 288 mμ (ϵ 7400). Reaction of III with piperidine in benzene at reflux yielded a product with $\lambda_{\max}$ 339 mμ (ϵ 13,500), presumed to be the enamine X.

In many condensation attempts the entire crude product was subjected to strong base cyclization. In the present instance 95 g. of oil was chromatographed on 1500 g. of acid-washed alumina, using ether–hexane as the eluent system. First to be eluted was a large amount of liquid (*ca.* 30 g.) in three fractions with consecutively stronger absorption at 238 mμ. Fractional distillation of these fractions afforded (1) a small amount (<1 g.) of mesityl oxide, identified by comparison of infrared spectrum and 2,4-dinitrophenylhydrazone with those of an authentic sample, and (2) material with b.p. 121–123 (27 mm.), $n^{25}\mathrm{D}$ 1.4530, and an infrared spectrum that was consistent with the presence of large amounts of I (lit.[24] $n^{25}\mathrm{D}$ 1.4571) and 2-methyl-2-carbomethoxycyclohexanone (lit.[4] $n^{25}\mathrm{D}$ 1.4570). Further identification was not attempted. After this material, there were eluted oils with $\lambda_{\max}$ *ca.* 224 mμ, and these were used for cyclization studies. The over-all yield of dienone was not improved by using these laboriously purified fractions rather than the entire crude product.

In a typical procedure, 2.6 g. of oil with $\lambda_{\max}$ 224 (ϵ 8100) (*ca.* 80% VIII and IX), was dissolved in 35 ml. of dry *t*-butyl alcohol and added to a solution of 0.31 g. of potassium in 45 ml. of dry *t*-butyl alcohol, under nitrogen. The dark red solution was refluxed for 21 hr. The cooled mixture then was poured into 250 ml. of ice-cold water and extracted with ether. The ether was washed with dilute sodium hydroxide solution and water, dried, and evaporated to yield 1.6 g. of oil, $\lambda_{\max}$ 243 (ϵ 4000). The loss in weight was characteristic of the base-catalyzed cyclizations. If the reaction mixtures were acidified, effervescence was observed.[15]

The 1.6 g. of oil was chromatographed on acid-washed alumina. With 2:3 ether–hexane was eluted *ca.* 0.5 g. of material which yielded 0.2 g. of crystals, m.p. 80–90°. Recrystallization from ether–pentane gave needles of **8α,10β-dimethyl-8β-carbomethoxy-$\Delta^{1,9;3,4}$-hexahydronaphthalone-2 (XI)**, m.p. 90.0–91.0°; $\lambda_{\max}^{\mathrm{EtOH}}$ 243 (ϵ 13,700); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.74, 5.99, and 6.13 μ.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.59; H, 7.62.

The 2,4-dinitrophenylhydrazone of XI had m.p. 130–132°.

When the cyclization was run with sodium methoxide as catalyst (2.5-hr. reflux), chromatography afforded a small amount (*ca.* 0.1 g. from 7.0 g. of III) of solid, m.p. 45–57°, eluted before XI. After repeated recrystallization from hexane this substance had m.p. 57–59°; $\lambda_{\max}^{\mathrm{EtOH}}$ 243 mμ (ϵ 11,200). Comparison of infrared spectrum[11] and mixture melting point of the 2,4-dinitrophenylhydrazone, m.p. 172–173° (m.p. 120–123° until seeded with authentic sample,[11] m.p. 171–172°), showed that it was XIII.

2,6-Dimethyl-2-carbomethoxycyclohexanone (I).—2-Methylcyclohexanone was prepared by oxidation of commercial 2-methylcyclohexanol with sodium dichromate in sulfuric acid in *ca.* 75% yield and was converted to I in one operation by sequential treatment with sodium methoxide in methanol, dimethyl carbonate, and methyl iodide, in *ca.* 15% yield, according to a procedure of Shafer.[25]

Cyanoethylation of I.—To a solution of 0.45 g. (0.012 mole) of potassium in 35 ml. of anhydrous *t*-butyl alcohol (distilled from calcium hydride) was added a solution of 10 g. (0.054 mole) of 2,6-dimethyl-2-carbomethoxycyclohexanone, b.p. 118–128° (30 mm.), $n^{25}\mathrm{D}$ 1.4530, in 10 ml. of *t*-butyl alcohol with magnetic stirring. The resulting yellow solution was allowed to stand for 10 min., and then a solution of 4.3 g. (0.081 mole) of acrylonitrile (b.p. 77°) in 10 ml. of *t*-butyl alcohol was added over a 10-min. period. The mixture, which turned orange, was stirred for 12 hr. at room temperature. Then 1.65 ml. of acetic acid was added, and the mixture was partitioned between water and chloroform. The organic layer was washed with dilute sodium hydroxide solution, water, and saturated sodium chloride solution, dried, and stripped of solvent. Fractionation of the residue afforded 6.54 g. (51%) of colorless oil, b.p. 126–127° (0.1 mm.); $n^{25}\mathrm{D}$ 1.4680; $\lambda_{\max}^{\mathrm{film}}$ 4.44, 5.72, and 5.83 μ. Upon standing, the oil partially crystallized affording 2.85 g. of material, m.p. 45–55°. Recrystallization from hexane yielded large clear crystals of one stereoisomer of **2,6-dimethyl-2-carbomethoxy-6-cyanoethylcyclohexanone (XV)**, m.p. 64.5–65.2°.

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[24] D. K. Banerjee and S. N. Mahapatra, *Tetrahedron*, **11**, 234 (1960).

[25] P. R. Shafer, private communication.

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.87; H, 7.93; N, 6.00.

The oil remaining after separation of the 64–65° material had an infrared spectrum very similar, both in principal bands and detail, to that of the crystalline material and is presumed to be the diastereoisomeric cyanoethylation product.

Condensation of I with Methyl Vinyl Ketone.—The annelation procedure was based on that of Cornforth and Robinson.[16] To a well-cooled solution of 23.3 g. (0.163 mole) of 1-diethylaminobutanone-3,[26] b.p. 66–68° (10 mm.), n^{25}_{D} 1.4318, in 150 ml. of dry ether was added, over a 30-min. period, 23.2 g. (0.163 mole) of methyl iodide with constant swirling. The ether then was removed under reduced pressure while swirling was continued, leaving a coating of white crystalline methiodide around the inside of the flask. Then a solution of 30 g. (0.163 mole) of 2,6-dimethyl-2-carbomethoxycyclohexanone, b.p. 118–128° (30 mm.), in 70 ml. of anhydrous *t*-butyl alcohol was added. While the flask was swirled in an ice bath, a solution of 7.63 g. (0.195 g.-atom) of potassium in 180 ml. of anhydrous *t*-butyl alcohol was added dropwise over a 30-min. period. The light yellow mixture was stirred magnetically in an ice bath for 20 min. and at room temperature for 5 hr., during which time it became light brown and cloudy. Excess acetic acid then was added, and the mixture was partitioned between ether and water. The aqueous layer was thoroughly extracted with ether, and the combined organic layers were washed with dilute sodium hydroxide solution, water, and saturated sodium chloride solution, dried, and stripped of solvent, yielding 31 g. of orange oil, λ_{max} 241 mμ (ϵ 1700) (11% yield of XVI and XVII based on ϵ of pure XVI). Attempts to enhance ϵ at 240 mμ by further treatment of small samples with potassium *t*-butoxide, pyrrolidine–acetic acid, and other bases failed. The entire product was chromatographed on acid-washed alumina. Elution with 1:4 ether–hexane gave *ca.* 4 g. with λ_{max} 240 (ϵ 8000–9000). Rechromatography gave 0.578 g. of oily crystalline material. Three recrystallizations from hexane gave 0.221 g. of **8α,10β-dimethyl-8β-carbomethoxy-$\Delta^{1,9}$-octalone-2 (XVI)**, m.p. 87.5–90.0°; the analytical sample had m.p. 89.5–90.5°; λ_{max}^{EtOH} 241 mμ (ϵ 12,500); $\lambda_{max}^{CHCl_3}$ 5.78, 6.00, and 6.21 μ; n.m.r.,[21] in carboh tetrachloride containing tetramethylsilane: τ 8.65 and 8.92 ($-\overset{|}{\underset{|}{C}}CH_3$), 6.38 (O–$CH_3$), and 4.12 ($-\overset{|}{C}=\overset{|}{C}H$).

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.33; H, 8.63.

Vapor phase chromatographic analysis (typically on a Wilkens A-90-P2 chromatograph with a silicone SE-30 column at 250°, using carbon tetrachloride solutions) showed that the chromophoric chromatographic fractions consisted primarily of two components, the first of which was identified by retention time as XVI. The later fractions contained progressively more of the other, minor (ratio <1:2) component, which had λ_{max}^{EtOH} 240 mμ and λ_{max}^{film} 5.75, 5.96, and 6.20 μ.

Selenium Dioxide Oxidation of XVI.—The oxidation of XVI to the dienone XI was conducted according to the procedure of Baran.[27] To a solution of 0.03 ml. of glacial acetic acid and 0.065 g. (5.0×10^{-4} mole) of selenous acid (Fisher, reagent grade) in 3 ml. of anhydrous *t*-butyl alcohol was added 0.118 g. (5.00×10^{-4} mole) of the α,β-unsaturated ketone XVI, m.p. 89.5–90.5°. The mixture was refluxed for 5 hr.; then 0.02 g. (1.6×10^{-4} mole) of selenous acid was added and refluxing was continued for 16 hr. The resulting yellow solution was filtered from a brown-black precipitate and concentrated *in vacuo*, and the residue was partitioned between methylene chloride and water. The organic layer was washed with dilute sodium bicarbonate solution and water, dried over sodium sulfate, and evaporated. The residual oil was chromatographed on 10 g. of Merck acid-washed alumina. Elution with 4:1 hexane–ether gave 0.076 g. (65%) of crude crystalline material. After recrystallization from hexane there was obtained 27 mg. (23%) of material with m.p. 88–92°. Further recrystallization gave material with m.p. 90–91°, which had an infrared spectrum identical with that of the previously prepared dienone XI. The mixture melting point was 89.5–91.0°.

8α,10β-Dimethyl-8β-carbomethoxy-*trans*-decalone-2 (XVIII).—A mixture of 0.050 g. (2.1×10^{-4} mole) of the unsaturated ketone XVI, m.p. 89–91°, and 0.05 g. of 10% palladium on carbon in 20 ml. of ethyl acetate was hydrogenated until the absorption maximum at 240 mμ disappeared (*ca.* 1 hr.). The mixture was filtered, and the filtrate was evaporated to give 0.051 g. of crude product which solidified on standing, m.p. 56–73°. Two recrystallizations from hexane afforded 0.025 g. of colorless needles, m.p. 76.5–77.5°; $\lambda_{max}^{CHCl_3}$ 5.80–5.87 μ; n.m.r.[21]: τ 8.85 and 9.07 ($-\overset{|}{\underset{|}{C}}CH_3$) and 6.36 (–$OCH_3$).

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.35; H, 9.54.

Sodium Borohydride Reduction of XVIII.—To a solution of 0.051 g. (2.1×10^{-4} mole) of ketone XVIII, m.p. 76.5–77.5°, in 3 ml. of absolute ethanol was added a solution of 0.080 g. of sodium borohydride in 3 ml. of absolute ethanol dropwise over a 15-min. period. The mixture was stirred magnetically at room temperature for 3 hr. (In an earlier run, a 45-min. reaction period yielded a product which v.p.c. analysis indicated to contain about one-third unreduced ketone.) The reaction mixture was then acidified with dilute hydrochloric acid and partitioned between water and chloroform. The organic layer, after drying and evaporation, yielded 0.056 g. of light yellow oil, λ_{max} 2.9, 5.80 μ. This product, which failed to solidify, was chromatographed on 1.3 g. of acid-washed alumina. V.p.c. analysis (Ucon polar column at 220°) of all fractions showed only a trace of unreduced ketone and two principal components: a minor one, absent in later fractions, with shorter retention time, and the major component, presumably XX. Suitable fractions, *i.e.*, almost all XX, were combined for attempted saponification.

Treatment of Sodium Borohydride Reduction Product from XVIII with Sodium Hydroxide Solution.—To a solution of 0.020 g. of the chromatographically purified sodium borohydride reduction product in 2 ml. of methanol was added 4 ml. of 3 *N* sodium hydroxide solution, and the mixture was refluxed for 24 hr. The reaction mixture was diluted with water and extracted with two 10-ml. portions of chloroform. The organic layer, after drying and evaporation, afforded 0.0195 g. of nearly colorless oil which had an infrared spectrum identical with that of the sodium borohydride product used as starting material. The original aqueous layer was acidified with dilute hydrochloric acid and extracted with chloroform in the same manner to yield 0.0015 g. of dark brown oil.

Reduction and Saponification of Crude XVII.—A sample from a chromatographic fraction from the reaction of I with methyl vinyl ketone, consisting primarily (*ca.* 90% by v.p.c. analysis on a silicone SE-30 column at 275°) of a substance other than XVI and assumed from the striking similarity of its infrared spectrum (λ_{max}^{film} 5.75, 5.96, and 6.20 μ) to that of XVI to be XVII, was reduced catalytically in the same manner as XVI. The uptake of hydrogen was much slower. The resulting oil (λ_{max} 5.80–5.84 μ) was treated with excess sodium borohydride in the same manner as XVIII. A 0.023-g. sample of the oily product from this reaction was refluxed with 4 ml. of 3 *N* sodium hydroxide solution and 2 ml. of methanol for 6 hr. Work-up in the usual manner afforded 0.013 g. of acidic material and 0.009 g. of neutral material. The acidic material crystallized to afford 0.006 g. of white solid, m.p. 200–202°. Recrystallization from acetone–hexane gave pure XXI, m.p. 201–203°; $\lambda_{max}^{CHCl_3}$ 2.9 (sh), 3–4 (broad), and 5.90 μ.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.86; H, 9.69.

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[26] A. L. Wilds and C. H. Shunk, *J. Am. Chem. Soc.*, **65**, 469 (1943).

[27] J. S. Baran, *ibid.*, **80**, 1687 (1958).