Conversion of Cyclohexanone to Spiro[3,4-cyclohexano-4-hydroxybicyclo[3.3.1]nonan-9-one-2,1′-cyclohexane][1]

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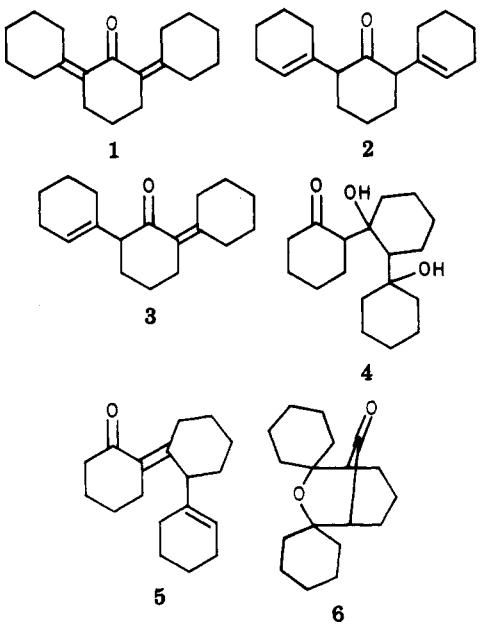
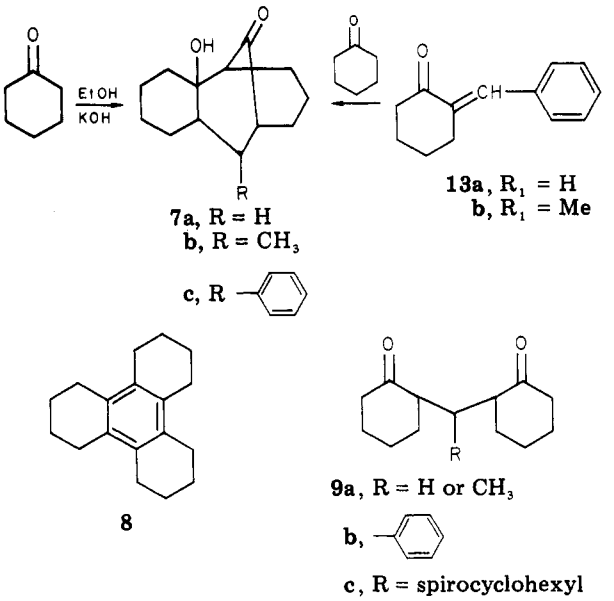
The course of cyclohexanone self-condensation, under a variety of reaction conditions, has been a classic problem for over 80 years. Self-condensation of cyclohexanone catalyzed by sodium methoxide–dimethylformamide has been shown to afford the title substance (**10**, mp 186.5–187 °C) in 40% yield. Structural elucidation of ketol **10** was undertaken by degradative methods and provided the interesting series of products illustrated by structures **11–14**, **16–21**, and **23**. Unequivocal confirmation for the skeletal arrangement of ketol **10** and the stereochemical assignments was obtained by solving the X-ray crystal structure.

The self-condensation of ketones under a variety of acid- and base-catalyzed reaction conditions has been of interest for over a century. Such studies involving cyclohexanone began with Wallach's report in 1896 and have resulted in a variety of reaction conditions and products (cf. **1–7**).[2a-t]



1 **2** **3** **4** **5** **6**

Even under neutral conditions the self-condensation of cyclohexanone can be directed at high pressure (5000 atm, and 100 °C) to yield dodecahydrotriphenylene (**8**).[3] Except for the latter hydrocarbon (**8**), the only other condensed ring system obtained from cyclohexanone prior to 1950 was a trimer ($C_{18}H_{28}O_2$, mp 186 °C) presumed by Cornubert[2g] in 1927 to correspond with structure **6**. By 1957 Plešek and Munk[2k] had proposed ketol **7** as the product obtained by condensing cyclohexanone with methyl alcohol (→ **7a**) or ethyl alcohol (→ **7b**) in the presence of potassium hydroxide. In the same period a



7a, R = H
b, R = CH_3
c, R —⟨ ⟩

13a, R_1 = H
b, R_1 = Me

8

9a, R = H or CH_3
b, —⟨ ⟩
c, R = spirocyclohexyl

Michael condensation between cyclohexanone and its benzylidene derivative was shown to yield an analogous product (**7c**). Presumably the reaction with primary alcohols proceeds via an oxidation–reduction reaction leading to the corresponding aldehyde and cyclohexanol with concomitant aldol and Michael condensation steps to afford 1,5-diketone **9a**. The analogous intermediate (**9b**) would ensue from the benzylidene precursor. Indeed diketone **9a** prepared by alternate synthesis readily provided ketones **7a** and **7b**.[2k,q] Some of the best evidence[2p] for structure **7** arose when reaction between cyclohexanone and benzyl alcohol in the presence of potassium hydroxide was shown to lead to ketone **7c**, the same substance obtained by the benzylidine route.

(1) Part 98 in the series Steroids and Related Natural Products. For the preceding part, see J. J. Einck and G. R. Pettit, *Acta Crystallogr., Sect. B*, **36**, 1398–1402 (1980). The present contribution was abstracted in part from the Ph.D. dissertation of Evan G. Thomas, submitted to the Graduate School, University of Maine, 1963.

(2) (a) O. Wallach, *Ber. Dtsch. Chem. Ges.*, **29**, 2955–2966 (1896); (b) C. Mannich, ibid., **40**, 153–158 (1907); (c) O. Wallach, *Justus Liebigs. Ann. Chem.*, **369**, 63–103 (1909); (d) A. Haller and E. Bauer, *Compt. Rend.*, **152**, 551–558 (1911); (e) J. V. Braun and H. Ritter, *Ber. Dtsch. Chem. Ges.*, *55*, 3792–3803 (1922); (f) K. Kunze, *ibid.*, **59B**, 2085–2088 (1926); (g) R. Cornubert, *Compt. Rend.*, **184**, 1258–1259 (1927); (h) J. Mleziva, *Chem. Listy*, **47**, 1031–1037 (1953); *Chem. Abstr.*, **48**, 13642f (1954); (i) N. Barbulescu, *Ser. Stiint. Nat.*, **13**, 101–112 (1956); *Chem. Abstr.*, **53**, 1178 (1959); (j) P. Munk and J. Plešek, *Coll. Czech. Chem. Commun.*, **22**, 1691–1694 (1957); (k) J. Plešek and P. Munk, *ibid.*, **22**, 1596–1602 (1957); (l) M. Horak and P. Munk, *ibid.*, **24**, 3024 (1959); (m) S. V. Svetozarskii, G. A. Razuvaev, E. N. Zil'berman, and G. S. Volkov, *J. Gen. Chem., U.S.S.R., (Engl. Transl.)*, **30**, 2023 (1960); (n) S. V. Svetozarskii, E. N. Zil'berman, and G. A. Razuvaev, *Zh. Obshch. Khim.*, **29**, 1454–1457 (1959); (o) G. A. Razuvaev, E. N. Zil'berman, and S. V. Svetozarskii, *Dokl. Akad. Nauk. U.S.S.R.*, **131**, 850–852 (1960); *Chem. Abstr.*, **54**, 16439 (1960); (p) M. N. Tilichenko and V. G. Kharchenko, *Zh. Obshch. Khim.*, **29**, 1909–1911 (1959); M. N. Tilichenko and V. G. Kharchenko, *J. Gen. Chem., U.S.S.R.*, **30**, 2264 (1960); (q) J. Pitha, L. Plešek and M. Horak, *Coll. Czech. Chem. Commun.*, **26**, 1209 (1961); (r) J. Colonge and R. Vuillemet, *Bull. Soc. Chim. Fr.*, 2235 (1961); (s) M. N. Tilichenko, N. S. Barbulescu, and V. I. Vusotskii, *J. Gen. Chem., U.S.S.R.*, **31**, 3787 (1961); (t) J. H. Clark and J. M. Miller, *J. Chem. Soc., Perkin Trans. 1*, 2063 (1977).

(3) W. Treibs, *Ber. Dtsch. Chem. Ges.* **61**, 683–687 (1928); A. D. Petrov, *Bull. Soc. Chim. Fr.*, **43**, 1272–1276 (1928); *Chem. Abstr.*, **23**, 4453 (1929); R. H. Sapiro and Shu-Lin P'eng, *J. Chem. Soc.*, 1171–1174 (1938).

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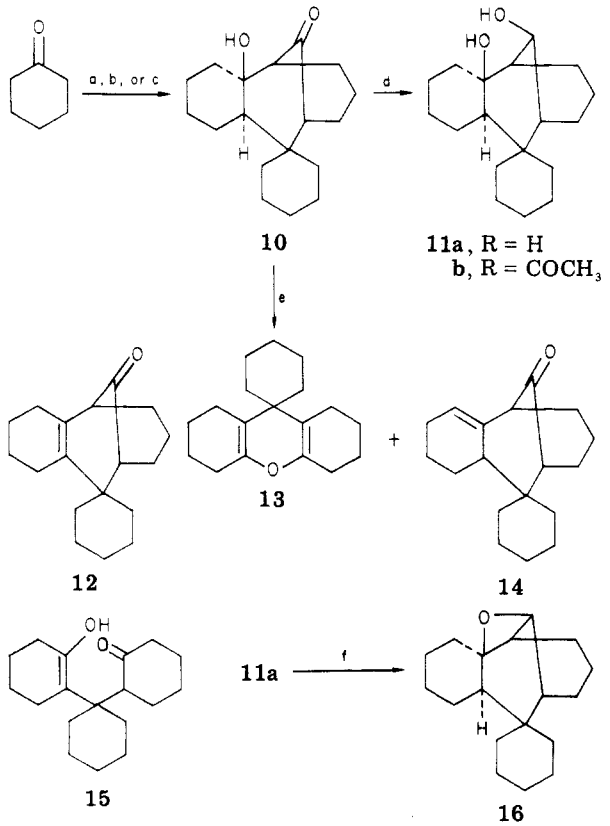
Scheme I[a]



[a] a, $(CH_3)_2NCHO$, $NaOCH_3$; b, KOH, hydroxycyclohexane; c, KOH, CH_3OH; d, $(CH_3CH_2)_2O$, $LiAlH_4$; e, $KHSO_4$, 190–200 °C, 7 h; f, $BF_3 \cdot (CH_3CH_2)_2O$, RT, 1.5 h.

The possibility that self-condensation products from certain naturally occurring ketones, such as the hormonally active oxo steroids, might have important biological properties led us to undertake a complete structural elucidation of the new ketol (mp 186.5–187 °C) we obtained by intramolecular condensation of cyclohexanone in a mixture of dimethylformamide and sodium methoxide[4] (Scheme I). When the cyclohexanone–dimethylformamide–sodium methoxide mixture was heated at reflux for several hours, only polymeric material was obtained. However, simply mixing the reactants at room temperature gave a mildly (31 °C) exothermic reaction lasting approximately 30 min. After 5 days at room temperature ketol **10** was routinely isolated in 40% yield. If the reaction was terminated after 1 h, the yield of ketol **10** was reduced to 12% and the most prominent substances appeared to be dimeric and trimeric condensation products.

Although the melting point of ketol **10** appeared to correspond to that reported by Cornubert[2g] for ketone **6**, the tertiary alcohol group of ketol **10** was clearly evident by infrared absorption at 3320 cm^{-1}. The carbonyl infrared absorption at 1706 cm^{-1} seemed in order, but the ultraviolet absorption at 294 nm (log ϵ 1.69) seemed unusual for a simple cyclohexanone derivative. For comparison of the spectral properties of ketol **10** with those of ketol **7a**, both methyl alcohol and cyclohexanol were separately allowed to react with cyclohexanone in the presence of potassium hydroxide. In both cases small yields (7.7 and 2.7%, respectively) of ketol **10** were instead obtained. Clearly ketol **10** represented a new but potentially important cyclohexanone intramolecular condensation product and a detailed structural examination was definitely required.

On the assumption that simple Michael addition of cyclohexanone to the α,β-unsaturated ketone (2-cyclohexylidene–cyclohexanone) derived from 2 mol of cyclohexanone would yield 1,5-diketone **9c** and that subsequent intramolecular cyclization would afford ketol **10**, this pathway was used as a working model and evaluated by a series of derivative and degradative reactions. The structure of each transformation product was ascertained by accomodation of elemental analyses, ultraviolet, infrared, nuclear magnetic resonance, and mass spectral measurements. Furthermore, two of the degradation products were confirmed by alternate syntheses, and the structure of ketol **10** was confirmed by an X-ray crystal structure determination.

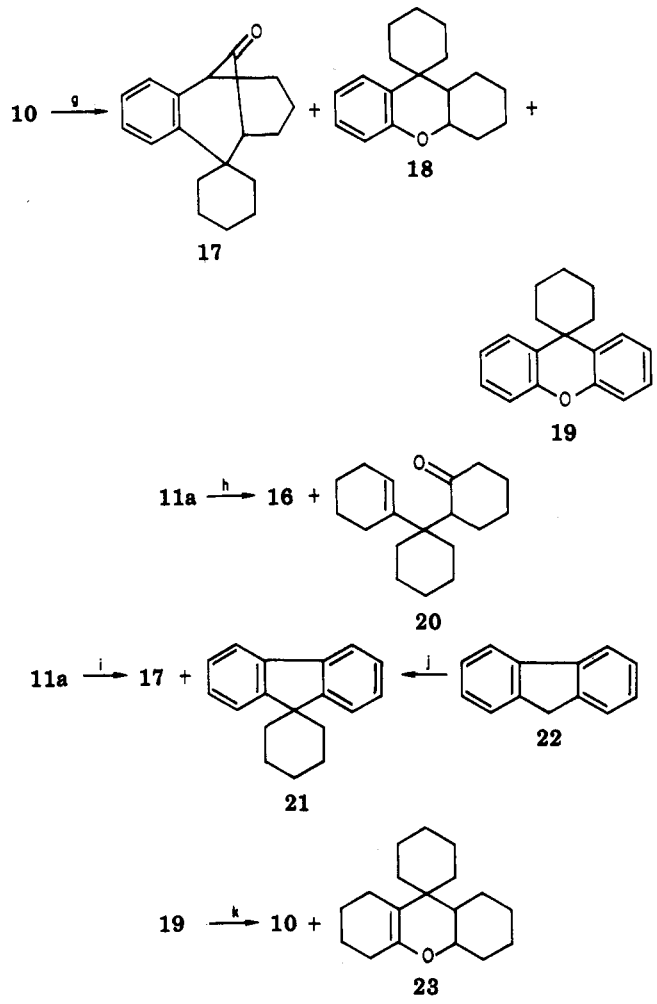
Lithium aluminum hydride reduction of ketol **10** readily provided diol **11a** as a higher melting (220–221 °C) derivative. A lower melting (78–78.5 °C) monoacetate (**11b**) was obtained by warming diol **11a** with acetic anhydride–pyridine. The same diol (**11a**) was obtained by sodium borohydride (in refluxing methanol) reduction of ketol **10**. However, ambient temperature treatment of ketol **10** with sodium borohydride in methanol gave a boron adduct that upon cleavage with hydrochloric acid in methanol led to olefin **12**. A planned dehydration of ketol **10** with potassium hydrogen sulfate at 190–200 °C gave instead pyran **13** and the isomeric monoolefin **14**. Initially, formation of pyran **13** seemed to complicate interpreting the structure of the precursor. But pyran **13** proved to be a key degradation product and provided the first real evidence for the skeletal arrangement of ketol **10**. With the potassium hydrogen sulfate mode of dehydration, apparently ketol **10** is cleaved to a skeletal counterpart of **15**, which recyclizes to pyran **13**. A classic example of this type of reaction occurs when the 1,5-diketone obtained from 5,5-dimethylcyclohexan-1,3-dione (dimedone) and an aldehyde are simply heated in ethanol (with a drop of concentrated hydrochloric acid) to afford the corresponding pyran. Interestingly, when ketol **10** was heated in methanol with concentrated hydrochloric acid, only olefin **12** was obtained. And with boron trifluoride etherate only the isomeric olefin **14** was produced. Isomerization of olefin **12** → **14** was easily realized with boron trifluoride etherate. Attempts to convert diol **11a** to an analogous monoolefin derivative with boron trifluoride etherate gave instead an ether tentatively assigned structure **16**.

In order to further ascertain the skeletal arrangement of ketol **10**, we next directed experiments at reducing the ketone by a Wolff–Kishner reaction or desulfurization of a thioketal derivative. Both approaches proved unsatisfactory when Wolff–Kishner reduction and use of propylenedithiol–boron trifluoride etherate to form a thioketal gave in each case only multicomponent products. Also, ketol **10** proved refractory to direct hydrogenation in acetic acid with Adams catalyst. But a small amount of ether **16** was formed when the hydrogenation was conducted in ethanol containing perchloric acid.

With the ring system of ketol **10** still in doubt, a series of dehydrogenation experiments were pursued. When ketol **10** was subjected to dehydrogenation with 10% palladium on carbon at temperatures up to 290 °C, the products were ketone **17**, benzopyran **18**, and xanthene **19** (Scheme II). The fact that totally aromatic products were not obtained from ketol **10** suggested the presence of a

(4) A preliminary report of this observation has been summarized: G. R. Pettit and E. G. Thomas, *Chem. Ind.*, 1758 (1963). The dimethylformamide–sodium methoxide reagent was initially found in our laboratory to very efficiently convert certain aromatic amines to formamides: G. R. Pettit, M. V. Kalnins, T. M. Liu, E. G. Thomas, and K. Parent, *J. Org. Chem.*, **26**, 2563–2566 (1961); G. R. Pettit and E. G. Thomas, *ibid.*, **24**, 895 (1959).

Scheme II[a]



[a] g, 10% Pd/C, 6 h, 275–290 °C; h, 10% Pd/C, 3 h, 225–230 °C; i, 30% Pd/C, 3.5 h, 270–315 °C; j, K, di, $Br(CH_2)_4Br$; k, 5% Rh/Al_2O_3, 50 psi, 3 days.

spirocyclohexane group. If the parent system was a linear arrangement of cyclohexane rings (e.g., 1 or 4), dehydrogenation would be expected to yield *o*- or *m*-terphenyl. The first clue to the spacial arrangement of ketone 17 was provided by the enhanced intensity (log ϵ = 2.79) of the ketone ultraviolet absorption at 290 nm attributable to close proximity of the benzene ring. Isolated ketone groups generally display a low-intensity absorption near 280 nm that shifts to an unusually intense absorption near 290 nm with β,γ-unsaturated ketones.[5] The single strong ether absorption at 1230 cm^{-1} displayed in the infrared spectrum of xanthene 19 first indicated the diaryl ether structure. Benzopyran 18 was assigned on the basis of its close relationship to xanthene 19. The xanthene system received further credibility when a lower temperature (225–230 °C) dehydrogenation of diol 11a with 10% palladium on carbon provided ether 16 and ketone 20. Furthermore, high-temperature (310–315 °C) dehydrogenation of diol 11a was found to yield fluorene 21 and ketone 17. Synthesis (by alkylating 9,9-dipotassiofluorene with 1,5-dibromopentane and comparison with dehydrogenation product 21) of spiro[cyclohexane-1,9′-fluorene] proved the identity of fluorene 21 and thereby provided the first unequivocal assignment to a ketol 10 degradation product. The same substance had previously been synthesized by condensing 1,3-butadiene with 9-bromo-9-bromomethylfluorene and hydrogenating the product.[6]

The second link of an important dehydrogenation product with a substance of known structure has been described as part of a related study.[7] Specifically, both pyran 13 and xanthene 19 were reduced to the common intermediate dihydropyran 23, and this substance was found identical with a specimen obtained by an unequivocal synthesis. From this evidence the structures proposed for ketol 10 and derived products seemed secure except for the stereochemistry of ketol 10 and diol 11. Since ketol 10 was found[8] by X-ray crystallographic techniques to possess the configurational and confirmational relationships shown, only configuration of the 9-hydroxy group of diol 11a remains to be established with certainty. If the hydride reduction (10 → 11a) of ketol 10 does indeed proceed as superficially expected from the least-hindered side of the 9-ketone, then the 9-hydroxy configuration shown by structure 11a would be appropriate. Two other experimental observations that point to the same conclusion concern isolation of a boron-containing intermediate from simple sodium borohydride reduction of ketol 10 and the formation of ether 16 by treating diol 11a with boron trifluoride etherate or under mild conditions of dehydrogenation. Presently the structures of diol 11a and ether 16 seem consistent with the experimental results and physical measurements.

The facile one-step conversion of cyclohexanone to ketol 10 with sodium methoxide and dimethylformamide offers a very inexpensive, structurally defined, and rigid ring system for further study. At the same time a foundation has been provided for pursuing and interpreting results of related ketone intramolecular condensation reactions.

Experimental Section

Anhydrous *N,N*-dimethylformamide was prepared by using Fisher Scientific Co. molecular sieve-type 4A.

All solvent extracts of aqueous solutions were dried over anhydrous magnesium sulfate. Ether refers to diethyl ether and ligroin to a fraction boiling at 35–40 °C. Solvents employed for chromatography were redistilled. Column chromatographic separations on basic alumina employed Merck (suitable for chromatography) or Alcoa (grade F-20) products. Merck acid-washed and neutral alumina were used as indicated.

Melting points were determined by using capillary tubes (silicone oil bath and borosilicate thermometer) or a Fisher-Johns hot stage unless otherwise specified and are uncorrected. Ultraviolet spectra were recorded by Dr. R. Hill, using a Perkin-Elmer spectracord. Infrared (KBr unless otherwise noted) spectra were obtained by Dr. R. Hill, using Baird (double-beam infrared spectrophotometer) and Beckman (Model 12) instruments. Both the ^1H NMR (deuteriochloroform solution, tetramethylsilane internal standard, Varian XL-100) and ^{13}C NMR (at 22.6 MHz, using a Bruker WH-90 NMR spectrometer, reported in parts per million downfield from tetramethylsilane) spectra were determined by Dr. J. Witschel, Jr. We also thank Drs. G. Slomp and R. O. Mumma for early help in obtaining several of the ^1H NMR spectra. Mass spectra (Varian MAT 312 mass spectrometer, EI mode) were determined by Mr. D. Adams and Miss M. J. Cullen. Microanalyses were determined in the laboratories of Dr. A. Bernhardt, 5251 Elbach über Engelskirche, Mulheim, West Germany, and Dr. G. Janssen, Beerse, Belgium.

Spiro[3,4-cyclohexano-4-hydroxybicyclo[3.3.1]nonan-9-one-2,1′-cyclohexane] (10). Method A. By Base-Catalyzed Condensation in *N,N*-Dimethylformamide. A mixture of cyclohexanone (49 g, 0.5 mol) and anhydrous *N,N*-dimethyl-

(5) R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 2302–2311 (1956).

(6) H. Wieland and O. Probst, *Justus Liebigs Ann. Chem.*, **530**, 274–290 (1937).

(7) G. R. Pettit and E. G. Thomas, *Can. J. Chem.*, manuscript submitted for publication.

(8) J. J. Einck and G. R. Pettit, *Acta Crystallogr.*, in preparation.

(9) C. W. H. Sherf and R. K. Brown, *Can. J. Chem.*, **38**, 697–711 (1960).

formamide (300 mL) added to freshly prepared sodium methoxide (54.0 g, 1.0 mol) was rapidly stirred. After the first hour a mild exothermic reaction (temperature rising to 31 °C) ensued. The reaction temperature returned to ca. 25 °C and stirring was continued for 5 days. The mixture was poured into 1 L of water and extracted with chloroform. Solvent was removed in vacuo from the chloroform extract to yield a transparent yellow oil which was partially soluble in cold ether. The insoluble portion, 18.3 g (40%) of crystalline solid (mp 183–184 °C), was recrystallized 3 times from benzene to afford needles melting at 186.5–187 °C (capillary): λ_{max} 292 nm (log ϵ = 1.69); ν_{max} 3320 (OH), 1706 (C=O) cm^{-1}; ^{13}C NMR δ 19.8, 21.2 (2-C), 21.6, 22.5, 25.9, 27.3, 29.9, 30.2, 30.7, 31.9, 38.0, 44.2, 49.5, 50.9, 60.2, 79.6 (COH), 220.2 (C=O); ^{1}H NMR δ 1.31–2.15 (27 H, m), 2.81 (1 H, s); mass spectrum, *m/e* 276 (M^+), 258 ($M^+ - H_2O$), 179, 178 (base peak).

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21; M_r 276.5. Found: C, 78.02; H, 10.06; M_r (Rast) 244.

In another typical experiment, with commercially prepared sodium methoxide and 98 g of cyclohexanone, the reaction was allowed to continue for 5 days. A 33-g (39%) crude yield of ketol **10**, mp 186.5–188 °C, was formed. In another experiment the basic aqueous solution left from extraction of ketol **10** was acidified to pH 6 and extracted again with chloroform. Only cyclohexanone and dimethylformamide were obtained from the acidified solution.

Method B. By Base-Catalyzed Condensation in Cyclohexanol. The reaction mixture prepared from cyclohexanone (28.0 g, 0.29 mol), cyclohexanol (13.9 g, 0.14 mol), and potassium hydroxide pellets (7.0 g, 0.12 mol) was allowed to stand at ca. 25 °C for 10 days in a dry, tightly stoppered flask. The mixture was filtered, the solid residue was washed with ether, and the combined filtrate was concentrated to an oil. When a hot benzene solution of the crude product was cooled, ketol **10** (0.70 g, 2.7% yield, mp 186–188 °C) crystallized. The melting point was undepressed upon admixture with a sample of ketol **10** prepared by method A.

Method C. By Base-Catalyzed Condensation in the Presence of Methyl Alcohol. The above procedure (method B) was repeated with a mixture of cyclohexanone (14 g), absolute methyl alcohol (5 mL), and potassium hydroxide (7 g). Only ketol **10** (1.0 g, 7.7% yield, mp at 185–186 °C) was isolated following a 2-week reaction period.

Spiro[3,4-cyclohexano-4,9-dihydroxybicyclo[3.3.1]nonane-2,1′-cyclohexane]. (11a). Procedure A. Using Lithium Aluminum Hydride. A slurry of ketol **10** (4.5 g, 0.0165 mol) in anhydrous ether (200 mL) was slowly added to a mixture of lithium aluminum hydride (1.15 g, 0.033 mol) and 100 mL of anhydrous ether. After the initial exothermic reaction had abated the mixture was maintained at reflux for 2 h. The excess lithium aluminum hydride was destroyed (wet ether, methanol, and finally water) and water (200 mL) was added along with sufficient hydrochloric acid to dissolve the precipitated aluminum hydroxide. A chloroform solution of the crude product was washed with 5% sodium bicarbonate and the solvent was evaporated. The product (**11a**; 4.2 g, mp 215–219 °C) was crystallized 3 times from benzene. An analytical specimen of diol **11a** melted at 219–219.5 °C; IR ν_{max} 3320 (OH) cm^{-1}; ^{1}H NMR δ 1.09–2.27 (27 H, m), 2.44 (1 H, s), 3.55 (1 H, s), 4.03 (1 H, t, J = 2.6 Hz); mass spectrum, *m/e* 278 (M^+), 260 ($M^+ - 18$), 242 ($M^+ - 36$, base peak), 179.

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.82. Found: C, 77.93; H, 10.93.

The monoacetate derivative **11b**, prepared by heating (100 °C) diol **11a** with 1:1 acetic anhydride–pyridine, was obtained as prisms from ethanol: mp 78–78.5 °C (Kofler hot stage); ν_{max} 3580 (OH), 1736, 1236 (acetate), 1118 cm^{-1}.

Procedure B. Using Sodium Borohydride. Sodium borohydride (0.685 g, 0.018 mol) was added to a refluxing solution of ketol **10** (5.0 g, 0.018 mol) dissolved in methanol (150 mL). When solution was complete, the reaction mixture was allowed to cool to room temperature. After 12 h diol **11a** (4.3 g) crystallized from the methanol solution as needles, mp 220–221·°C. The melting point was not depressed upon admixture with diol **11a** prepared by procedure A and a comparison infrared spectra (KBr) confirmed its identity.

Spiro[3,4-cyclohexano-$\Delta^{3,4}$-bicyclo[3.3.1]nonen-9-one-2,1′-cyclohexane] (12). The experiment described in procedure B (above, same quantities) was performed entirely at room temperature. After 12 h, the methanol solution was diluted with an equal volume of water, acidified with hydrochloric acid, and extracted with ether. Removal of solvent from the ether extract left a solid which melted with decomposition above 230 °C and gave a green flame upon ignition. The boron-containing intermediate was hydrolyzed by heating (1 h) in a refluxing methanol solution containing a few drops of concentrated hydrochloric acid. The product (**12**; 4.5 g of an oil) was chromatographed on acid-washed (150 g) alumina.

Elution with 1:1 ligroin (bp 35–40 °C)–benzene led to 1.95 g of olefin **12** melting at 56–59 °C. Tetranitromethane and olefin **12** gave a pale yellow color in chloroform solution. After three recrystallizations from ethanol the melting point was raised to 62.5–63.5 °C (Kofler hot stage): λ_{max} 291 (log ϵ = 1.89) nm; ν_{max} 1714 (C=O) cm^{-1}.

Anal. Calcd for $C_{18}H_{26}O$: C, 83.66; H, 10.14; M_r 258.4. Found: C, 83.68, 83.65; H, 9.92, 10.00; M_r (Rast) 238.

A second product (0.316 g of oil) was obtained by continued elution with 1:1 ligroin–benzene. Crystallization from ethanol–water gave 0.250 g (mp 36–39 °C) which appeared to be an alcohol (ν_{max} 3360 cm^{-1}) and possibly corresponded to the opposite 9-hydroxy epimer of diol **11** but was not characterized further.

Dehydration of Spiro[3,4-cyclohexano-4-hydroxybicyclo[3.3.1]nonan-9-one-2,1′-cyclohexane] (10). Method A. By Fusion with Potassium Bisulfate. Ketol **10** (10.0 g) and anhydrous potassium bisulfate (2.0 g) were heated together in a nitrogen atmosphere for 7 h at 190–200 °C. The crude product was dissolved in ligroin and chromatographed on 200 g of basic alumina (Alcoa). A fraction (3.00 g, mp 40–41 °C) eluted by ligroin was found to be **spiro[cyclohexane-1,9′-1′,2′,3′,4′,5′,6′,7′,8′-octahydroxanthene] (13)** and was shown to be identical with a specimen of pyran **13** prepared directly from cyclohexanone[7] by means of infrared spectra and an undepressed mixture melting point. A benzene fraction yielded (5.22 g, mp 65–73 °C) crude **spiro[3,4-cyclohexano-$\Delta^{3,3''}$-bicyclo[3.3.1]nonen-9-one-2,1′-cyclohexane] (14)** which was purified by three crystallizations from 95% ethanol: mp 81–82 °C (capillary); λ_{max} 297 (log ϵ = 2.01) nm; ν_{max}(CCl_4) 1720 (C=O) cm^{-1}; ^{1}H NMR 0.98–2.24 (22 H, m), 2.68–2.87 (3 H, m), 5.46 (1 H, q, J = 3 Hz); mass spectrum, *m/e* 258 (M^+), 187, 148, 134.

Anal. Calcd for $C_{18}H_{26}O$: C, 83.66; H, 10.14. Found: C, 83.74, 83.73; H, 10.16, 9.98.

Method B. By Boron Trifluoride Etherate. A solution of ketol **10** (2.0 g) in boron trifluoride etherate (15 mL) was allowed to remain at room temperature for 1.5 h. The solution was poured onto ice and the crude product extracted by chloroform was neutralized by passing through a bed of anhydrous potassium carbonate. Removal of solvent gave an oil (2.0 g) that was induced to crystallize (mp 81–82 °C) from methanol. The melting point was undepressed upon admixture with **spiro[3,4-cyclohexano-$\Delta^{3,3''}$-bicyclo[3.3.1]nonen-9-one-2,1′-cyclohexane] (14).**

Method C. By Methanolic Hydrochloric Acid. A solution of ketol **10** (5.0 g) in methanol (100 mL) containing 5 mL of concentrated hydrochloric acid was heated at reflux for 25 h. The reaction mixture was diluted with an equal volume of water, and the products were isolated in chloroform. The extract was washed with 10% sodium carbonate and concentrated to an oil (5.6 g), which was triturated with hexane. An insoluble fraction (**10**, 1.5 g) melted at 183–185 °C and was identical (undepressed melting point upon admixture) with ketol **10**. The hexane-soluble fraction (3.0 g) crystallized from ethanol, 0.80 g, mp 63–63.5 °C, and a second crop weighing 0.17 g (mp 60–64 °C with sintering at 55 °C). A mixture melting point of the first crop with **spiro[3,4-cyclohexano-$\Delta^{3,4}$-bicyclo[3.3.1]nonen-9-one-2,1′-cyclohexane] (12)** was undepressed and comparison infrared spectra were identical.

Isomerization of Spiro[3,4-cyclohexano-$\Delta^{3,4}$-bicyclo[3.3.1]nonen-9-one-2,1′-cyclohexane] (12) to Spiro[3,4-cyclohexano-$\Delta^{3,3''}$-bicyclo[3.3.1]nonen-9-one-2,1′-cyclohexane] (14). A solution of ketone **12** (0.10 g) in boron trifluoride etherate (2 mL) was allowed to remain 4 h at room temperature and then neutralized by adding sufficient 5% sodium bicarbonate solution. The oil isolated by extraction with ether was obtained from ethanol as crystals melting at mp 65–70 °C. One recrystallization (ethanol) elevated the melting point to 78–79 °C. The melting point was undepressed after admixture with spiro[3,4-cyclohexano-$\Delta^{3,3''}$-bicyclo[3.3.1]nonen-9-one-2,1′-cyclohexane] (**14**), and

comparison infrared spectra were identical.

Spiro[3,4-cyclohexano-4,9-epoxybicyclo[3.3.1]nonane-2,1′-cyclohexane] (16). A solution of spiro[3,4-cyclohexano-4,9-dihydroxybicyclo[3.3.1]nonane-2,1′-cyclohexane] (**11a**, 1.0 g) in boron trifluoride etherate (20 mL) was left at room temperature for 1.5 h and poured onto ice, and the crude product was isolated by extraction with ether. The ether solution was washed with 5% sodium bicarbonate and the solvent removed in vacuo. The residual oil was chromatographed on 32 g of basic alumina (Alcoa). A benzene fraction (0.442 g, mp 55–57 °C) was identified by a mixture melting point and comparison of infrared spectra with those of the ether (**16**) obtained from pyrolysis of diol **11a**.

Dehydrogenation of Spiro[3,4-cyclohexano-4-hydroxybicyclo[3.3.1]nonan-9-one-2,1′-cyclohexane] (10) by Pyrolysis with Palladium on Charcoal. A mixture of ketol **10** (5.0 g) and 10% palladium on charcoal (2.0 g) was heated in a nitrogen atmosphere for 3 h from room temperature to 200 °C for 2 h from 200 to 275 °C, and for 4 h from 275 to 290 °C. The crude product (4.5 g) was chromatographed on 150 g of basic alumina (Merck). Elution with ligroin led to 1.77 g of **spiro[cyclohexane-1,9′-1′,2′,3′,4,4a′,9a′-hexahydroxanthene] (18)**. Two recrystallizations from absolute ethanol afforded needles melting at 77.5–78.5 °C (Kofler hot stage): ν_{max} 1604, 1580, 1486 (aromatic system), 1450 (CH_2), 1234 (aryl ether) cm^{-1}; ^1H NMR δ 1.10–2.23 (19 H, m), 4.37 (1 H, m), 6.73–7.32 (4 H, m); mass spectrum, m/e 256 (M^+), 213, 185, 131, 107.

Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.28, 84.34; H, 9.87, 9.77.

Further elution with ligroin provided **spiro[cyclohexane-1,9′-xanthene] (19)** as an oil (0.250 g) that crystallized from ethanol, yielding 0.160 g melting at 53–54.5 °C. Two additional recrystallizations from ethanol raised the melting point to 56–56.5 °C (capillary); λ_{max} 302 (log ϵ = 2.03), 277.5 (log ϵ = 3.44), 273.5 (log ϵ = 3.93) nm; ν_{max} 1594, 1570, 1470 (aromatic), 1446 (CH_2), 1230 (aryl ether), 758, 746 (ortho-substituted phenyl) cm^{-1}; ^1H NMR δ 1.52–2.03 (10 H, m), 6.99–7.63 (8 H, m).

Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25; M_r 250.3. Found: C, 86.73, 86.53; H, 7.26, 7.33; M_r (Rast) 236.

A fraction eluted by benzene corresponded to **spiro[3,4-benzobicyclo[3.3.1]nonan-9-one-2,1′-cyclohexane] (17**; 1.28 g of oil). Recrystallization from ethanol yielded 0.545 g, mp 69–74 °C. Two recrystallizations raised the melting point to 79–80 °C (capillary): λ_{max} 290 (log ϵ = 2.79), 273.4 (log ϵ = 3.67), 266.2 (log ϵ = 3.71), 260.0 (log ϵ = 3.59) nm; ν_{max} 1712 (C=O), 1488 (aromatic), 1450 (CH_2), 760 (1,2-disubstituted phenyl) cm^{-1}; ^1H, NMR δ 1.19–2.29 (16 H, m), 2.98 (1 H, m), 3.46 (1 H, m), 6.88–7.47 (4 H, m); mass spectrum, m/e 254 (M^+), 211, 141.

Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72; M_r 254.4. Found: C, 84.60, 84.54; H, 8.65, 8.70; M_r (Rast) 241.

Dehydrogenation of Spiro[3,4-cyclohexano-4,9-dihydroxybicyclo[3.3.1]nonane-2,1′-cyclohexane] (11a). Procedure A. By Pyrolysis with Palladium on Charcoal. A mixture of diol **11a** (3.0 g) and 10% palladium on charcoal (1.0 g) was heated in a nitrogen atmosphere at 225–230 °C for 3 h. A vigorous reaction occurred initially when this temperature was attained. The crude product (2.7 g, oil) was chromatographed on 75 g of basic alumina (Alcoa F-20). An oily fraction (0.12 g) eluted by ligroin was not characterized. Elution with 1:1 ligroin–benzene afforded the **spiro[3,4-cyclohexano-4,9-epoxybicyclo[3.3.1]nonane-2,1′-cyclohexane] (16**; 0.80 g, mp 53–56 °C). Recrystallization from methanol (gave mp 56–58 °C) followed by benzene and methanol–water provided a pure sample: mp 56–58 °C; ν_{max} 1010, 992, 950 cm^{-1}; ^1H NMR 0.87–2.07 (25 H, m), 3.98 (1 H, dd, J = 5.0, 4.5 Hz); mass spectrum, m/e 242, 225, 215, 166, 152 (base peak).

Anal. Calcd for $C_{18}H_{26}O$: C, 83.02; H, 10.84; M_r 258.4. Found: C, 83.01, 83.03; H, 10.60, 10.59; M_r (Rast) 242.

A fraction obtained by continued elution with 1:1 ligroin–benzene led to **1-(2-oxocyclohexanyl)-1-(1-cyclohexenyl)-cyclohexane (20**; 0.353 g, mp 74–78 °C). Three recrystallizations from ethanol afforded pure ketone **20** as needles: mp 91–91.6 °C (Kofler hot stage); ν_{max} 1712 (C=O), 1452 (CH_2) cm^{-1}.

Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 82.90, 83.44; H, 10.93, 11.01.

Procedure B. A mixture of diol **11a** (2.0 g) and 30% palladium on charcoal (1.3 g) was heated in a nitrogen atmosphere at 215 °C for 1.5 h at 270 °C for 2 h and at 310–315 °C for 1.5 h. The crude product (1.64 g, oil) was chromatographed on 40 g of basic alumina (Merck). A fraction (0.781 g of oil) eluted by ligroin was dissolved in methanol and **spiro[cyclohexane-1,9′-fluorene] (21)** and crystallized in low yield (0.034 g): mp 81.5–82 °C; λ_{max} 302 (log ϵ = 4.12), 291 (log ϵ = 3.91), 268 (log ϵ = 4.34), 228.5 (log ϵ = 3.890) nm; ^1H NMR δ 1.78–1.83 (10 H, m), 7.25–7.78 (8 H, m); mass spectrum, m/e 258, 234, 178.

Anal. Calcd for $C_{18}H_{18}$: C, 92.26; H, 7.74; M_r 234.1. Found: C, 92.07, 92.29; H, 7.71, 7.76; M_r (Rast) 224.

Continued elution with benzene provided **spiro[3,4-benzobicyclo[3.3.1]nonan-9-one-2,1′-cyclohexane] (17**, 0.692 g) as an oil that crystallized (mp 77–80 °C). Two additional recrystallizations elevated the melting point to 80–81 °C (Kofler hot stage). The specimens of ketone **17** obtained (see above) by dehydrogenating ketol **10** and as just described from diol **11a** were found to be identical by an undepressed mixture melting point and identical infrared (KBr) spectra.

Synthesis of Spiro[cyclohexane-1,9′-fluorene] (21). The following procedure is based upon work reported by Sherf and Brown.[9] A mixture of potassium (0.78 g, 0.02 mol) and a solution of fluorene (1.66 g, 0.01 mol) in dry dioxane (80 mL distilled from sodium) was heated at reflux for 11 h in a nitrogen atmosphere, forming a deep red solution. A solution of 1,5-dibromopentane (2.3 g, 0.01 mol) in dry dioxane (40 mL) was rapidly added. The mixture was stirred vigorously and heated at reflux for 7 h, cooled to ca. 25 °C, and diluted with an equal volume of water. An ether solution of the crude product was dried, solvent was removed in vacuo, and the residue (2.60 g) was chromatographed on 60 g of basic alumina (Alcoa). Crude spiro[cyclohexane-1,9′-fluorene] (**21**, 0.817 g) was isolated as an oil from the ligroin fraction. Xanthene **21** was purified by recrystallization from ethanol and finally by sublimation (Towers Micro Sublimator): mp 81.5–81.8 °C; λ_{max} 302 (log ϵ = 4.03), 290 (log ϵ = 3.83), 268 (log ϵ = 4.33), 228.8 (log ϵ = 3.69) nm; ν_{max} 1478, 1448, 760, 739 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}$: C, 92.26; H, 7.74; M_r 234.1. Found: C, 92.44; H, 7.69; M_r (Rast) 219.

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