TABLE IV

ACTIVITIES OF THE HYOSCYAMINE (I) AND HYOSCINE (II) AND THEIR DEGRADATION PRODUCTS (C.P.M./MM.[18])

Precursor fed	Phenylalanine-3-C^{14}		Sodium formate-C^{14}		Formaldehyde-C^{14}	
	I	II	I	II	I	II
Alkaloid hydrochloride	7.6×10^3	4.5×10^3	2.1×10^4	9.0×10^3	3.1×10^3	1.4×10^3
Tropine or oscine picrate	$<0.3 \times 10^3$	$<0.2 \times 10^3$	1.8×10^4	9.2×10^3	2.8×10^3	1.5×10^3
Triethylmethylammonium iodide	....	....	1.5×10^4	....	....	....
Tropic acid	7.1×10^3	4.3×10^3	$<0.05 \times 10^4$	0	$<0.05 \times 10^3$	$<0.06 \times 10^3$
Benzoic acid	7.1×10^3	4.2×10^3	....	....	....	....
Barium carbonate	6.9×10^3	4.0×10^3	....	....	....	....

then absorbed in a cooled ethanolic solution of triethylamine to yield triethylmethylammonium iodide.

(c) **Oxidation of the Tropic Acid.**—Tropic acid (50 mg.), obtained from the phenylalanine feeding experiment was refluxed with sodium hydroxide (0.2 ml. of 10%), and potassium permanganate (0.15 g.) in 5 ml. of water for 2 hr. The boiling solution was filtered, and the filtrate made acid with hydrochloric acid and extracted with ether. Evaporation of the dried ether extract yielded benzoic acid (29 mg.) which was purified by sublimation. The benzoic acid (20 mg.) was decarboxylated in boiling quinoline (5 ml.) in the presence of copper chromite catalyst (10 mg.). The evolved carbon dioxide was absorbed in barium hydroxide to yield barium carbonate (14 mg.). The activities of the degradation products are summarized in Table IV.

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[18] Counts were carried out in a Nuclear-Chicago model D-47 Q gas flow counter using a "Micromil" window. Determinations were carried out on samples of finite thickness, making corrections for efficiency and self absorption.

MINNEAPOLIS 14, MINN.

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

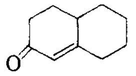
The Nature of the Intermediary Ketols in the Robinson Annelation Reaction[1]

BY WILLIAM S. JOHNSON, JAMES J. KORST,[2] R. A. CLEMENT[3] AND J. DUTTA[4]

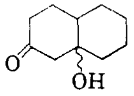
RECEIVED JUNE 22, 1959

The epimeric ketols-a and -b produced from the condensation of the tricyclic ketone IV (R = H) with methyl vinyl ketone have been shown through n.m.r. spectroscopic and degradation studies to have the bridged-ring structure VIII rather than the formerly proposed constitution VI and VII, respectively. On the basis of this study doubt is cast on the latter type of structural assignments that have been made in other cases (see ref. 7). Further studies with the ketols-a and -b have shown that their configurations and conformations correspond to those shown by expressions XIIa and XIIb, respectively. N.m.r. spectroscopic studies have proved that a ketol obtained from cyclohexanone and methyl vinyl ketone has the normal structure II, but a pair of ketols derived from the octalindione XX has the bridged-ring constitution XXII.

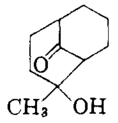
The Robinson annelation reaction is typified, in its simplest form, by an example described in the present work, namely the condensation of methyl vinyl ketone with cyclohexanone to produce $\Delta^{1,9}$-octalone-2 (I).[5] Of all of the known methods for the synthesis of fused hydroaromatic ring systems this reaction holds a unique position of importance. Thus every one of the successful total syntheses of natural non-aromatic steroids to date[6] have depended upon the use of this reaction at some stage.



I



II



III

In several instances, when the Robinson annelation method was being used, intermediary ketols have been isolated.[7] These substances have invariably been formulated as that ketol (*e.g.*, II) which is the direct precursor of the unsaturated ketone formed by a β-elimination process (*e.g.*, II → I). In the present work it is demonstrated that such ketols may be, on the contrary, correctly represented by a bridged-ring expression like that represented by formula III.[8] Indeed,

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[1] This represents paper XI of the series entitled "Steroid Total Synthesis—Hydrochrysene Approach." For paper X see W. S. Johnson, B. Bannister, R. Pappo and J. E. Pike, THIS JOURNAL, **78**, 6354 (1956).

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[3] National Science Foundation Postdoctoral Project Associate, 1954–1955.

[4] Upjohn Co. Postdoctoral Project Associate, 1955–1956.

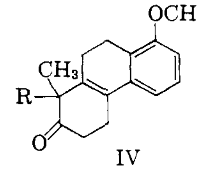
[5] A variation that is frequently employed involves the use of a progenitor of methyl vinyl ketone such as the Mannich base methiodide derived from acetone. A number of such cases have been summarized by J. H. Brewster and E. L. Eliel in Adams', "Organic Reactions," Vol. VII, 1953, p. 99. In this form the annelation process has sometimes been referred to as the "Robinson-Mannich base reaction."

[6] For a summary see paper I, W. S. Johnson, THIS JOURNAL, **78**, 6278 (1956). For subsequent work see A. Lardon, O. Schindler and T. Reichstein, *Helv. Chim. Acta*, **40**, 666 (1957); W. J. Van Der Burg, D. A. Van Dorp, O. Schindler, C. M. Siegmann and S. A. Szpilfogel, *Rec. trav. chim.*, T **77**[2], 171 (1958); K. Heusler, P. Wieland, H. Ueberwasser and A. Wettstein, *Chimia*, **12**, 121 (1958); and W. S. Johnson, J. C. Collins, R. Pappo and M. B. Rubin, THIS JOURNAL, **80**, 2585 (1958).

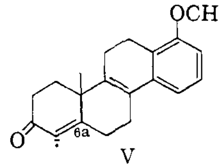
[7] See for example (a) C. Mannich, W. Koch and F. Borkowsky, *Ber.*, **70**, 355 (1937); (b) P. Wieland, H. Ueberwasser, G. Anner and K. Miescher, *Helv. Chim. Acta*, **36**, 1231 (1953); (c) V. Georgian, *Chemistry & Industry*, 930 (1954); (d) J. Colonge, J. Dreux and J. P. Kehlstadt, *Bull. soc. chim. France*, 1404 (1954); (e) G. Stork, *ibid.*, 256 (1955); (f) F. J. McQuillin, *J. Chem. Soc.*, 528 (1955); (g) R. Howe and F. J. McQuillin, *ibid.*, 2423 (1955); (h) W. S. Johnson, J. Ackerman, J. F. Eastham and H. A. DeWalt, Jr., THIS JOURNAL, **78**, 6302 (1956); (i) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **33**, 2215 (1950).

[8] K. D. Zwahlen, W. J. Horton and G. I. Fujimoto, *ibid.*, **79**, 3131 (1957), have described the formation of this type of ketol by the reaction of phenylmagnesium bromide with an enol lactone, i → ii, which they considered to proceed through rearrangement of the primary Grignard adduct. The same ketol ii was produced by the condensation of 1-methyl-2-tetralone with β-dimethylaminopropiophenone—a reaction which is quite analogous to that described in the

except for those cases that have been examined in the present work, the structures of the previously reported ketols[7] formed in the Robinson annelation reaction remain in doubt.

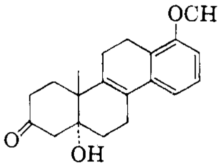


IV

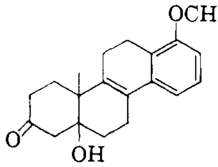


V

Paper IV of this series[7h] describes the methoxide-catalyzed reaction of the tricylic ketone IV (R = H) with methyl vinyl ketone to give a mixture of isomeric ketols, a and b. Since each of these ketols, on further treatment with methoxide, underwent facile dehydration to give the α,β-unsaturated tetracyclic ketone, V, they, like others,[7] were formulated as the two epimeric racemic ketols VI and VII. Our discovery that this structural assignment was erroneous evolved from some tangential observations that are described below.



VI



VII

In the course of further work, since the previous report,[7h] on the ketols in question we had occasion to carry out a sequence of reactions on the a-isomer which constituted an alternative method of effecting dehydration. These steps involved: (1) reduction with lithium aluminum hydride to the diol-a[7h]; (2) selective acetylation to give diol-a monoacetate, m.p. 130–131.5°; (3) dehydration by heating with phosphorus oxychloride in pyridine; (4) saponification of the dehydro acetate; (5) oxidation of the olefinic alcohol with Sarett reagent. The unsaturated ketone that was isolated from step 5 melted at 126.5–128.5° and was clearly different from the product V, m.p. 174–175°, of methoxide-catalyzed dehydration. All attempts to isomerize the 128° ketone, λ_{max} 5.82 μ (unconjugated C=O), into V failed, thus excluding the β,γ-unsaturated ketone structure.[9] The untraviolet spectrum of the 128° ketone, as well as of the dehydro acetate of step 3, was identical with that of 6a,7-dihydro-V; hence the olefinic bond that was introduced in step 3 was not in conjugation with either the keto group or the dihydronaphthalene system. We were thus forced to the conclusion that the 128° ketone did not have the same carbon skeleton as V, but all attempts to rationalize our findings on the basis of a rearrangement at the dehydration step 3 were abortive.

The enigma remained unresolved until we turned to nuclear magnetic resonance spectroscopy at the instigation of Professor J. D. Roberts whose expert help in determining and interpreting the spectra we acknowledge with pleasure.[10] The spectrum of the diol-a monoacetate of step 2 showed two sharp maxima at high applied magnetic field characteristic of proton resonance for the $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$ group. This observation is clearly incompatible with the postulated structure (formula VI with AcO in place of O=) which would have only one such absorption maximum. One of the products (see below) of the dehydration of diol-a monoacetate (step 3), moreover, showed in the n.m.r. spectrum only a single $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$ resonance at high field. The absence of the second $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$ band was replaced by the appearance of two vinyl proton peaks at low field suggesting the dehydration process $\mathrm{CH_3}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{-OH} \rightarrow \mathrm{CH_2{=}C} <$, which was indeed confirmed by infrared spectroscopy (see below). The foregoing evidence cast doubt on the original structural assignment of ketol-a. Indeed its n.m.r. spectrum, like that of the monoacetate, exhibited two, instead of one, sharp maxima at high field corresponding to $\mathrm{CH_3}\overset{|}{\underset{|}{\mathrm{C}}}-$. We, therefore, were forced to discard the old formula VI ketol-a and to consider the bridged-ring expression VIII with which the n.m.r. spectral data were entirely compatible (see Experimental). Proof that this structural assignment is correct follows.

When ketol-a was dehydrated with phosphorus oxychloride in pyridine it was converted, not to V, but into a mixture of anhydro ketones which was shown, with some difficulty (see below), to consist of two isomeric unsaturated ketones, m.p. 132–133.5° and 139–141°. The former, which was the preponderant product, proved to be identical with that ketone produced in step 5 of the indirect dehydration sequence described above. The structure of this 133° isomer was proved to be IXa as follows. Hydroxylation with osmium tetroxide afforded a glycol, m.p. 231–233.5°. This substance (Xa) was stable to sodium metaperiodate, but underwent cleavage with either periodic acid or lead tetraacetate to yield an oily product that gave a red-violet color with ferric chloride and formed a

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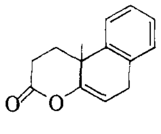
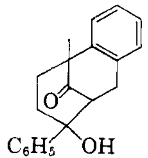
present work except that no alternative mode of ketol formation is possible.



i

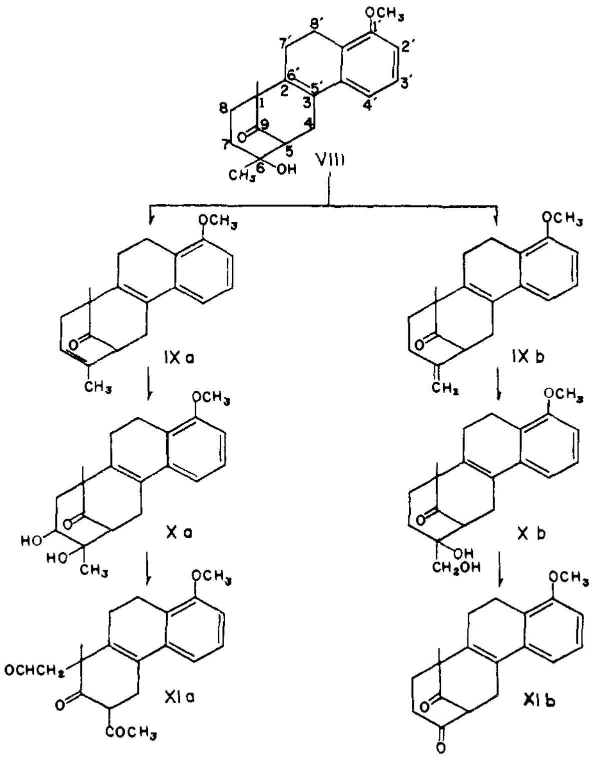


ii

Bridged-ring ketols of the type under discussion are also clearly involved as intermediates in the formation of bridged-ring unsaturated keto esters from the condensation of medium-sized ring β-keto esters with methyl vinyl ketone; V. Prelog, L. Ruzicka, P. Barman and L. Frenkiel, *Helv. Chim. Acta*, **31**, 92 (1948).

(9) *Cf.* the facile isomerization of Δ^5- into Δ^4-cholestene-3-one; L. F. Fieser, THIS JOURNAL, **75**, 5421 (1953).

(10) For a preliminary account of the early n.m.r. study see J. D. Roberts, "Nuclear Magnetic Resonance," McGraw–Hill Book Co., Inc., New York, N. Y., 1959, p. 36.



crystalline gray-green copper derivative, m.p. 253–253.5°, corresponding in composition to the copper enolate of the β-diketo aldehyde XIa.

The structure of the 141° isomer was established as IXb from the following evidence. The infrared spectrum exhibited a strong maximum at 11.16 μ characteristic of the terminal methylene group. Hydroxylation with osmium tetroxide afforded a glycol (Xb), isolated in dimorphic forms melting at 139–141° and 163.5–164.5°, which, in contrast to its isomer Xa, underwent facile cleavage with sodium metaperiodate to give the bridged β-diketone XIb, m.p. 168.5–170°, and formaldehyde isolated as the dimedon derivative in 81% yield.

Structure of Ketol-b.—This substance, formerly postulated to correspond to the structure VII, was more soluble and formed in lesser amount than ketol-a; hence its isolation from the mixture of epimers by fractional crystallization was difficult. In the present work ketol-b was separated by chromatography and thus obtained in a higher state of purity (m.p. 192.5–195°) than previously reported (m.p. 185–188°).[7h] The n.m.r. spectrum of ketol-b as well as of its acetate showed the pair of sharp maxima at high field characteristic of $-\overset{|}{\underset{|}{C}}CH_3$. This evidence clearly excludes the structures VI or VII and is compatible with the bridged-ring expression VIII for ketol-b, which is, therefore, epimeric with ketol-a about C_6. Dehydration of ketol-b with phosphorus oxychloride in pyridine afforded a mixture which was shown to consist of the two unsaturated ketones IXa and IXb, predominantly the latter. The separation of these products was seriously complicated by the fact that they formed a 1:1 complex melting sharply at 121°. The authenticity of this complex was established by its preparation from equimolar amounts of the pure 133° and 141° unsaturated ketones. The dehydration product from ketol-a was separated by chromatography into the 121° complex and the 133° unsaturated ketone IXa and although the separation was not quantitative it was clear that the 121° complex was preponderant. Similarly ketol-b afforded the 141° unsaturated ketone IXb and the 121° complex, the former in preponderance.

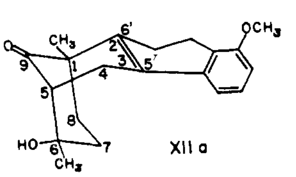
A quantitative determination of the proportion of products produced on dehydration of the two ketols was obtained by hydroxylation of the crude dehydration product with osmium tetroxide and treatment of the mixture of glycols with sodium metaperiodate which effected selective cleavage of the glycol Xb (see above). The resulting mixture of glycol Xa and diketone XIb was readily separated in 51 and 33% yield, respectively, from ketol-a and in 24 and 62% from ketol-b.

Attention is now turned back briefly to the product of dehydration (step 3) of diol-a monoacetate. Although obtained as a sharp-melting form, m.p. 127–128°, this product was clearly a mixture of the two bond isomers corresponding to IXa and IXb (with AcO in place of O=), predominantly the former, as shown by the infrared spectrum and further partial separation experiments (see Experimental part). Moreover, both pure epimeric (at C_9) forms of the isomer with the endocyclic double bond have been prepared by lithium aluminum hydride reduction of pure IXa followed by acetylation. These melted at 141–142° and 130.7–131.3° and were clearly different from the 127–128° substance as shown by the infrared spectra. In the final step (5) of the dehydration sequence it is not surprising that the preponderant unsaturated ketone IXa was the only product isolated.

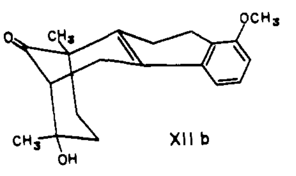
Configuration, Conformation and Interpretation of Reactions of Ketols.—With the structures of ketols-a and b- firmly established, it follows that their ready dehydration, in the presence of methoxide, to the unsaturated ketone V must involve a reverse aldol reaction to give the diketone IV (R = $CH_2CH_2COCH_3$), followed by recyclization to give the originally postulated aldol structure VI and/or VII which undergoes β-elimination, *i.e.*, VIII (mixture of C_6 epimers) $\rightleftarrows$ IV (R = $CH_2CH_2COCH_3$) $\rightleftarrows$ VI and/or VII $\rightarrow$ V.

Each of the epimeric ketols under consideration may be represented by one of the expressions XIIa or XIIb, if it is assumed that rings A and B adopt the chair and quasi-chair conformations, respectively.[11] Catalytic reduction of ketol-a over platinum oxide gave, after absorption of one mole-equivalent of hydrogen, a glycol which was identical with the preponderant product of lithium aluminum hydride reduction, namely diol-a.[7h] Treatment of ketol-b with lithium aluminum hydride afforded diol-b, m.p. 153–155° and 165–

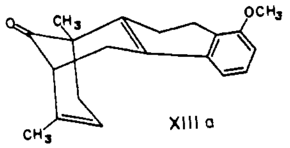
[11] Inspection of models indicate that this assumption is entirely reasonable so long as the carbon atom at position 5' is trigonal. In those substances with the 5', 6'-double bond reduced (see below), either ring A or B may adopt a boat conformation to relieve the serious non-bonded interaction between the axial substituents at $C_{1'}$ and C_7 in the all-chair conformation.



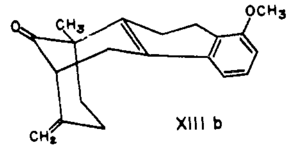
XIIa



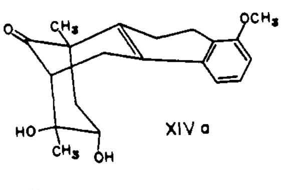
XIIb



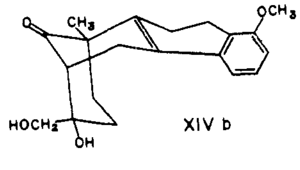
XIIIa



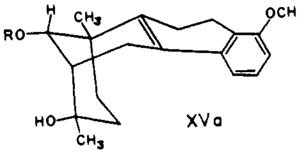
XIIIb



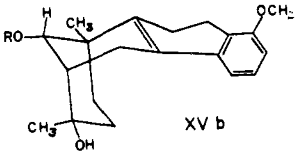
XIVa



XIVb



XVa

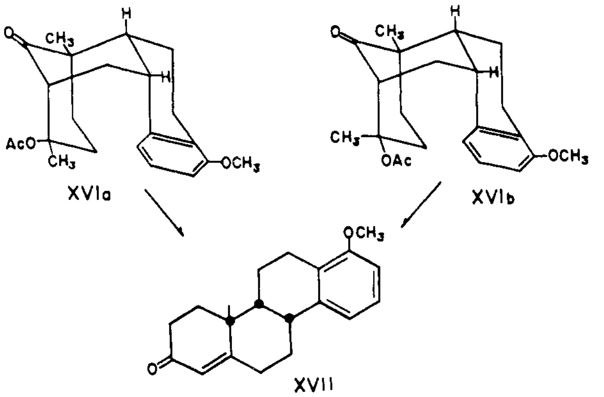


XVb

168°, as the major product. The C_9-epimer, m.p. 150–151°, was also isolated in the present study as a by-product. The structures XIIa and XIIb are both less hindered to catalyst approach from the top (β) face of the molecule than from the side (*exo*) face which has an interfering axial substituent at C_6; hence the hydroxyl group at C_9 is in the α-configuration for the preponderant diols which accordingly correspond to formulas XVa and XVb (R = H). Experiments described below show that the hydroxyl groups of diol-a have a *cis*-1,3-diaxial relationship, formula XVa (R = H); therefore ketol-a is correctly represented by formula XIIa. Diol-b and ketol-b, then, correspond to formulas XVb (R = H) and XIIb, respectively. It follows, moreover, that the minor lithium aluminum hydride reduction product, m.p. 188.2–188.8°,[7h] from ketol-a is now correctly represented as the C_9-epimer of XVa (R = H). Similarly the 151° minor product from reduction of ketol-b corresponds to the C_9-epimer of XVb (R = H).

The *cis*-1,3-diaxial relationship of the hydroxyl groups of diol-a was shown by the following considerations. On treatment with thionyl chloride in the presence of pyridine diol-a was converted into a cyclic sulfite ester, m.p. 137–139°; diol-b, in contrast, failed to give such a derivative.[12] Infrared spectroscopic examination[13] of the diol monoacetates XVa and its C_9-epimer (R = Ac) showed evidence for intramolecular hydrogen bonding in the former but not the latter.[14] Moreover, the former, diol monoacetate, but not XVb (R = Ac), underwent facile methanolysis in the presence of triethylamine, a manifestation of the Henbest–Kupchan 1,3-diaxial facilitation of solvolysis.[14,15] The strong intramolecular hydrogen bonding found[13] in the diol XVa (R = H) and the monoacetate XVa (R = Ac) clearly confirms the chair conformation of ring A.[11]

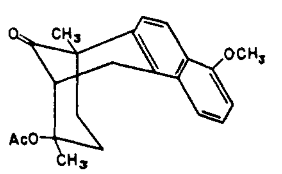
From the foregoing conclusions it follows that the bridged-ring dehydration products of the ketols XIIa and XIIb are correctly represented by the conformations XIIIa and XIIIb with rings A and B quasi-chair. These expressions in turn provide a clue to the configuration of the glycols produced therefrom on hydroxylation (see above). The olefinic bond in ring A of XIIIa is exceedingly hindered to axial approach at C_7; hence osmylation would certainly give rise to the product XIVa which corresponds therefore to the 233° glycol. The course of the osmylation of XIIIb is less certain, but an equatorial approach to C_6 appears to be preferred *a priori*. The 164° glycol accordingly is tentatively assigned the configuration shown in formula XIVb.



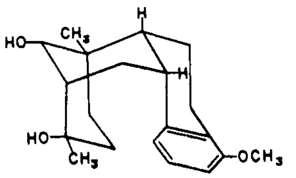
XVIa XVIb

XVII

Several structures that were previously proposed[7h] for substances derived from the ketols are now subject to revision. Catalytic hydrogenation of the acetates of ketol-a and ketol-b effected stereoselective reduction of the styrene bond. The resulting dihydro compounds, on treatment with sodium methoxide, both were converted to the same α,β-unsaturated ketone which has been proved unequivocally to have the *syn-cis* configuration, formula XVII. The stereochemical course of the reaction was rationalized with some difficulty on the basis of the old formulation.[7h] Now it is clear that β-side hydrogenation would be strongly favored with both ketols because approach of the catalyst to the α-side of the styrene double bond would be seriously hindered by the bridge composed of carbons 6, 7 and 8. The a- and b-dihydro ketol acetates, m.p. 181 and 147°, there-



XVIII



XIX

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[12] This was the method employed by Zwahlen, Horton and Fujimoto (ref. 8) for elucidation of configuration in similar compounds.

[13] R. West, J. J. Korst and W. S. Johnson, unpublished observation.

[14] *Cf.* H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1965 (1957).

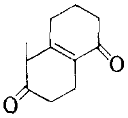
[15] S. M. Kupchan and W. S. Johnson, THIS JOURNAL, **78**, 3864 (1956).

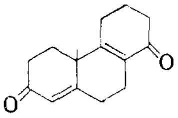
fore are correctly represented by structures XVIa and XVIb, respectively. The preferred conformations, however, may be those in which ring A or B is in the boat form.[11] It should be noted in passing that the naphthalenic by-product produced in the hydrogenation of ketol-a acetate is now reformulated as the bridged-ring substance XVIII.

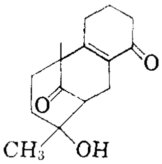
The major product of mild Birch reduction of ketol-a or of the diol XVa (R = H) was shown to have the same configuration as the product XVIa of catalytic reduction, and is now properly represented by formula XIX (see below for consideration of conformation). The stereochemical course of this reduction of the styrene bond still constitutes an exception to the generalities,[16] because XVIb is probably the least stable of the possible stereoisomers and is therefore a product of kinetic control.

Some evidence pertaining to the conformation of the diol XIX was obtained by examining the 9-monoacetate, m.p. 196–198°, which was found to undergo the facile triethylamine-catalyzed methanolysis indicative of 1,3-diaxial disposition of the hydroxy and acetoxyl groups. This result is consistent with a chair conformation of ring A and, probably, a boat for ring B.[11] Ring B would be expected to be more stable in the boat conformation than ring A because the boat form of the latter is destabilized by the α-OH at C_9. Further support for the chair conformation of ring A follows from the infrared spectral studies of XIX and its monoacetate, both of which exhibited intramolecular hydrogen bonding.[13]

Other Ketols.—In connection with another problem under investigation in this Laboratory, Tsatsos[17] developed a new procedure for the preparation of the octalone I which consisted of condensing methyl vinyl ketone with cyclohexanone (used in excess to serve as solvent) in the presence of Triton-B methoxide at 0°. A crystalline adduct separated from the reaction mixture in 25% yield. A pure material melting at 147–148.5° was separated from this mixture and was clearly a ketol as demonstrated by the infrared spectrum, $\lambda^{CS_2}_{max}$ 2.9 μ (OH), 5.85 (C=O). This substance, on treatment with sodium methoxide underwent dehydration to produce the octalone I. N.m.r. spectroscopy has now been used to distinguish between the structures II and III for the ketol. The spectrum showed no proton resonance for a methyl group; hence the originally proposed[17] formula II represents the structure of the 148° ketol. The crude ketol product melted at 115–141.5°, and was obviously a mixture which may have contained a stereoisomeric form of the 148° substance and/or one or two forms of the bridged-ring ketol III. This possibility has not been further examined. Confirmation of the structure II for the 148° ketol was obtained by dehydration with phosphorus oxychloride and pyridine which also afforded the octalone I. It was noted, moreover, that the ketol II underwent facile dehydration I simply upon heating with oxalic acid, a procedure which failed to effect dehydration of the bridged-ring ketol-a. Possibly this test will serve as a reliable criterion of the basic structure of such ketols, but n.m.r. spectroscopy is surely preferable. The ketol of Wieland and Miescher[7i] thus may be formulated correctly as the normal ketol.


XX


XXI


XXII

Wilds[18] has described the condensation of the octalindione XX with methyl vinyl ketone to produce an adduct, m.p. 142.5–143°, convertible by the action of acid into an isomer, m.p. 195.5–197°. These substances, originally considered to be open-chain triketones,[18] have since been shown to be ketols.[19] Both ketols, on treatment with alkali, were converted into the tricyclic dehydro compound XXI. Professor Wilds kindly supplied us with specimens of the acetates of his two ketols for n.m.r. examination. Both spectra exhibited three sharp maxima attributable to the proton resonance of methyl groups: a pair at high applied magnetic field $(-\overset{|}{\underset{|}{\text{C}}}\text{CH}_3)$ and one at lower field (OCOCH_3). These results show clearly that the ketols (and their acetates) are bridged-ring epimers with the structure XXII. Details of this study will be reported by Professor A. L. Wilds.

Acknowledgments.—We wish to acknowledge help provided by agencies mentioned in references 2–4 as well as by the National Science Foundation and the National Institutes of Health (Grant A-2134). We are grateful to J. E. Cole, Jr., P. R. Shafer and K. L. Williamson for assistance in the n.m.r. determinations.

Experimental[20]

1β,6-*endo*-Dimethyl-6-*exo*-hydroxy-2,3-(1′-methoxy-7′,8′-dihydro-6′,5′-naphtho)-Δ^2-bicyclo[3.3.1]nonene-9-one (XIIa).—This substance, "ketol-a," has been described pre-

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[16] D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

[17] W. T. Tsatsos, Ph.D. Dissertation, University of Wisconsin, 1954.

[18] A. L. Wilds, J. W. Ralls, W. C. Wildman and K. E. McCaleb, This Journal, **72**, 5794 (1950).

[19] Unpublished studies, A. L. Wilds.

[20] (a) All melting points are corrected for stem exposure. (b) Ultraviolet spectra were determined with a model 11 MS Cary recording spectrophotometer and 95% ethanol was employed as solvent. (c) Infrared spectra were determined with a model B Baird Double Beam infrared recording spectrophotometer. (d) N.m.r. spectra were determined at 40 megacycles/second with a Varian Associates V-4300-B high resolution n.m.r. spectrometer with associated 12″ magnet system equipped with a V-K3506 flux stabilizer. Deuteriochloroform, carbon disulfide or pyridine (as indicated) were employed as solvents. Benzene, contained in a small melting point tube capillary and added to the sample tube, was employed for reference. When pyridine was used as solvent, water was used for reference and the values corrected to benzene as 0 c.p.s. (estimated accuracy ±2 c.p.s.). It should be noted that n.m.r. signals of a compound dissolved in pyridine appear about 30 c.p.s. toward higher field than when dissolved in chloroform or carbon disulfide. Audiofrequency side bands for calibration were generated and measured with a Hewlett-Packard 200-CD audio oscillator and 521-C frequency counter. (e) The ketols and their progeny described in this paper are all racemic compounds, but the prefix "*dl*" has been omitted and only one enantiomer is illustrated in the formulas.

viously as melting at 214–215.5° (in an evacuated capillary).[7h] Material of comparable quality, m.p. 214–217.5°, was used for n.m.r. spectral studies, major n.m.r. signals (pyridine), c.p.s.: +35.5 (OH), +135 (OCH_3), +227.5 (HO$\overset{|}{\underset{|}{\mathrm{C}}}$$CH_3$), +234 (–$\overset{|}{\underset{|}{\mathrm{C}}}$$CH_3$).

1β,6-*exo*-Dimethyl-6-*endo*-hydroxy-2,3-(1′-methoxy-7′,8′-dihydro-6′,5′-naphtho)-Δ^2-bicyclo[3.3.1]nonene-9-one (XIIb).—This substance, "ketol-b," has been described previously as melting at 185–188°.[7h] In the present work it was found that this isomer could be separated nicely from its epimer and obtained in a higher state of purity by chromatography. Thus 20 g. of ketol mixture, m.p. 179–183°, in benzene solution was adsorbed on 1 kg. of Florisil. The fractions eluted with 6% ether in benzene amounted to 1.1 g. of oily material that crystallized on trituration wih ether. Crystallization from methanol afforded 0.78 g. of crude ketol-b, m.p. 178–193°. Recrystallization from dilute solution (seeding with ketol-b) afforded 0.46 g. of large prisms, m.p. 191.5–193.5°. A further recrystallization raised the m.p. to 192.5–195°; $\lambda^{\mathrm{mull}}_{\mathrm{max}}$ 2.84 μ (OH), 5.86 (C=O); major n.m.r. signals (pyridine), c.p.s.: +28 (OH), +135 (OCH_3), +228 (HO$\overset{|}{\underset{|}{\mathrm{C}}}$$CH_3$), +236 (–$\overset{|}{\underset{|}{\mathrm{C}}}$$CH_3$).

Dehydration of Ketol-a by Indirect Method. Step 1.—Ketol-a (XIIa) was reduced with lithium aluminum hydride as already described[7h] and the total crude reaction product, m.p. 145–155° (quantitative yield), containing the two epimeric diols was used in the next step.

Step 2.—A solution of 2.04 g. of crude diol mixture in 40 ml. of pyridine and 20 ml. of acetic anhydride was heated on the steam-bath for 3 hr., then diluted with benzene and washed with 10% hydrochloric acid followed by cold 10% potassium hydroxide solution. The solution was dried over anhydrous magnesium sulfate, evaporated, and the solid residue was chromatographed on 100 g. of Florisil. The major fraction eluted with 5–10% ether in benzene amounted to 1.71 g. (76% yield from ketol-a) of crystalline material which appeared to be fairly pure diol-a monoacetate XVa (R = Ac), namely **1β,6-*endo*-dimethyl-6-*exo*-hydroxy-9α-acetoxy-2,3-(1′-methoxy-7′,8′-dihydro-6′,5′-naphtho)-Δ^2-bicyclo[3.3.1]nonene**, as ascertained by the identity of the infrared spectrum with that of the analytical specimen. Two recrystallizations from dilute methanol gave colorless platelets, m.p. 130–131.5°; $\lambda^{\mathrm{film}}_{\mathrm{max}}$ 2.79 μ (OH), 5.77 (C=O), 6.13 (C=C); λ_{max} 222 mμ (log ε 4.41), 268 (4.07); $\lambda_{\mathrm{min.}}$ 244 (3.70); major n.m.r. signals ($CDCl_3$), c.p.s.: +50 (doublet, J = 2–3, AcO$\overset{\mathrm{H}}{\underset{|}{\mathrm{C}}}$– split by proton at C_5), + 104 (–OCH_3), +123 (OH), +170 ($OCOCH_3$), +190 (CH_2), +209 (HO$\overset{|}{\underset{|}{\mathrm{C}}}$$CH_3$), +215 (–$\overset{|}{\underset{|}{\mathrm{C}}}$$CH_3$).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.2; H, 7.9.

In a later preparation of this monoacetate, a lower-melting modification (m.p. 112–116°) was encountered which was converted to the higher-melting form by seeding experiments.

Further elution of the above described Florisil column with 1% ethanol in benzene yielded 0.335 g. (15% yield from ketol-a) of the **C_9-epimer of XVa (R = Ac)**. Recrystallization from petroleum ether (b.p. 60–68°) followed by two recrystallizations from ethanol–water afforded colorless prisms, m.p. 195–199°; $\lambda^{\mathrm{CH_2Cl_2}}_{\mathrm{max}}$ 2.86 μ (OH), 5.78 (C=O).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.2; H, 8.2.

Step 3.—A solution of 1.03 g. of the aforementioned monoacetate XVa (R = Ac), m.p. 126–131°, in 50 ml. of pyridine and 2.0 g. of phosphorus oxychloride was heated at 90° for 2.5 hr., then diluted with 200 ml. of benzene and washed thoroughly with cold 10% hydrochloric acid followed by cold 10% potassium hydroxide solution. The solution was dried over anhydrous magnesium sulfate, evaporated, and the colorless crystalline residue recrystallized from dilute ethanol to give 0.83 g. (85% yield) of colorless prisms, m.p. 124–126°. Two more recrystallizations raised the m.p. to 127–128°.

Anal. Calcd. for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.3; H, 7.7.

In spite of the sharp melting point this material was shown to be a mixture of the two dehydration isomers with the newly formed olefinic bond exocyclic and endocyclic, predominantly the latter. Chromatography of a sample of the dehydration product, m.p. 119–126°, on Florisil gave successive crystalline fractions melting from 119–125° to 128–132°. The infrared spectra of early fractions exhibited strong absorption at 11.16 and 6.11 μ indicating that they were richer in the isomer with the exocyclic olefinic bond. The infrared spectra of the later fractions showed much weaker absorption in these regions, indicative of the isomer with the endocyclic double bond. Further evidence for the non-homogeneity of this dehydration product was obtained from the saponification experiment described below (step 4) which gave a mixture of diols as indicated by the m.p.

Step 4.—A solution of 0.66 g. of the dehydration product of step 3, m.p. 126–128°, in 50 ml. of 95% ethanol and 20 ml. of water containing 3 g. of potassium hydroxide was heated under reflux on the steam-bath for 4.7 hr., then diluted with 700 ml. of water. The mixture was extracted with benzene, and the benzene solution washed with water and dried over anhydrous magnesium sulfate. Crystallization of the residue, obtained on evaporation of the solvent, from dilute ethanol afforded colorless crystals, m.p. 105–122°. Two recrystallizations raised the m.p. to 112–123°; λ_{max} 222 mμ (log ε 4.37), 269 (4.05); λ_{min} 224 (3.64).

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.0; H, 8.1.

Step 5.—A solution of 0.052 g. of the crude unsaturated alcohol of step 4 in 0.5 ml. of pyridine was treated with the complex prepared from 0.6 ml. of pyridine and 0.053 g. of chromium trioxide. The mixture was allowed to stand overnight at room temperature. Ether and benzene were then added and the mixture washed thoroughly with dilute hydrochloric acid followed by 10% potassium bicarbonate solution, and water. The solution was dried over anhydrous magnesium sulfate, evaporated, and the residue crystallized from ethyl acetate–petroleum ether (b.p. 60–68°). This material (0.0345 g.) was evidently a mixture as indicated by the broad melting point range, 120–127°. Two recrystallizations from absolute ethanol gave 0.0257 g. (50% yield) of product, m.p. 126.5–128.5°, undepressed on admixture with the unsaturated ketone XIIIa, m.p. 132–133.5°, described below. The close similarity of the infrared spectra of these two materials confirmed the identity of the 128° ketone.

Phosphorus Oxychloride–Pyridine Dehydration. (a) Of Ketol-a (XIIa).—A solution of 0.633 g. of ketol-a, m.p. 214–217.5°, and 1.2 g. of phosphorus oxychloride in 25 ml. of dry pyridine was heated at 90° for 2.5 hr. The mixture was treated as described above (step 2), and the crude semi-crystalline product (0.581 g.) was crystallized from petroleum ether (b.p. 60–68°) to give 0.437 g. (73% yield) of colorless prisms, m.p. 121–123.5°. Repeated recrystallization from petroleum ether (b.p. 60–68°) gave colorless prisms of a mixture of XIIIa and XIIIb (see below), m.p. 121.5–125°, $\lambda^{\mathrm{CHCl_3}}_{\mathrm{max}}$ 5.82 μ (C=O) and 11.16 (C=CH_2, medium intensity). A sample of this mixture was partially separated by chromatography on Florisil. Elution with 25% benzene in petroleum ether (b.p. 60–68°) afforded successive fractions with melting points increasing from 117–120° to 131°. The lower melting fractions consisted mainly of a 1:1 mixture (see below). Later fractions gradually were enriched in that isomer XIIIa with the endocyclic olefinic bond, as indicated by the somewhat lower intensity of the 11.16 μ band in the infrared spectrum. Repeated recrystallization of the highest melting fractions from petroleum ether (b.p. 60–68°) yielded **1β,6-dimethyl-2,3-(1′-methoxy-7′,8′-dihydro-6′,5′-naphtho)-Δ^{2,6}-bicyclo[3.3.1]-nonadiene-9-one (XIIIa)** as colorless prisms, m.p. 132–133.5°; $\lambda^{\mathrm{CHCl_3}}_{\mathrm{max}}$ 5.82 μ (C=O), 6.14 (C=C, weak). The infrared spectrum showed no band in the 11.2 μ region.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.4; H, 7.6.

(b) Of Ketol-b (XIIb).—A 0.299-g. sample of ketol-b, m.p. 192–194°, was treated with 1.68 g. of phosphorus oxychloride in 15 ml. of pyridine as described in the preceding experiment. The crude product amounted to 0.270 g. of pale yellow crystals, m.p. 123–131°, which was chromatographed on Florisil, yielding 0.244 g. (87%) of crystalline material. About 60% of the product was eluted with 20% benzene in petroleum ether (b.p. 60–68°). Most of this material, which melted above 120°, appeared by the infrared spectrum to be mainly **1β-methyl-6-methylene-2,3-(1'-methoxy-7',8'-dihydro-6',5'-naphtho)-Δ²-bicyclo[3.3.1]-nonene-9-one (XIIIb)**.—An early fraction, melting at 135.5–137.5°, after repeated recrystallization from petroleum ether (b.p. 60–68°) gave colorless prisms, m.p. 139–141°; $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.82 μ (C=O), 6.11 (C=C, strong), 11.16 (C=CH$_2$, strong); major n.m.r. signals (CS$_2$), c.p.s.: +67 (doublet, $J = 2$, >C=CH$_2$), +105 (OCH$_3$), +211 ($-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$).

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.8; H, 7.5.

Further elution of the column with 20–40% benzene in petroleum ether (b.p. 60–68°) gave fractions with melting points that gradually decreased to a minimum of 117.5–119.5°, undepressed on admixture with the 1:1 mixture of dehydration products obtained from ketol-a. The infrared spectra of these two specimens were identical.

The 1:1 Mixture of XIIIa and XIIIb.—Five milligrams each of the anhydro ketones XIIIa, m.p. 131–133°, and XIIIb, m.p. 138–140.5°, was mixed and fractionally crystallized from petroleum ether (b.p. 60–68°). The first crop (0.003 g.) melted at 118.5–121° and the second (0.005 g.) at 118.5–120.5°. On admixture of the second crop material with the comparably melting fraction obtained in the dehydration of ketol-b (see above), there was no depression of the m.p.

Chromatography of the 1:1 mixture prepared from XIIIa and XIIIb on Florisil effected very slight separation on elution with 10–20% benzene in petroleum ether (b.p. 60–68°). The first fractions were enriched in XIIIb as shown by the intense 11.16 μ band in the infrared spectrum. Succeeding fractions were largely the 1:1 mixture, and the very last fractions were enriched in XIIIa since the 11.16 μ band in the infrared spectrum was noticeably weaker than found for the 1:1 mixture.

1β,6-*endo*-Dimethyl-6-*exo*-7-*exo*-dihydroxy-2,3-(1'-methoxy-7',8'-dihydro-6',5'-naphtho)-Δ²-bicyclo[3.3.1]nonene-9-one (XIVa).—Osmium tetroxide (0.118 g.) was added to a solution of 0.118 g. of the unsaturated ketone XIIIa, m.p. 131–133°, in 3 ml. of purified[21] dioxane. The mixture, which turned brown immediately, was stirred at room temperature for 20 hr. The solvent was then evaporated in a stream of nitrogen, the black residue dissolved in 15 ml. of chloroform and hydrogen sulfide passed through the solution until the supernatant liquid was colorless. The mixture was filtered from the black precipitate which was washed well with chloroform, and the combined chloroform filtrates were evaporated in a stream of nitrogen. The residue amounted to 0.116 g. of colorless prisms, m.p. 195–220°. Recrystallization from ethyl acetate–petroleum ether (b.p. 60–68°) yielded 0.097 g. (73%) of colorless prisms, m.p. 217–225°. Repeated recrystallization from 95% ethanol afforded pure material as small elongated prisms, m.p. 231–233.5°; $\lambda_{\max}^{\mathrm{mull}}$ 2.88 μ (OH), 3.04 (OH), 5.84 (C=O), 6.11 (C=C).

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.2; H, 7.4.

Oxidative Cleavage of the Glycol XIVa. (a) With Lead Tetraacetate.—Freshly recrystallized lead tetraacetate (0.097 g.) was added to a solution of 0.071 g. of the glycol, m.p. 217–225°, in 3 ml. of glacial acetic acid containing 3 drops of acetic anhydride. After 1 hr. at room temperature the yellow solution gave a negative test with starch–iodide paper, and an additional 0.005 g. of lead tetraacetate was introduced. After 0.5 hr. the solution, which now gave a weakly positive reaction to starch–iodide paper, was concentrated under reduced pressure. The residual yellow oil was dissolved in ethyl acetate, and the solution was washed well with water, then evaporated. The residue was dissolved in 10 ml. of ether, and stirred with 6.5 ml. of saturated aqueous cupric acetate solution at room temperature overnight. The precipitated gray-green **copper enolate of 1-methoxy-6-acetyl-7-keto-8-methyl-5,6,7,8,9,10-hexahydro-8-phenanthrylacetaldehyde (XIa)** was separated by filtration and washed thoroughly with water and with ether. The yield was 0.041 g. (53%), m.p. 218–232° dec. Repeated recrystallization from chloroform–ethyl acetate afforded small gray-green needles, m.p. 253.0–253.5° dec.; $\lambda_{\max}^{\mathrm{mull}}$ 3.66 μ (aldehydic C–H, weak), 5.80 (C=O), 5.85 (C=O), 6.30 (chelated β-diketone).[22]

Anal. Calcd. for $C_{40}H_{42}O_8Cu$: C, 67.25; H, 5.93; CuO (residue), 11.14. Found: C, 67.1; H, 5.9; residue, 11.3.

(b) **With Periodic Acid.**—To a solution of 0.014 g. of the glycol, m.p. 230–234°, in 2 ml. of purified[21] dioxane was added 0.5 ml. of water (dropwise to prevent precipitation of the glycol) followed by 0.013 g. of periodic acid. After standing for 2 days at room temperature the yellow solution was diluted with water, extracted with ethyl acetate and the organic solution was washed with sodium bicarbonate solution. The ethyl acetate was evaporated yielding a yellow oil which gave a red-violet color with alcoholic ferric chloride solution. The oil was dissolved in 5 ml. of ether and stirred overnight with 5 ml. of saturated aqueous solution of cupric acetate. The precipitated copper enolate, isolated as described above, amounted to 0.009 g. (59% yield), m.p. 220–235° dec.

When the cleavage was tried with sodium metaperiodate, the glycol was recovered quantitatively.

1β-Methyl-6-*exo*-hydroxymethyl-6-*endo*-hydroxy-2,3-(1'-methoxy-7',8'-dihydro-6',5'-naphtho)-Δ²-bicyclo[3.3.1]-nonene-9-one (XIVb).—The procedure described above for the preparation of the isomer XIVa was followed. Thus from 0.082 g. of the unsaturated ketone XIIIb, m.p. 137.5–140°, and 0.085 g. of osmium tetroxide there was obtained 0.106 g. of colorless needles, m.p. 77–85° with evolution of gas (probably chloroform of solution). This material was dissolved in ethyl acetate, the solution boiled to remove any chloroform, and petroleum ether (b.p. 60–68°) added to the point of incipient crystallization. On cooling, the glycol crystallized as small colorless platelets, m.p. 156–162.5°, yield 0.065 g. (71%). An additional 0.011 g. of colorless oily crystals was obtained from the mother liquor. Repeated recrystallization of the first crop material raised the m.p. to 163.5–164.5°; $\lambda_{\max}^{\mathrm{mull}}$ 2.96 μ (OH), 5.85 (C=O).

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.1; H, 7.4.

In another similar experiment this glycol was obtained in a polymorphic modification as leaflets, m.p. 139–141°, which was convertible to the higher melting modification.

Oxidative Cleavage of the Glycol XIVb to 1β-Methyl-2,3-(1'-methoxy-7',8'-dihydro-6',5'-naphtho)-Δ²-bicyclo-[3.3.1]nonene-6,9-dione (XIb).—To a solution of 0.039 g. of the glycol, m.p. 161.5–164°, in 3.5 ml. of 95% ethanol was added 1 ml. of water (dropwise with stirring to prevent precipitation of the glycol) followed by 0.026 g. of finely powdered sodium metaperiodate. The flask was stoppered and the mixture stirred at room temperature for 3 hr. The mixture was then diluted with water and distilled so that the distillate passed directly into a solution of 0.067 g. of dimedon in 1 ml. of 95% ethanol contained in the receiver which was cooled in an ice-bath. Water was added as necessary and the distillation continued until about 60 ml. of distillate was collected. This distillate was diluted with water until the volume was about 230 ml. and the mixture allowed to stand at 6° overnight. The dimedon–formaldehyde derivative which crystallized amounted to 0.019 g., m.p. 184–188° (reported[23] 189–190°). After further dilution of the filtrate and cooling overnight an additional 0.010 g. of the derivative, m.p. 183–188°, was obtained. The total yield was thus 81%. The m.p. was undepressed on admixture with authentic material.

The aqueous residue from the distillation described above was extracted with ethyl acetate. The organic solution was dried over anhydrous sodium sulfate, and the solvent was evaporated leaving a brown oily residue which crystallized upon trituration with ether. This residue was chromatographed on 1.5 g. of Florisil. Elution with benzene and with 5% ether in benzene afforded a total of 0.029 g. (82% yield) of small colorless prisms, m.p. 164–168°. Repeated recrystallization of this diketone from ethyl acetate–petroleum ether (b.p. 60–68°) yielded colorless prisms, m.p. 168.5–170°, $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.78 μ (C=O), 5.85 (C=O), 6.13 (C=C).

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.8; H, 6.9.

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[21] L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath and Co., Boston, Mass., 1955, p. 284.

[22] *Cf.*, H. F. Holtzclaw, Jr., and J. P. Collman, THIS JOURNAL, **79**, 3318 (1957).

[23] R. E. Reeves, *ibid.*, **63**, 1476 (1941).

Hydroxylation and Selective Oxidative Cleavage of the Mixtures of Unsaturated Ketones XIIIa and b from Dehydration of the Ketols.—A 0.200-g. sample of the aforementioned mixture of unsaturated ketones (m.p. 118–123°) obtained from the dehydration of ketol-a (see above) was oxidized with 0.185 g. of osmium tetroxide according to the procedure described above. The crude mixture of glycols (0.215 g.) was then oxidized with 0.147 g. of sodium metaperiodate (see above) to give 0.217 g. of oily crystalline mixture. Extraction with hot benzene left 0.042 g. of insoluble glycol XIVa, m.p. 217–228°. Chromatography of the benzene-soluble material on Florisil yielded, on elution with 1% acetone in benzene, a total of 0.066 g. (33% yield) of crude diketone XIb which, after trituration with ether, melted at 161–166°. Further elution with 2–25% acetone in benzene gave an additional 0.072 g. of glycol XIVa, m.p. 212–221°, making the total yield of this material 51%.

A 0.154-g. sample of mixture of the unsaturated ketones XIIIa and b obtained from the dehydration of ketol-b (see above) was treated just as described in the preceding section. A total of 0.041 g. (24% yield) of glycol XIVa, m.p. 209–224°, and 0.097 g. (62% yield) of diketone, m.p. 167–169° after trituration with ether, was isolated.

Lithium Aluminum Hydride Reduction of the Unsaturated Ketone XIIIa.—A 0.165-g. specimen of the unsaturated ketone, m.p. 131–133°, was reduced with 0.123 g. of lithium aluminum hydride in 10 ml. of tetrahydrofuran (purified by distillation from lithium aluminum hydride) as described previously for ketol-a[7h] except that a reaction period of 3 hr. at room temperature was used. The crude product amounted to 0.168 g. of a colorless oil which crystallized on adding a little ether, m.p. 90–157°. Slow crystallization from ethyl acetate–petroleum ether (b.p. 60–68°) yielded a mixture of clusters of small prisms, m.p. 160–179°, and of large prisms, m.p. 92–122°, which were separated mechanically. Recrystallization of the former fraction (0.086 g.) from the same solvent pair gave 0.079 g. (48% yield) of prisms, m.p. 178–181°. Repeated recrystallization raised the m.p. to 180.0–181.5°; $\lambda_{max}^{CH_2Cl_2}$ 2.78 μ, 2.90 (OH), 6.15 (C=C).

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 80.9; H, 8.3.

After one of the recrystallizations a polymorphic form was obtained melting partially at 130–145°, resolidifying, and remelting at the higher temperature.

The acetate, prepared with pyridine and acetic anhydride, crystallized from petroleum ether (b.p. 60–68°) as colorless prisms, m.p. 141–142°; $\lambda_{max}^{CHCl_3}$ 5.81 μ (C=O), 6.11 (C=C).

Anal. Calcd. for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.4; H, 7.6.

A polymorphic form of the acetate was obtained as platelets, m.p. 146–149°, which was convertible to the 142° modification by slow recrystallization. In the presence of chloroform this acetate crystallized as a solvate, m.p. 72–95°.

The 92–122° fraction (0.048 g.) from the first crystallization was combined with the residue from the mother liquor and chromatographed on 3 g. of Merck and Co. acid-washed alumina. Elution with 25% benzene in petroleum ether (b.p. 60–68°) afforded 0.069 g. (42% yield) of mixtures of colorless prisms and rods, with m.p.'s ranging from 80–90° to 93–103°. Recrystallization from various solvents failed to improve the m.p., nor did further chromatography on Florisil effect any change in m.p. behavior. Repeated recrystallization from petroleum ether (b.p. 60–68°) gave colorless prisms, m.p. 92–108°. Sublimation and repeated recrystallization from the same solvent of a sample of this alcohol prepared by saponification of its acetate (see below), m.p. 128–129°, gave colorless rods, m.p. 132–134°; $\lambda_{max}^{CH_2Cl_2}$ 2.80 μ, 2.88 (OH), 6.13 (C=C).

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.1; H, 8.2.

Further elution of the alumina column with benzene and ether yielded an additional 0.011 g. of crude 182° isomer.

The acetate, prepared from alcohol, m.p. 90–120° (infrared spectrum identical with that of analytical specimen), with pyridine and acetic anhydride, was obtained after two recrystallizations from petroleum ether (b.p. 60–68°), in 65% yield as colorless prisms, m.p. 128–129°. Repeated recrystallization from the same solvent gave colorless prisms, m.p. 130.7–131.3°; $\lambda_{max}^{CHCl_3}$ 5.81 μ (C=O), 6.11 (C=C).

Anal. Calcd. for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.1; H, 7.7.

Catalytic Hydrogenation of Ketol-a.—A 0.309-g. sample of ketol-a, m.p. 214–217.5°, which had been treated with Raney nickel in refluxing ethanol, was hydrogenated over 0.112 g. of platinum oxide in 40 ml. of absolute ethanol at room temperature and atmospheric pressure. The reaction was incomplete and very slow after 20 hr., so an additional 0.100 g. of catalyst was introduced and hydrogenation continued until gas uptake ceased (2 hr.). The mixture was filtered and the filtrate concentrated. The oily residue, which crystallized on trituration with ether, was recrystallized twice from ethyl acetate–petroleum ether (b.p. 60–68°) to give 0.234 g. (75% yield) of the diol XVa (R = H) as a dimorphic mixture of prisms and rods, m.p. 143–160°. Except for a weak band at 5.82 μ indicating unreduced ketonic impurity, the infrared spectrum was essentially identical with that of the major product, m.p. 163–166°, from the lithium aluminum hydride reduction of ketol-a.[7h] The ultraviolet spectrum of the 143–160° material showed that the styrene double bond was intact; λ_{max} 222 mμ (log ε 4.39), 268 (4.07).

The Cyclic Sulfite Ester of 1β,6-*endo*-Dimethyl-6-*exo*,9α-dihydroxy-2,3-(1′-methoxy-7′,8′-dihydro-6′,5′-naphtho)-Δ²-bicyclo[3.3.1]nonene (XVa, R = H).—The following is an adaptation of a previously reported procedure.[12] A solution of 0.089 g. of purified[24] thionyl chloride in 10 ml. of dry ether was added dropwise over a 15-min. period to a cooled (ice-bath) and stirred mixture of 0.157 g. of the aforementioned diol XVa (R = H), m.p. 142–162°, 0.130 g. of dry pyridine and 15 ml. of dry ether. Stirring was continued for 1.25 hr. while the reaction mixture was allowed to warm to room temperature. The mixture was filtered to remove pyridine hydrochloride which was washed well with ethyl acetate. The combined organic solutions were washed twice with water and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded 0.176 g. of pale yellow oil which was chromatographed on 7 g. of Florisil. Elution with benzene and with 10% ether in benzene yielded a total of 0.153 g. (85% yield) of colorless crystals, m.p. 109–134°. Repeated recrystallization from ethyl acetate–petroleum ether (b.p. 60–68°) afforded clusters of colorless platelets, m.p. 137–139°, decomposing with evolution of gas (SO_2) at about 170°; $\lambda_{max}^{CH_2Cl_2}$ 6.15 μ (C=C), 8.30 (S → O).[25]

Anal. Calcd. for $C_{20}H_{24}O_4S$: C, 66.65; H, 6.71; S, 8.88. Found: C, 66.6; H, 6.7; S, 9.0.

An attempt to form the cyclic sulfite ester of the diol-b **XV**b (**R = H**) (see below) under conditions identical with those described directly above resulted in the quantitative recovery of diol-b.

1β,6-*exo*-Dimethyl-6-*endo*-9α-dihydroxy-2,3-(1′-methoxy-7′,8′-dihydro-6′,5′-naphtho)-Δ²-bicyclo[3.3.1]nonene (XVb, **R = H) and the C₉-Epimer.**—A 0.312-g. specimen of ketol-b, m.p. 191.5–193.5°, was reduced in 20 ml. of tetrahydrofuran with 0.120 g. of lithium aluminum hydride as described previously for ketol-a.[7h] The crude product, a colorless oil, was crystallized from ethyl acetate–petroleum ether (b.p. 60–68°) to give a mixture of colorless crystals which was separated mechanically into rods (0.203 g.), m.p. 160–173°, and prisms (0.024 g.), m.p. 163–193°. Chromatography of the mother liquor residue on Florisil yielded in the fractions eluted with benzene through ether, an additional 0.070 g. of colorless rods, m.p. 163–173°.

Diol-b (XVb, R = H) apparently exists in at least three polymorphic forms, one melting at 153–155°, another at 168–171°, and a third melting above 190° that was not obtained pure. The 0.024-g. fraction of prisms evidently consisted in part of this highest-melting form because on recrystallization from ethyl acetate–petroleum ether (b.p. 60–68°) it afforded 0.013 g. of diol-b, m.p. 166–171°, as colorless rods. The major 0.203-g. fraction consisted mainly of this same material which, however, could not be separated by fractional crystallization from the C_9-epimer. A 0.197-g. portion of this fraction was therefore chromatographed on 6 g. of acid-washed alumina. Elution with 2–25% ether in benzene gave a total of 0.151 g. of diol-b, m.p. 160–170°. Recrystallization from ethyl acetate–petroleum ether (b.p. 60–68°) afforded 0.126 g. of colorless rods, m.p. 167–170°. Repeated recrystallization raised

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(24) *Cf.*, ref. 21, p. 345.

(25) *Cf.*, H. H. Szmant and W. Emerson, THIS JOURNAL, **78**, 454 (1956).

the m.p. to 168–171°. Occasionally, on recrystallization material of this m.p. was converted into material, m.p. 170–185°, evidently containing some of the elusive higher-melting form, and on other occasions into material m.p. 153–155° followed by solidification and remelting at 165–168°. The infrared spectrum of the purified product showed $\lambda_{\max}^{\mathrm{CH_2Cl_2}}$ 2.79 μ (OH) and 6.15 (C=C).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.4; H, 8.4.

Further elution of the alumina column with 50% ether in acetone gave 0.046 g. of the **C_9-epimer of XVb (R = H)** as small rods, m.p. 133–148°. Crystallization from ethyl acetate–petroleum ether (b.p. 60–68°) gave 0.035 g., m.p. 138–148°. Repeated recrystallization afforded colorless rods, m.p. 150–151°; $\lambda_{\max}^{\mathrm{CH_2Cl_2}}$ 2.94 μ (OH, broad), 6.14 (C=C).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.6; H, 8.1.

The monoacetate XVb (R = Ac) of diol-b was prepared by the procedure described above for the a-isomer. From 0.036 g. of diol-b, m.p. 167–171°, 0.5 ml. of acetic anhydride and 1.0 ml. of pyridine, there was thus obtained 0.041 g. of oily product. Crystallization from ether–petroleum ether (b.p. 60–68°) afforded 0.008 g. of rods, m.p. 135–138°. The residue from the mother liquor was chromatographed on Florisil. Elution with 4% ether in benzene yielded an additional 0.024 g. of monoacetate, m.p. 124–140°. Repeated recrystallization from ethyl acetate–petroleum ether (b.p. 60–68°) gave thin colorless rods, m.p. 142.5–144°; $\lambda_{\max}^{\mathrm{CH_2Cl_2}}$ 2.79 μ (OH), 5.84 (C=O), 6.15 (C=C).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.2; H, 8.0.

In the course of recrystallizing this monoacetate a polymorphic modification was encountered as thin rods, m.p. 160.5–161.5°.

The monoacetate of the diol XIX[7h] was similarly prepared from 0.100 g. of the diol, m.p. 212–218°.

Trituration of the crude product with isopropyl ether afforded 0.103 g. (90% yield) of pale yellow prisms, m.p. 183–194°. Repeated recrystallization from ethyl acetate–petroleum ether (b.p. 60–68°) afforded colorless prisms, m.p. 196–198° (in an evacuated capillary); $\lambda_{\max}^{\mathrm{CH_2Cl_2}}$ 2.79 μ (OH), 5.78 (C=O).

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.5; H, 8.3.

Methanolysis Experiments. (a) **With Diol-a Monoacetate.**—A solution of 0.030 g. of the monoacetate XVa (R = Ac), m.p. 127.5–129°, and 0.005 g. of freshly distilled triethylamine in 4 ml. of absolute methanol was allowed to stand at room temperature for 19 hr. The volatile components were evaporated in a stream of nitrogen leaving 0.030 g. of oily residue which crystallized on trituration with ether. Recrystallization of this material from ethyl acetate–petroleum ether (b.p. 60–68°) gave 0.0075 g. of diol-a as small prisms, m.p. 146–150°, $\lambda_{\max}^{\mathrm{film}}$ 2.98 μ (OH) and no absorption in the carbonyl region. The residual oil isolated from the mother liquors was chromatographed on Florisil. Elution with 1–2% ether in benzene afforded 0.011 g. (37%) of the starting monoacetate, m.p. 119–126°. From the fractions eluted with 5–10% ether in benzene there was isolated an additional 0.0085 g. of diol-a as small prisms, m.p. 140–150° (no carbonyl absorption in the infrared spectrum). Thus the total yield of diol-a was over 50%.

(b) **With Diol-b Monoacetate.**—A 0.029-g. sample of the monoacetate XVb (R = Ac), m.p. 140–141.5°, was treated exactly as described in the preceding experiment. The crude product amounted to 0.029 g. of thin rods, m.p. 155.5–158°. Recrystallization from ethyl acetate–petroleum ether (b.p. 60–68°) gave 0.028 g., m.p. 155–159°, undepressed on admixture with the 160.5–161.5° form of the starting monoacetate (see above). The infrared spectra of the two specimens were identical.

(c) **With Diol-XIX Monoacetate.**—A 0.030-g. sample of the acetate, m.p. 195–197°, was treated as described above under part a. Crystallization and chromatography on Florisil afforded a total of 0.015 g. of starting material, and 0.010 g. of material, m.p. 205–220°. The infrared spectrum of the latter showed that it was the diol XIX.

Condensation of Methyl Vinyl Ketone with Cyclohexanone.[17]—A mixture of 196 g. of cyclohexanone and 18 ml. of 37% Triton-B methoxide (Rohm and Haas Co.) was maintained at −5 to 5° and stirred while 140 g. of pure methyl vinyl ketone in 196 g. of cyclohexanone was added over a period of 30 min. The mixture was then allowed to stir at 0° for 3 hr. during which colorless crystals of ketol separated. After standing overnight at 0°, 3 ml. of acetic acid was added and the solid was separated. The crude ketol amounted to 83 g., m.p. 115–141.5°. Trituration with 500 ml. of boiling methylcyclohexane left 57 g. of cream-colored prisms, m.p. 146–148°. Repeated recrystallization of a specimen from methylcyclohexane, followed by sublimation at 115° (0.4 mm.), gave colorless platelets, m.p. 147–148.5°; $\lambda_{\max}^{\mathrm{CS_2}}$ 2.9 μ (OH), 5.85 (C=O); major n.m.r. signals ($CHCl_3$), c.p.s.: +157 (OH), +162 ($\mathrm{OC\underset{|}{C}H_2}$–), +193 (–$CH_2$–).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.6; H, 9.6.

The filtrate was taken up in ether, washed with water, and dried over anhydrous sodium sulfate. Distillation through a small Vigreux column gave, after removal of lower boiling fractions, 96 g. of a mixture of liquid and solid, b.p. 106–113° (0.6–0.8 mm.). A 42.8-g. sample of this product—presumably a mixture of ketols and, perhaps, some uncyclized diketone—was added to a solution of 6.9 g. of sodium in 500 ml. of absolute alcohol, which was then heated under reflux (nitrogen atmosphere) for 3.5 hr. The mixture was cooled, acidified with hydrochloric acid, concentrated, diluted with water and extracted with ether. The combined ether layers were washed with saturated sodium bicarbonate solution, water, and saturated sodium chloride, then dried over anhydrous sodium sulfate. Distillation through a short Vigreux column gave, after removal of lower-boiling fractions, 2.3 g., b.p. 85–94° (0.9 mm.), $n^{25.5}_{\mathrm{D}}$ 1.5191, and 17.0 g., b.p. 94–99° (0.9–1.0 mm.), $n^{25.5}_{\mathrm{D}}$ 1.5198. On redistillation the major fraction boiled at 91.5–92° (0.9 mm.), n^{25}_{D} 1.5204; $\lambda_{\max}$ 238 mμ (log ε 4.22); $\lambda_{\max}^{\mathrm{film}}$ 5.95 μ (C=O), 6.15 (C=C). The identity of this material with $\Delta^{1(9)}$-2-octalone was confirmed by conversion to the 2,4-dinitrophenylhydrazone, m.p. 174–175°, and semicarbazone, m.p. 209° dec., and comparison, by mixed m.p. determinations, with the corresponding derivatives from authentic material prepared by the classical method.[26]

Dehydration of the Ketol. (a) **With Oxalic Acid.**—A mixture of 8.25 g. of the aforementioned ketol, m.p. 146–148°, 33 ml. of toluene and 1 g. of oxalic acid was refluxed for 45 min. in a system with a continuous water separator. The product was isolated as described directly above to give 4.73 g. (62% yield) of the octalone, b.p. 91–95° (*ca.* 1.5 mm.). The identity of this material was established through the 2,4-dinitrophenylhydrazone (see above).

(b) **With Phosphorus Oxychloride.**—The procedure described above for the dehydration of ketol-a was used. The crude octalone thus obtained from 0.286 g. of the ketol, m.p. 148–149°, and 1.3 g. of phosphorus oxychloride in 8 ml. of pyridine was converted directly into the 2,4-dinitrophenylhydrazone. The over-all yield was 0.291 g. (57%), m.p. 174–176°, undepressed on admixture with authentic material.

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[26] E. C. du Feu, F. J. McQuillin and R. Robinson, *J. Chem. Soc.* 53 (1937).