[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DARTMOUTH COLLEGE, HANOVER, N. H., AND THE DEPARTMENT OF CHEMISTRY, MOUNT HOLYOKE COLLEGE, SOUTH HADLEY, MASS.]

Synthesis of 1,9-*cis*-Diacetoxy-$\Delta^{5,10}$-octalone-6; Stereochemical Course of the Robinson Annelation Reaction

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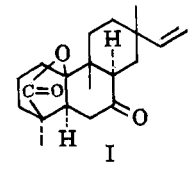
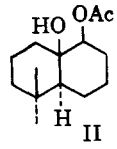
Michael addition of methyl vinyl ketone to 2-acetoxycyclohexane-1,3-dione (IV) affords an excellent yield of 2-acetoxy-2-(3-oxobutyl)cyclohexane-1,3-dione (XIV), which can be cyclized and dehydrated in a stepwise manner under mild conditions to afford 9-acetoxy-$\Delta^{5,10}$-octalin-1,6-dione (III). The unconjugated ketone group of III can be selectively reduced with sodium borohydride, yielding *cis*-1-acetoxy-9-hydroxy-$\Delta^{5,10}$-octalone-6 (XL), which results from acetyl migration following reduction. A much better yield of reduced material can be obtained by direct acetylation of the crude sodium borohydride product, which afforded 1,9-*cis*-diacetoxy-$\Delta^{5,10}$-octalone-6 (XLIII) in about 20% yield from IV. The structures of several by-products resulting from cleavage of β-diketone systems, from aromatization, and from alternate aldol cyclization of XIV to a bridged system have been elucidated. The use of various catalysts for aldol cyclization of XIV has been investigated. The isolation of 9-hydroxy-$\Delta^{5,10}$-octalin-1,6-dione upon acid treatment of the predominant ketol formed in the cyclization implies that this ketol is *cis*-9-acetoxy-10-hydroxydecalin-1,6-dione (XXX). This marks the first time that it has been possible to deduce the complete stereochemistry of the ketol intermediate which is the direct precursor of the α,β-unsaturated ketones isolated from Robinson annelation reactions. An explanation for the selective formation of the *cis*-fused XXX is advanced.

One approach to the synthesis of the intriguing structure assigned to the biogenetically significant diterpenoid rosenonolactone (I)[2] would be to generate its lactone bridge by transannular oxidation of the axial member of the *gem*-dimethyl group of a compound such as II, using one of the recently developed methods for such functionalization of classically unactivated sites. Barton's elegant synthesis of aldosterone[3] can be cited as one striking realization of the potential utility of this type of *trans*-spatial reaction. In order to explore such an approach to rosenonolactone we wished to prepare a substance, like II, which had structural features that would permit a study of the conditions necessary for generation of the lactone bridge and which also would possess functionality that would make possible the eventual elaboration of the entire structure I.

The initial route we chose to investigate for the synthesis of II proceeds by way of the unsaturated diketoester III, which we hoped to prepare by the condensation of 2-acetoxycyclohexane-1,3-dione (IV) with methyl vinyl ketone. This paper reports our study of this condensation, which eventually afforded an efficient route to III, describes the structures of the several by-products encountered, and discusses the stereochemistry of the aldol cyclization step of the condensation.



I



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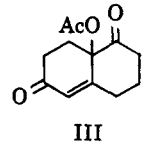
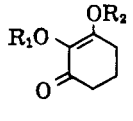
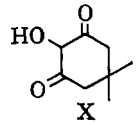


III





X

IV, R_1 = Ac, R_2 = H
V, R_1 = H, R_2 = H
VI, R_1 = H, R_2 = Ac
VII, R_1 = H, R_2 = CH_3
VIII, R_1 = CH_3, R_2 = H
IX, R_1 = Ac, R_2 = CH_3

Reaction of 2-Acetoxycyclohexane-1,3-dione with Methyl Vinyl Ketone.—Pecherer, Jampolsky, and Wuest[4] have described the catalytic reduction of pyrogallol to dihydropyrogallol (V), and reported that this substance forms a monoacetate, m.p. 154–155.5°, upon treatment with acetic anhydride and pyridine, but did not assign a structure (presumably either IV or VI) to the compound. The properties of this acetate left no doubt that it was the desired starting material IV. It was soluble in dilute sodium bicarbonate with evolution of gas, which indicated a degree of acidity consistent with a cyclohexane-1,3-dione,[5] but greater than that to be expected from an enolized α-diketone such as VI.[6]

Mayer has studied the methylation of dihydropyrogallol and found that diazomethane effected monomethylation to give 2-hydroxy-3-methoxy-Δ^2-cyclohexenone (VII),[7] whereas dimethyl sulfate and alkali gave the 2-methoxyl derivative VIII.[8] In the present work dihydropyrogallol acetate was found to react with diazomethane to give a methyl ether, m.p. 98–99.5°, consistent with formulation of dihydropyrogallol acetate as the 2-acetate IV, and with assignment of the enol ether as structure IX. Eistert has reported[9] that 2-hydroxy-5,5-dimethyldihydroresorcinol (X) likewise undergoes acetylation at the two position.

The use of 2-methylcyclohexane-1,3-dione (methyldihydroresorcinol) in the Robinson annelation reaction[10] has been the subject of much study. The conditions for optimum yield of 9-methyl-$\Delta^{5,10}$-octalin-1,6-dione[11] consist of Michael addition catalyzed by a trace of hydroxide ion, followed by amine-catalyzed aldol condensation. The reaction has also been successfully applied to 2-hydroxycyclohexanone and 2-acetoxycyclohexanone by Szmuszkovicz and Born,[12] who were able, using 1-diethylamino-3-pentanone methiodide, to demonstrate the formation of excellent yields of com-

(1) (a) Department of Chemistry, Dartmouth College, Hanover, N. H.; (b) Department of Chemistry, Mount Holyoke College, South Hadley, Mass.

(2) A. Harris, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1799 (1958); W. B. Whalley, B. Green, D. Arigoni, J. J. Britt, and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 5520 (1959). For a recent reference to the stereochemistry and biosynthesis of diterpenoids, including rosenonolactone and related compounds, see A. I. Scott, G. A. Sim, G. Ferguson, D. W. Young, and F. McCapra, *ibid.*, **84**, 3197 (1962).

(3) D. H. R. Barton and J. M. Beaton, *ibid.*, **82**, 2641 (1960). For recent discussions of such functionalizations see K. Heusler, J. Kalvoda, C. Meystre, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **45**, 2161 (1962), and references cited therein.

(4) B. Pecherer, L. M. Jampolsky, and H. M. Wuest, *J. Am. Chem. Soc.*, **70**, 2587 (1948).

(5) G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, **23**, 1147 (1940).

(6) G. Schwarzenbach and C. Wittwer, *ibid.*, **30**, 663 (1947).

(7) W. Mayer and M. Neymeyr, *Ann.*, **572**, 212 (1951).

(8) W. Mayer, R. Bachmann, and F. Kraus, *Ber.*, **88**, 316 (1955).

(9) B. Eistert, H. Elias, E. Kosch, and R. Wollheim, *ibid.*, **92**, 130 (1959).

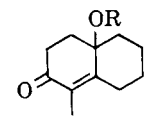
(10) The term "Robinson annelation reaction" is used here in its most general sense to refer to ring extension by condensation of a cycloalkanone derivative with a methylene vinyl ketone or its functional equivalent, as is done by W. S. Johnson, *et al.* (ref. 17).

(11) S. Ramachandran and M. S. Newman, *Org. Syntheses*, **41**, 38 (1961).

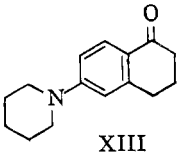
(12) J. Szmuszkovicz and H. Born, *J. Am. Chem. Soc.*, **75**, 3350 (1953).

pounds XI and XII, respectively, although the latter substance eliminated acetic acid upon distillation. It seemed, therefore, that IV should be a suitable Michael acceptor.

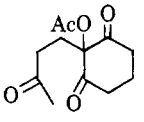
When dihydropyrogallol acetate and methyl vinyl ketone were allowed to react under the conditions of Ramachandran and Newman,[11] direct chromatography of the reaction mixture resulting from the piperidine-catalyzed aldol condensation step afforded four distinct crystalline fractions, whose formation accounted for at least 80% of the starting material. The first compound to be eluted, m.p. 70.5–71.5°, had an elemental analysis corresponding to a molecular formula of $C_{15}H_{19}NO$. This substance, obtained in 21% yield, possessed absorption maxima in the ultraviolet at 251 (ϵ 6700) and 341 mμ (ϵ 26,600) and in the infrared at 6.00, 6.25, and 6.64 μ. These spectral properties were the source of considerable consternation until it was appreciated that the substance contained nitrogen, whereupon the assignment of the *p*-ketoaniline structure XIII became possible. The ultraviolet absorption is very similar to that reported[13] for the chromophorically analogous *p*-N,N-dimethylaminoacetophenone, which exhibits maxima at 240 (ϵ 7100) and 333 mμ (ϵ 24,000). The aminotetralone XIII undoubtedly arises by a sequence involving initial formation of the Michael adduct XIV, aldol cyclization, dehydration, and formation of an enamine,[14] which in the tautomeric form XV can lose the elements of acetic acid to form the aromatic system.



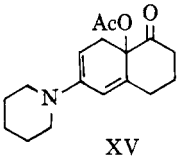
XI, R = H
XII, R = Ac



XIII



XIV



XV

The second crystalline substance to be eluted was obtained in 29% yield, melted at 68–69°, and had an elemental analysis corresponding to a molecular formula of $C_{12}H_{16}O_5$. On the basis of its spectral properties (no strong ultraviolet absorption, acetate and ketone bands in the infrared), this compound could be assigned the structure of the Michael adduct XIV formed from 2-acetoxycyclohexane-1,3-dione and methyl vinyl ketone. The n.m.r. spectrum in deuteriochloroform showed one very sharp peak at 2.11 p.p.m. and subsidiary multiplets centered at 2.65 p.p.m. This single sharp peak was shown to consist of two equally intense peaks due to methyl groups when the spectrum was run in a different solvent,[15] benzene, thus confirming the structural assignment.

Upon treatment with excess ethylene glycol in the presence of *p*-toluenesulfonic acid, this adduct XIV formed a monoketal, m.p. 70.5–71.5°, in 73% yield. The structure of this monoketal, from which XIV could be regenerated by acid hydrolysis, was assigned as XVI on the basis of its n.m.r. spectrum, which had methyl peaks at 1.16 and 2.0 p.p.m., and a single sharp peak at 3.72 p.p.m. which has been assigned to the four protons of the ethylene ketal. Since there is no chemical shift between these protons, they must be located in a symmetrical environment. Ketal formation at one of the other, hindered, carbonyl groups can also be ruled out on the basis of the chemical shift (1.16 p.p.m.) of the methyl group of the side chain, which is found at 2.11 p.p.m. in XIV, where the methyl is adjacent to a carbonyl group.

Next to be eluted was material, m.p. 173–176°, in 22% yield, which was isomeric with the Michael adduct XIV. It lacked strong absorption in the ultraviolet, but showed infrared bands indicating the presence of a hydroxyl group in addition to the carbonyl functions. The n.m.r. spectrum of this substance showed an unsplit methyl peak at 1.42 p.p.m. corresponding to a methyl group on the carbon bearing the hydroxyl group,[16] a peak of equal intensity at 2.14 p.p.m. corresponding to the acetate methyl, and a less intense single peak at 2.12 p.p.m., which was assigned to the hydroxyl proton. These data indicated that this substance was one of the bridged ketols XVII resulting from an aldolization alternate to the one which would lead to the desired product III, and subsequently observed reactions of the compound (*vide infra*) confirmed this structural assignment. Such bridged ketols are now recognized as being often encountered in Robinson annelation sequences.[17]

The fourth substance also had an analysis corresponding to a molecular formula of $C_{12}H_{16}O_5$ and was an acid which melted at 121–122°. This material, obtained in 7% yield, exhibited absorption in the ultraviolet at 243 mμ (ϵ 10,000) and showed bands in the infrared which suggested the presence of an α,β-unsaturated ketone group in addition to a carboxyl group and an acetate. The formation of two compounds possessing such functionality can be envisaged by considering hydroxide ion cleavage of the vinylogous β-diketone system of the desired product III to give XVIII, or similar cleavage of the Michael product XIV to give XIX, which can then undergo internal aldol cyclization to afford either XVIII, or the alternate structure XX.

Distinction between these two possibilities, XVIII and XX, was accomplished by means of the n.m.r. spectrum. In addition to the characteristic quartet at 5.1 p.p.m. due to the proton on an acetoxyl-bearing carbon atom,[18] there were two sharp methyl peaks at 1.9 and 2.0 p.p.m. (again it was necessary to use benzene rather than deuteriochloroform to see two separate peaks), consistent with structure XX, but not with XVIII. Chemical confirmation of this structural assignment was attained by conversion of the substance with palladium-on-carbon at 250° to the known 5-methylcoumarin (XXI), m.p. 65–67°.[19]

The obtainment of XX as a product of nucleophilic cleavage in the course of the Robinson annelation sequence parallels the observations of Wendler, Slates, and Tishler,[20] who obtained XXII from the methoxide-catalyzed reaction of methyl vinyl ketone with methyldihydroresorcinol, and identified the product by its conversion to 5,8-dimethylcoumarin (XXIII). Such cleavage would be facilitated in the 2-acetoxycyclohexane-1,3-dione case by the enhanced stability afforded

(13) P. Grammaticakis, *Bull. soc. chim. France*, **20**, 93 (1953).

(14) No implication is intended here as to the exact nature or order of events in this sequence. Our observations on this type of amine-catalyzed aldol condensation, some of which are recorded in this paper, and the interpretation we place on them, have been published: T. A. Spencer and K. K. Schmiegel, *Chem. Ind.* (London), 1765 (1963).

(15) G. Slomp and F. MacKellar, *J. Am. Chem. Soc.*, **82**, 999 (1960).

(16) See, for example, spectrum 297 in the "Varian NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962.

(17) W. S. Johnson, J. J. Korst, R. A. Clement, and J. Dutta, *J. Am. Chem. Soc.*, **82**, 614 (1960).

(18) Similar quartets in α-acetoxy ketones have been observed at 5.1 p.p.m. in 2α- and 2β-acetoxycholestane-3-one; see K. L. Williamson and W. S. Johnson, *ibid.*, **83**, 4623 (1961).

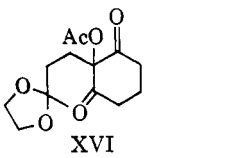
(19) P. Chuit and F. Bolsing, *Bull. soc. chim. France*, [3] **35**, 76 (1960).

(20) N. L. Wendler, H. L. Slates, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 3816 (1951).

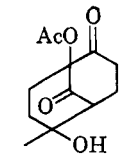
the intermediate carbanion XXIV by the electron-withdrawing acetoxyl group.

Although none of the desired bicyclic intermediate III had been obtained in this reaction, the structures of the products described above served to elucidate the two major sources of difficulty one might expect to encounter in attempts to condense 2-acetoxycyclohexane-1,3-dione with methyl vinyl ketone: first, the enhanced tendency toward facile β-diketone cleavage and, second, aromatization of III or equivalent. It seemed evident that each step in the formation of III would have to be investigated separately in order to find conditions that would minimize the opportunities for these undesired side reactions.

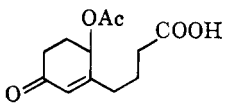
The first step, Michael addition to form XIV, was found to proceed in excellent yield (89%) under the conditions used by Ramachandran and Newman[11] (a trace of sodium hydroxide in refluxing absolute methanol) when the reaction time was reduced from 2.5 hr. to 45 min.[21] That this Michael adduct was indeed subject to facile cleavage was demonstrated by its reaction in 40 min. at room temperature with 6% sodium hydroxide in methanol, which afforded the α,β-unsaturated keto hydroxy acid XXV, m.p. 97.5–98.5°, in 56% yield. This substance could also be obtained (84% yield) by treatment of the acetate XX with dilute sodium hydroxide solution.



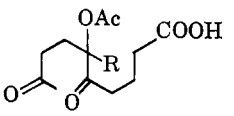
XVI



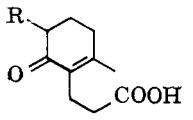
XVII



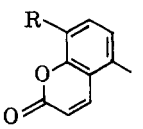
XVIII



XIX, R = H
XXIV, R = ⊖



XX, R = OAc
XXII, R = CH_3
XXV, R = OH



XXI, R = H
XXIII, R = CH_3

Aldol Cyclization of Michael Adduct XIV.—In order to effect cyclization of XIV without incurring cleavage, we first tried *p*-toluenesulfonic acid as a reaction catalyst. Boyce and Whitehurst[21] found that although the adduct XXVI of methyl vinyl ketone with methyldihydroresorcinol does not form 9-methyl-$\Delta^{5,10}$-octalin-1,6-dione upon reaction with *p*-toluenesulfonic acid in refluxing benzene, cyclization of the adduct XXVII from 2-methylcyclopentane-1,3-dione proceeds very efficiently under these conditions. When XIV was subjected to these conditions, no evidence of cyclization or cleavage was observed, as in the case of the more closely analogous XXVI.

Wendler, Slates, and Tishler[20] were able to cyclize XXVI in 40% yield using aluminum tri-*t*-butoxide in benzene. However, when XIV was treated briefly with potassium *t*-butoxide in *t*-butyl alcohol, the only isolable product was the familiar acetoxy keto acid XX resulting from nucleophilic cleavage of the β-diketone system.

Attention was then turned to the use of various amines as cyclization catalysts, for the products obtained in the original attempt using piperidine on the crude Michael product mixture indicated that some successful cyclization to a hydronaphthalene system had occurred, as indicated by isolation of the aromatic amine XIII. However, when *pure* Michael adduct XIV was treated with piperidine in refluxing benzene for 14 hr., starting material was recovered in 86% yield.

Pyrrolidine proved to be much more effective as a cyclization catalyst. When the Michael adduct XIV was treated with an equivalent of pyrrolidine in refluxing benzene for just 10 min., only a trace of starting material was recovered, and three other crystalline substances were isolated. One of these, m.p. 103–103.5°, obtained in about 25% yield, exhibited absorption at 250 (ϵ 7700) and 346 mμ (ϵ 32,500) in the ultraviolet and thus was readily identified as XXVIII, the pyrrolidine analog of the previously obtained XIII.

The remaining two substances were isolated as a mixture in 27% yield, but could be separated by careful rechromatography. One of them was found to be the previously isolated bridged ketol XVII, in a crystalline modification melting at 192–194°.[22]

The other component of the mixture, m.p. 192–193°, also gave an analysis corresponding to a molecular formula of $C_{12}H_{16}O_5$, and exhibited infrared bands indicating the presence of hydroxyl, acetate, and ketone functions. The n.m.r. spectrum of this substance, however, showed only a single (acetate) methyl peak, at 2.16 p.p.m., indicating that the compound could not be the bridged ketol epimeric to XVII at the hydroxyl-bearing carbon, but had to be one of the ketols XXIX or XXX, possessing the desired hydronaphthalene skeleton. The chemical behavior of this ketol (*vide infra*) confirmed this assignment, and in addition showed that the substance possessed a *cis* ring fusion, and hence should be written as XXX.

Some degree of success in attaining the desired cyclization had therefore been achieved, but it was obviously desirable to increase the yield of the hydronapthalenic ketol. Running the reaction at room temperature for several hours rather than briefly at reflux lowered the relative yield of aromatic amine to 14% *vs.* 49% ketol mixture, but did not completely suppress the undesired aromatization.

The most effective method found for the cyclization involved the use of equimolar amounts of pyrrolidine and acetic acid.[23] Under these conditions aldol formation proceeded at temperatures as low as 0°, and the ketol mixture could be isolated in 63% yield[24] when XIV was stirred with pyrrolidine and acetic acid in ether in an ice bath for 2 hr. The ketol mixture thus formed was found to consist of *ca.* 80% of the desired

(21) C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 2022 (1959). These workers report that the adduct XXVI from methyl vinyl ketone and methyldihydroresorcinol can be isolated in 85% yield and the adduct XXVII from 2-methylcyclopentane-1,3-dione in 83% yield under similar conditions.

(22) Although the infrared spectra of the 173–176° material and the 192–194° material are essentially identical, we cannot exclude the possibility that the lower melting material is contaminated. The melting point behavior of this substance is described in the Experimental section.

(23) The use of ammonium salts for the catalysis of aldol condensations is well known (see, for example, A. C. Cope, *et al.*, *J. Am. Chem. Soc.*, **63**, 3452 (1941)). For the use of piperidine–acetic acid in a similar ketol formation reaction see P. Wieland and K. Miescher, *Helv. Chim. Acta*, **33**, 2215 (1950).

(24) Isolation of intermediate ketols in such condensation sequences appears often to be the result of precipitation of the ketol from the reaction mixture, which prevents its dehydration (see, for example, ref. 17 and W. S. Johnson, J. Ackerman, J. F. Eastham, and H. A. DeWalt, Jr., *J. Am. Chem. Soc.*, **78**, 6302 (1956)). In the present work a precipitate did form during the pyrrolidine–acetic acid cyclization, but was found to contain less isolable ketol mixture than the separately investigated supernatant liquid. This observation leads to the conclusion that separation of the ketol XXX from the reaction mixture is *not* the chief reason for inhibition of dehydration at 0°.

XXX and *ca.* 20% of XVII. Careful chromatography of the product remaining after separation of the 63% of crystalline ketols afforded no aminotetralone XXVIII.

There could, however, be isolated in addition to the mixture of ketols a new crystalline substance, m.p. 94–95°, which had an elemental analysis consistent with a dehydration product of XXX or XVII. The lack of strong ultraviolet absorption indicated derivation from the bridged ketol XVII. The substance showed bands in the infrared at 5.70–5.77 and 8.05 μ, but no band at 11.0–11.2 μ, indicating that it was XXXI, rather than the alternate dehydration product XXXII, with a terminal methylene. The n.m.r. spectrum of this substance showed a vinyl proton peak at 5.13 p.p.m. and a single sharp peak at 1.97 p.p.m. due to the two superimposed methyl group peaks of XXXI. The ratio of the methyl proton peak area to the vinyl proton peak area was 4.6:1 (theoretical for XXXI, 6:1; for XXXII, 1.5:1), so that the n.m.r. data confirmed the structural assignment.

The use of acetic acid in combination with other amines was found also to result in enhanced rates of cyclization. When XIV was subjected to prolonged treatment with equimolar amounts of piperidine and acetic acid in refluxing benzene, no starting material was recovered, as opposed to the results with piperidine alone (*vide supra*), and the major product from the reaction was XIII, isolable in 32% yield. Similar use of *n*-butylamine and acetic acid afforded 40% of 6-*n*-butylamino-1-tetralone (XXXIII), m.p. 95.5–96.0°, with absorption at 247 (ϵ 7200) and 335 mμ (ϵ 25,300).

Although dehydration during the amine-catalyzed cyclizations was, at least to a great extent, followed by aromatization, as evidenced by the isolation of the various aminotetralones, dehydration to give the desired α,β-unsaturated ketone III could be effected by brief (20 min.) treatment of XXX with a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene. The development of the ultraviolet absorption indicative of the α,β-unsaturated ketone could be followed and the reaction stopped when this peak reached a maximum, and before a peak appeared at 280 mμ, due to the aromatic compound XXXIV described below. In practice, the mixture of XXX and XVII was used in the dehydration step, and the reaction mixture was poured directly onto an acid-washed alumina column which effected separation of 9-acetoxy-$\Delta^{5,10}$-octalin-1,6-dione (III), as an oil with ϵ *ca.* 9000 at 238 mμ, from some unreacted ketol mixture. The yield of crude III, based on unrecovered starting material, was 80–90%.[25] A small amount of aromatic material, m.p. 150–152°, was also eluted and was found to be the known 6-hydroxy-1-tetralone[26] (XXXIV). The identity of the oily III was confirmed by its conversion in excellent yield to this same phenol upon prolonged heating with *p*-toluenesulfonic acid in benzene.

When pure bridged ketol XVII was treated with *p*-toluenesulfonic acid in refluxing benzene it did *not* lose the elements of water but underwent reversal of the aldol formation to afford the Michael adduct XIV. It is interesting to note that this same reconversion to XIV was observed when XVII was heated for a few minutes at about its melting point; the cooled melt afforded crystals of XIV. Ketol XXX was recovered unchanged from a similar heating.

Careful chromatography of the dehydration reaction mixture led, on one occasion, to the isolation of another crystalline substance, m.p. 114.5–115.5°, which had an analysis corresponding to a molecular formula of $C_{10}H_{12}O_3$. This substance absorbed at 233 mμ (ϵ 11,000) in the ultraviolet, and showed infrared bands which indicated the presence of conjugated and unconjugated ketones, and a hydroxyl, plus loss of the acetate function, suggesting that it might be the unsaturated hydroxydiketone XXXV. This assignment was confirmed by the n.m.r. spectrum of the compound, which showed a vinyl proton peak, but no methyl proton peak, and by conversion of the substance to XXXIV upon further treatment with *p*-toluenesulfonic acid in benzene. The rate of aromatization of XXXV was much slower than that of the crude acetoxy compound III. That XXXV arose from ketol XXX was demonstrated by its preparation from pure XXX rather than the customarily-used ketol mixture.

Stereochemical Course of the Robinson Annelation Reaction.—The formation of XXXV from XXX can be most easily explained by postulating initial acid-catalyzed migration of the acetyl group to form XXXVI, which then suffers loss of acetic acid to yield the unsaturated hydroxydiketone. This acetyl migration could be expected under the conditions of the reaction only if the hydroxyl and acetoxyl groups of the ketol are *cis*, as in XXX, rather than *trans*, as in XXIX. Such a migration of an acetyl group under acidic conditions has been observed in the monoacetates of 3β,4β-dihydroxy-Δ^5-cholestene by several investigators,[27] whereas no precedent for a similar reaction of a diaxial 1,2-*trans*-hydroxyacetate is available. Treatment of a model compound of this type, 2β-acetoxy-3α-hydroxycholestane, with *p*-toluenesulfonic acid in benzene under the conditions used in the preparation of XXXV from XXX yielded almost pure recovered starting material.[28] That XXXV did not arise by a sequence XXIX → XIV → XXX → XXXV is evident from the failure (*vide supra*) of the Michael adduct XIV to cyclize with *p*-toluenesulfonic acid in benzene.

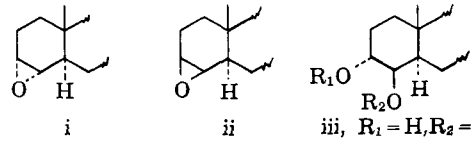
Thus, on the basis of the isolation of XXXV, the complete stereochemistry of the hydronaphthalenic ketol XXX may be assigned. This is the first instance in which it has been possible to deduce the stereochemistry of the ring fusion of a ketol in the Robinson annelation sequence which is the direct precursor of the usually isolated α,β-unsaturated ketone. Indeed, in many cases the carbon skeleton of those intermediate ketols which have been isolated remains in question.[17]

(25) All yields reported which include consideration of this dehydration step are necessarily only the best estimates possible, since the exact composition of the ketol mixture recovered from this step was not determined. That the *p*-toluenesulfonic acid treatment had not effected selective removal of XXX from the ketol mixture was demonstrated by comparison of the infrared spectra of starting and recovered ketol mixtures. These were essentially identical, and very similar to that of pure XXX, while distinctly different from that of pure XVII.

(26) (a) G. Haberland, *Ber.*, **69B**, 1380 (1936); (b) J. W. Cornforth, O. Kauder, J. E. Pike, and R. Robinson, *J. Chem. Soc.*, 3348 (1955); (c) D. Papa, E. Schwenk, and H. Breiger, *J. Org. Chem.*, **14**, 366 (1949); (d) K. Mitsuki, *J. Pharm. Soc. Japan*, **61**, 277 (1941)

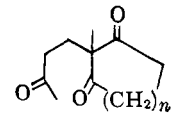
(27) (a) V. A. Petrow, O. Rosenheim, and W. W. Starling, *J. Chem. Soc.*, 135 (1943); (b) M. F. C. Paige, *ibid.*, 437 (1943); (c) R. W. Jailer, D. K. Fukushima, and S. Lieberman, *J. Am. Chem. Soc.*, **74**, 5220 (1952), by chromatography on acid-washed alumina.

(28) In this connection an investigation by A. Fürst and R. Scotoni (*Helv. Chim. Acta*, **36**, 1332 (1953)) is noteworthy. When oxide i was heated for 2 hr. with acetic acid an excellent yield of iii was obtained; similar treatment of ii gave only iv. If such a rearrangement as is involved in XXIX → XXXV were possible under these conditions, which were more vigorous than those which effected rearrangement of 3β-acetoxy-4β-hydroxy-Δ^5-cholestene (see ref. 27), then one would have expected formation of different products (probably *cis*-diacetates; *cf.* S. Winstein, H. V. Hess, and R. E. Buckles, *J. Am. Chem. Soc.*, **64**, 2796 (1942)) from i and ii.

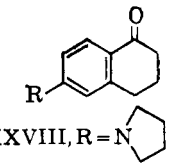


i ii iii, $R_1 = H, R_2 = Ac$

iv $R_1 = Ac, R_2 = H$

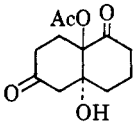


XXVI, $n = 2$
XXVII, $n = 1$

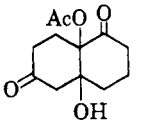


XXVIII, R = N

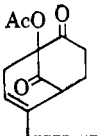
XXXIII, R = $NHCH_2CH_2CH_2CH_3$
XXXIV, R = OH



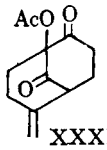
XXIX



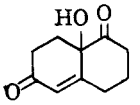
XXX



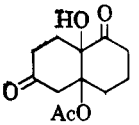
XXXI



XXXII



XXXV

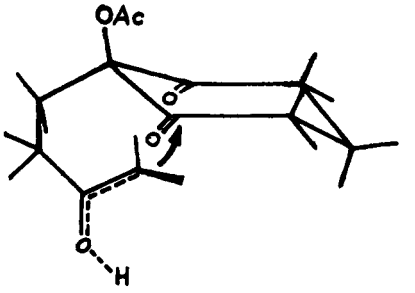


XXXVI

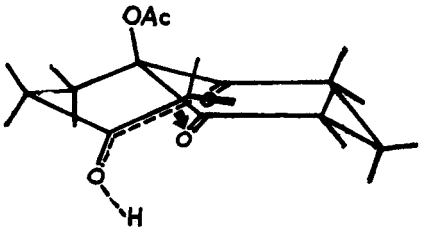
Ketol XXX is formed selectively either because it is thermodynamically more stable than the *trans*-fused XXIX, or because the cyclization is kinetically controlled to yield the *cis*-fused XXX. Several considerations, notably the uncertainty of the nature of the interaction between the hydroxyl and acetoxyl groups in XXX,[29] make it impossible to obtain a meaningful estimate of the (probably small) free energy difference between XXIX and XXX by simple conformational analysis. However, it seems improbable *a priori* that the cyclization process is an equilibrium one, or that XXX is the distinctly more stable isomer.

On the other hand, examination of molecular models indicates that the transition state leading to XXX may be more favorable than the transition state leading to XXIX. In bringing together the two carbon atoms to be bonded in a manner which will lead to a *trans*-fused ring system there is steric interference by the acetoxyl group to the approach of the carbon atom of the side chain (presumably sp^2-hybridized). Schematic conformational drawings showing the position of the atoms nearing the transition states for the generation of XXIX and XXX are shown in XXXVII and XXXVIII.[30] Insofar as this steric explanation for the selective formation of the *cis*-fused ketol is correct, the effect would be expected to be more pronounced in those cases where a methyl or other larger group is present in place of the acetoxyl. Accordingly, one would predict that in these cases the ketol progenitors of the α,β-unsaturated ketones isolated from Robinson annelation reactions possess *cis*-fused decalin systems. Experiments designed to test this hypothesis are in progress.

Completion of the Synthesis of 1,9-*cis*-Diacetoxy-$\Delta^{5,10}$-octalone-6.—Selective reduction of the unconjugated carbonyl of the dione III was achieved by the use of one equivalent of purified sodium borohydride.[31] A crystalline reduction product, m.p. 106–106.5°, was



XXXVIII



XXXVII

obtained in 25% yield, which had an elemental analysis and spectral properties consistent with the expected dihydro derivative XXXIX. However, examination of the n.m.r. spectrum of this substance (see Fig. 1)

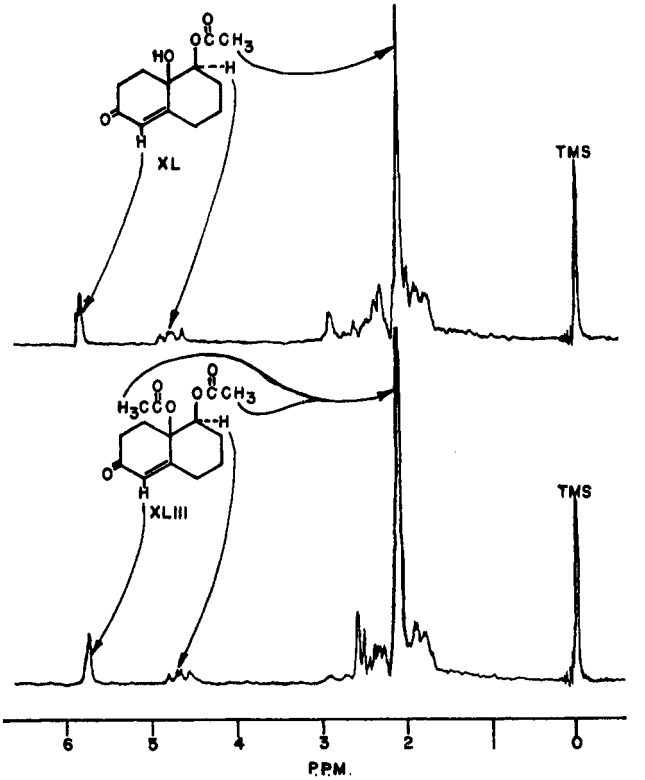


Figure 1.

indicated that it was not XXXIX, but instead was the isomeric hydroxyacetate XL, resulting from migration of the acetyl group during the course of the reduction. In addition to the vinyl proton resonance at 5.89 p.p.m. and the acetate methyl resonance at 2.12 p.p.m., the spectrum contained a quartet at 4.83 p.p.m. which

(29) The angular hydroxyl and acetoxyl of XXX may interact by (a) steric repulsion, (b) dipolar repulsion, or (c) hydrogen bond formation. Such hydrogen bonding, if detectable, would, of course, serve as excellent confirmation of the *cis*-fused nature of the ketol under consideration. We intend to investigate model *cis*-1,2-hydroxyacetates and to attempt to apply the results to a study of XXX. However, H. M. Fales and W. C. Wildman (*J. Am. Chem. Soc.*, **85**, 784 (1963)) have recently claimed that internal hydrogen bonding can occur in a 3-*axial*-hydroxyketone, and this structural unit is present in both XXIX and XXX, so that detection of the appropriate hydrogen bond may not be possible.

(30) Cyclization from the presumably less stable flip form of Michael adduct XIV, with the four-carbon moiety axial, can lead only to the *cis*-ketol XXX. For previous speculation on the geometrical requirements of similar ketol formation see F. J. McQuillin, *J. Chem. Soc.*, 528 (1955), and E. Wenkert and T. E. Stevens, *J. Am. Chem. Soc.*, **78**, 2318 (1956). Each of these authors tentatively assigns *cis* fusion to a ketol of undetermined structure on the basis of the stereochemical factors involved in the particular case considered.

(31) C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 2680 (1960).

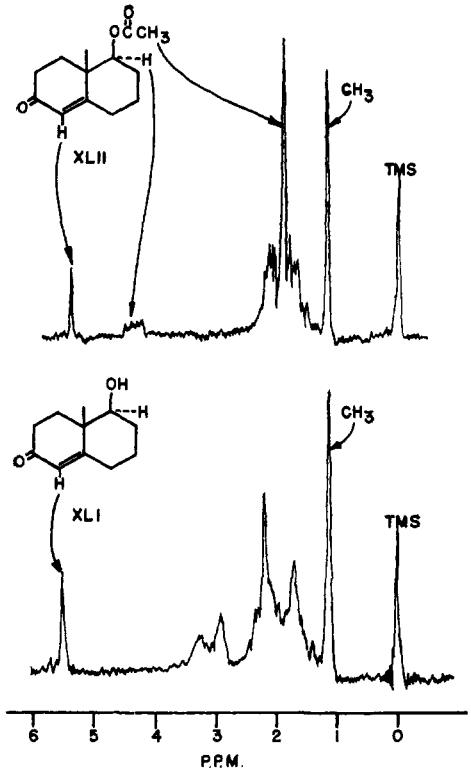


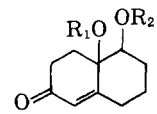
Figure 2.

is not consistent with the unrearranged reduction product XXXIX when compared with the n.m.r. spectrum of the known 1β-hydroxy-9β-methyl-$\Delta^{5,10}$-octalone-6 (XLI)[32] (see Fig. 2), which displays no such quartet. The spectrum of 1β-acetoxy-9β-methyl-$\Delta^{5,10}$-octalone-6 (XLII),[31] on the other hand, was quite similar in all respects, including a quartet at 4.46 p.p.m. due to the proton on the acetoxyl-bearing carbon,[18] to the spectrum of the reduction product obtained in the present work.

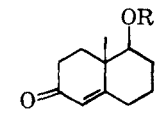
The assignment of the β-configuration to the acetate in XL necessarily follows from the acetate interchange reaction, which must involve hydroxyl and acetoxyl functions in a *cis* relationship. A similar rearrangement has been observed by Kupchan and co-workers,[33] who obtained 3β-hydroxy-4β-acetoxycholestane from the sodium borohydride reduction of 3β-acetoxycholestane-4-one. The β-orientation of the acetoxyl in XL also would be expected by analogy with the sodium borohydride reduction of 9-methyl-$\Delta^{5,10}$-octalin-1,6-dione, which yields XLI.[34]

The chemical behavior of the 106° reduction product was also consistent with its assignment as XL. It failed to react with acetic anhydride in pyridine, whereas XLI affords XLII without difficulty under these conditions.[31] Acetylation could be achieved in good yield by the use of isopropenyl acetate and an acid catalyst, which afforded the diacetate XLIII, m.p. 134.5–135.0°. The n.m.r. spectrum (see Fig. 1) showed two acetate methyl peaks (resolvable on a slow scan) at 2.06 p.p.m., the quartet due to the proton on an acetoxyl-bearing carbon at 4.85 p.p.m., and a vinyl proton peak at 5.77 p.p.m.

A better yield of crystalline reduction product could be obtained by direct acetylation of the crude sodium borohydride reduction product with isopropenyl acetate, which afforded approximately 35% yield,[25] based on the ketol mixture of XXX and XVII, of 1,9-*cis*-diacetoxy-$\Delta^{5,10}$-octalone-6 (XLIII). It is not known whether the preparation of the diacetate enables isolation of a better yield of crystalline material by affording a substance easier to separate, or by conversion to XLIII of some unrearranged XXXIX, and possibly some dihydroxyketone XLIV (from XXXV), in addition to the XL present.



XXXIX, R_1 = Ac, R_2 = H
XL, R_1 = H, R_2 = Ac
XLIII, R_1, R_2 = Ac
XLIV, R_1, R_2 = H



XLI, R = H
XLII, R = Ac

Thus, procedures which permitted cyclization of XIV and dehydration to be effected without concomitant cleavage or aromatization were developed, and 1,9-*cis*-diacetoxy-$\Delta^{5,10}$-octalone-6 (XLIII) can be prepared in approximately 20% over-all yield[25] from dihydropyrogallol acetate. Exploration of the reactions of this substance and of other routes to intermediates for the synthesis of rosenonolactone is presently being pursued.

Experimental

Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points were taken either in an open capillary or on a micro hot-stage; those of analytical samples are corrected. Boiling points are uncorrected. Ultraviolet spectra were determined in 95% ethanol solution on a Bausch & Lomb Spectronic 505 recording spectrophotometer; infrared spectra were determined on a Perkin–Elmer Model 21 double beam recording spectrophotometer; n.m.r. spectra were determined on 20% solutions in carbon disulfide (unless otherwise stated) containing 1% tetramethylsilane, on a Varian DP-60 spectrometer. Spectra were calibrated by the audio side-band method with subsequent interpolation.

2-Acetoxycyclohexane-1,3-dione.—Dihydropyrogallol was prepared by the catalytic reduction of pyrogallol according to the procedure of Pecherer, Jampolsky, and Wuest,[4] except that additional measures to ensure the maintenance of a nitrogen atmosphere, such as bubbling nitrogen through all solutions before use, were found to be essential to success in the reduction. The yield of pure dihydropyrogallol, m.p. 113–114° (lit.[4] m.p. 114°), was usually about 50%.

Dihydropyrogallol monoacetate was prepared[4] in 91% yield, m.p. 154–156° (lit. m.p. 154–155.5°); λ_{max}^{EtOH} 258 mμ (ε 14,900); λ_{max}^{Nujol} 5.62, 6.11, and 6.40 μ.

2-Acetoxy-3-methoxy-Δ^2-cyclohexenone (IX).—To a solution of 0.179 g. (0.00105 mole) of 2-acetoxycyclohexane-1,3-dione in methanol was added a slight excess of freshly distilled ethereal diazomethane. The excess diazomethane was decomposed with acetic acid and the solvents were evaporated to afford a residue which yielded 0.158 g. (86%) of the enol ether, m.p. 97–99°. Recrystallization from ethyl acetate raised the m.p. to 98–99.5°; λ_{max}^{EtOH} 261 mμ (ε 16,000); $\lambda_{max}^{CHCl_3}$ 5.70, 6.00, 6.15, and 7.92 μ; n.m.r.: 2.11 (CH_3–COO–) and 3.77 p.p.m. (CH_3–O–).

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.70; H, 6.52. Found: C, 58.69; H, 6.59.

Reaction of 2-Acetoxycyclohexane-1,3-dione with Methyl Vinyl Ketone. A. By the Procedure of Ramachandran and Newman.[11]—To 5.00 g. (0.0294 mole) of 2-acetoxycyclohexane-1,3-dione, m.p. 154–156°, were added 3.10 g. (0.0441 mole) of methyl vinyl ketone (Matheson Coleman and Bell, technical) and a solution of one pellet (*ca.* 0.18 g.) of potassium hydroxide in 15 ml. of absolute methanol. The mixture was refluxed for 2.5 hr. and the methanol and excess methyl vinyl ketone were removed by distillation at reduced pressure. To remove any water and the last traces of methanol, 20 ml. of benzene was added, 5 ml. of which was distilled at atmospheric pressure. A Dean-Stark water separator was attached; 1.1 ml. of piperidine, b.p. 104–106°, was added, and the mixture was refluxed for 5 hr. during which time a small amount of water collected in the trap. The solvent was then removed by distillation at reduced pressure, and the residue was chromatographed directly on 120 g. of Merck acid-washed alumina.

6-Piperidino-1-tetralone (XIII).—Elution with 1:9 acetone–hexane yielded 1.40 g. (21%) of 3,4-dihydro-6-piperidino-1(2H)-naphthalenone (XIII), m.p. 67–69°. Four recrystallizations from acetone–hexane gave white crystals, m.p. 70.5–71.5°;

(32) A. J. Birch, J. A. K. Quartey, and H. Smith, *J. Chem. Soc.*, 1768 (1952).

(33) S. M. Kupchan, P. Slade, R. J. Young, and G. W. A. Milne, *Tetrahedron*, **18**, 499 (1962).

(34) J. D. Cocker and T. G. Halsall, *J. Chem. Soc.*, 3441 (1957).

λ_{max}^{EtOH} 251 (ϵ 6700) and 341 mμ (ϵ 26,600); $\lambda_{max}^{CHCl_3}$ 6.00, 6.25, and 6.64 μ; n.m.r.: multiplet at 7.2 p.p.m. due to aromatic hydrogens and multiplets between 1.62 and 3.05 p.p.m. (methylene protons).

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.58; H, 8.34; N, 6.11; mol. wt., 229. Found: C, 78.52; H, 8.18; N, 6.29, mol. wt. (Rast), 256.

2-Acetoxy-2-(3-oxobutyl)-cyclohexane-1,3-dione (XIV).—Further elution with 1:4 acetone–hexane gave 2.06 g. (29%) of 2-acetoxy-2-(3-oxobutyl)-cyclohexane-1,3-dione (XIV), m.p. 64–66°. Three recrystallizations from ether–hexane afforded material melting at 68–69°; $\lambda_{max}^{CHCl_3}$ 5.75, 5.81, and 8.03 μ; n.m.r.: in $CDCl_3$ an intense singlet at 2.11 p.p.m. (resolved into two equally intense peaks due to CH_3–COO– and CH_3–$COCH_2$– in benzene) and subsidiary multiplets centered at 2.65 p.p.m.

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.98; H, 6.71. Found: C, 59.80; H, 6.91.

1-Acetoxy-6-hydroxy-6-methylbicyclo[3.3.1]nonane-2,9-dione (XVII).—Elution with 2:3 acetone–hexane afforded 1.53 g. (22%) of the bridged ketol XVII, m.p. 164–174°. Five recrystallizations from ethyl acetate–hexane gave white crystals, m.p. 173–176°; $\lambda_{max}^{CHCl_3}$ 2.8, 5.79 (broad), 8.04 μ; n.m.r.: (pyridine solution) 1.35 (CH_3–C(–OH)–) and 1.97 p.p.m. (CH_3COO–).

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.98; H, 6.71. Found: C, 59.79; H, 6.68.

3-(2-Methyl-5-acetoxy-6-keto-1-cyclohexenyl)propionic Acid (XX).—Finally, elution with 2:3 methanol–acetone afforded 0.50 g. (7%) of 3-(2-methyl-5-acetoxy-6-keto-1-cyclohexenyl)-propionic acid (XX), m.p. 119–120°. A small sample recrystallized from ethyl acetate had m.p. 121–122°; λ_{max}^{EtOH} 243 mμ (ϵ 10,000); $\lambda_{max}^{CHCl_3}$ 2.9 (very broad shoulder), 5.72, 5.82, 5.92, 6.12, and 8.05 μ; n.m.r.: in CS_2 an intense singlet at 2.0 p.p.m. (resolved into two equally intense peaks at 1.9 and 2.0 p.p.m. due to CH_3—COO— and CH_3—C(=C)— in DMF–benzene–CS_2) and a quartet at 5.1 p.p.m. (H—C(—OAc)).

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.98; H, 6.71. Found: C, 60.06; H, 6.69.

Treatment of XX with 10% palladium-on-carbon at 255° for 4.5 hr. produced **5-methylcoumarin**, m.p. 65–67°; λ_{max}^{EtOH} 287 mμ (ϵ 11,700); $\lambda_{max}^{CHCl_3}$ 5.80, 6.21 μ (lit.[19] m.p. 65.0–65.8°; lit.[35] m.p. 66.5°; λ_{max}^{EtOH} 287.5 mμ (ϵ 11,500)).

B. Preparation of 2-Acetoxy-2-(3-oxobutyl)cyclohexane-1,3-dione (XIV).—The following reaction conditions were found to give optimum yield of the Michael adduct XIV. To 10.0 g. (0.0587 mole) of 2-acetoxycyclohexane-1,3-dione were added 6.22 g. (0.0889 mole) of methyl vinyl ketone and 3 ml. of a solution of one pellet (*ca.* 0.18 g.) of sodium hydroxide in 10 ml. of absolute methanol. The mixture was refluxed for 45 min., cooled, and neutralized with 0.09 ml. (0.0015 mole) of acetic acid. Evaporation of excess methyl vinyl ketone and methanol afforded a crystalline residue which, after washing with cold ether, amounted to 12.6 g. (89%) of the Michael adduct XIV, m.p. 64–68°.

2-Acetoxy-2-(3,3-ethylenedioxybutyl)cyclohexane-1,3-dione (XVI).—The monoethylene ketal of the Michael adduct XIV was prepared according to a procedure of Johnson.[36] To a solution of 5.19 g. (0.0216 mole) of XIV in 100 ml. of dry benzene were added 5.25 g. (0.0847 mole) of redistilled ethylene glycol, b.p. 60–61° (1.6 mm.), and approximately 0.005 g. of *p*-toluenesulfonic acid monohydrate. The mixture was refluxed for 21 hr. attached to a water separator, cooled, diluted with 200 ml. of ether, washed successively with 5% sodium bicarbonate solution and water, and dried over magnesium sulfate. Upon removal of the solvent by distillation there was obtained 4.50 g. (73%) of white solid which melted, after washing with 1:1 ether–hexane, at 69–70°. Two recrystallizations from ether–hexane raised the melting point to 70.5–71.5°; $\lambda_{max}^{CHCl_3}$ 5.74, 5.81, and 8.1 μ; n.m.r.: 1.16 (CH_3 adjacent to ketal), 2.0 (CH_3–COO–), and 3.72 p.p.m. (singlet due to the four ketal protons).

Anal. Calcd. for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.24; H, 6.95.

The ketal XVI could be reconverted to the triketone XIV by treatment with a mixture of alcohol and hydrochloric acid for 2 hr. at room temperature. The reaction mixture was diluted with sodium bicarbonate solution and extracted with ether. The organic extracts were dried and evaporated, yielding crystals, m.p. 66.5–68°, which did not depress the melting point of a known sample of XIV, and had an infrared spectrum identical with that of XIV.

(35) T. Nakabayashi, T. Tokoroyama, H. Miyazaki, and S. Isono, *J. Pharm. Soc. Japan*, **73**, 669 (1953).

(36) W. S. Johnson, *et al.*, *J. Am. Chem. Soc.*, **78**, 6289 (1956).

3-(2-Methyl-5-hydroxy-6-keto-1-cyclohexenyl)propionic Acid (XXV).—To 3.29 g. (0.0137 mole) of the Michael adduct XIV was added a solution of seven pellets (*ca.* 1.25 g.) of sodium hydroxide in 20 ml. of absolute methanol. The mixture was allowed to stand at room temperature under nitrogen for 40 min. Then the mixture was diluted with 200 ml. of ether, acidified with dilute hydrochloric acid, washed with water, and dried over magnesium sulfate. Removal of the solvent gave a residue which crystallized to yield 1.51 g. (56%) of the hydroxy keto acid XXV, m.p. 95–98°. A small sample was recrystallized three times from ethyl acetate–ether and once from acetone–hexane, raising the m.p. to 97.5–98.5°; λ_{max}^{EtOH} 244 mμ (ϵ 12,000); $\lambda_{max}^{CHCl_3}$ 2.86, 3.0–3.3 (broad shoulder), 5.82, 5.99, and 6.13 μ; n.m.r.: 2.2 p.p.m. (a single intense peak due to superimposed CH_3–COO— and CH_3—C(=C)—), a quartet at 4.08 p.p.m. (H—C(—OH)), and a broad peak at 7.35 p.p.m. which became quite sharp upon the addition of a trace of acid and was thus assigned to the hydroxyl and carboxyl protons.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.61; H, 7.07. Found: C, 60.49; H, 7.19.

The hydroxy keto acid XXV could also be obtained from 3-(2-methyl-5-acetoxy-6-keto-1-cyclohexenyl)propionic acid (XX) by hydrolysis with dilute sodium hydroxide solution at room temperature for 40 min. in a yield of 84%.

The Reaction of 2-Acetoxy-2-(3-oxobutyl)cyclohexane-1,3-dione (XIV) with Potassium *t*-Butoxide.—To a stirred solution of 2.40 g. (0.0100 mole) of the Michael adduct XIV in 10 ml. of anhydrous *t*-butyl alcohol in a nitrogen atmosphere was added a solution of 0.39 g. (0.010 mole) of potassium in 25 ml. of anhydrous *t*-butyl alcohol. The mixture, which immediately turned red, was allowed to stand at room temperature for 10 min. and then was acidified with dilute hydrochloric acid, evaporated *in vacuo*, and partitioned between water and ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated. Chromatography of the residual oil afforded 0.936 g. of oil which had an infrared spectrum essentially identical with that of the acetoxy keto acid XX and which solidified to give 0.639 g. (27%) of material, m.p. 117.5–121.5°.

6-Pyrrolidino-1-tetralone (XXVIII).—This aromatic amine was first isolated (*ca.* 25% yield), along with the ketols XXX and XVII, when the Michael adduct XIV was treated with one equivalent of pyrrolidine in refluxing benzene for 10 min. A much better yield of XXVIII was obtained in the experiment described below, in which acetic acid was used in combination with pyrrolidine under the same conditions.

A solution of 4.00 g. (0.0167 mole) of the Michael adduct XIV, 1.4 ml. (0.0169 mole) of pyrrolidine, and 1.0 ml. (0.0167 mole) of glacial acetic acid in 75 ml. of dry benzene was refluxed for 10 min., cooled, and poured onto a column of 57 g. of acid-washed alumina. Elution with benzene gave 3.4 g. of oil from which crystallized 1.66 g. (46%) of 6-pyrrolidino-1-tetralone (XXVIII), m.p. 101–103°. Three recrystallizations from ether–hexane afforded material, m.p. 103.0–103.5°; λ_{max}^{EtOH} 250 (ϵ 7700) and 346 mμ (ϵ 32,500); $\lambda_{max}^{CHCl_3}$ 6.04, 6.28, 6.60, and 6.71 μ.

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.11; H, 8.08; N, 6.40.

Treatment of 1.00 g. (0.00417 mole) of XIV with 0.53 g. (0.0062 mole) of piperidine and 0.37 g. (0.0062 mole) of acetic acid in 50 ml. of refluxing benzene for 44 hr. afforded, after the usual work-up and chromatographic separation, 0.307 g. (34%) of **6-piperidino-1-tetralone (XIII)**, previously described. The ultraviolet spectrum of an aliquot from the reaction mixture after 22 hr. indicated that the reaction had proceeded to completion (42%) by that time. When only piperidine was used as catalyst, the Michael adduct XIV was essentially unaffected by 14-hr. treatment at the temperature of refluxing benzene, 86% of crystalline starting material being recovered.

6-*n*-Butylamino-1-tetralone (XXXIII).—To a solution of 1.00 g. (0.00417 mole) of the Michael adduct XIV in 50 ml. of dry benzene were added 0.30 g. (0.00417 mole) of *n*-butylamine (Eastman Kodak Co., White Label) and 0.25 g. (0.00417 mole) of acetic acid. The mixture was refluxed attached to a Dean–Stark water separator for 70 min. The yellow solution was cooled and the solvent removed by distillation *in vacuo*. The residue was chromatographed on 30 g. of acid-washed alumina. Elution with 1:5 acetone–hexane gave 0.541 g. of oil from which crystallized 0.358 g. (40%) of gray-white 6-*n*-butylamino-1-tetralone (XXXIII), m.p. 94–96°. Three recrystallizations from acetone–hexane afforded 0.301 g. of colorless material, m.p. 95.5–96.0°; λ_{max}^{EtOH} 247 (ϵ 7200) and 335 mμ (ϵ 25,300); $\lambda_{max}^{CHCl_3}$ 2.90, 6.00, 6.23, 6.59, and 6.74 μ.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.16; H, 8.62; N, 6.54.

Cyclization of 2-Acetoxy-2-(3-oxobutyl)cyclohexane-1,3-dione (XIV) with Pyrrolidine and Acetic Acid to Obtain Optimum Yield

of Ketol Mixture.—The optimum yield of a mixture of ketols XVII and XXX, containing approximately 80% of the desired hydronaphthalene derivative XXX, was obtained by the following procedure. To 10.2 g. (0.0425 mole) of the Michael adduct XIV, m.p. 67–69°, suspended in 120 ml. of ether, cooled in an ice bath, and stirred mechanically, were added 3.02 g. (0.0425 mole) of pyrrolidine (distilled from sodium hydroxide, b.p. 85°) and then slowly (over 3 min.) 2.55 g. (0.0425 mole) of glacial acetic acid. The mixture was stirred for 2 hr. at 0° and poured directly onto a column of 300 g. of acid-washed alumina. Some 1:9 acetone–hexane was used to aid in the transfer of solid material from the reaction flask to the column.

1-Acetoxy-6-methyl-$\Delta^{6,7}$-bicyclo[3.3.1]nonene-2,9-dione (XXXI).—Elution with 3:7 acetone–hexane gave 1.29 g. of an oil which crystallized upon standing to afford 0.72 g. (8%) of solid, m.p. 80–86°. Recrystallization from ether raised the melting point to 94–95°; $\lambda_{max}^{CHCl_3}$ 5.70–5.77 (broad peak) and 8.05 μ; n.m.r.: 1.97 (CH_3—C=C— and CH_3—COO—, area 4.6) and 5.13 p.p.m. (H—C=C—, area 1).

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.88; H, 6.56.

Further elution with 3:7 acetone–hexane afforded 6.39 g. (63%) of a mixture of ketols, m.p. 171–196°. Although the entire mixture was customarily used for subsequent steps, the ketols could be separated by careful rechromatography. Elution with 1:4 acetone–hexane yielded material which melted, after recrystallization from acetone–hexane, at 192–194° (dependent on rate of heating and temperature of insertion of sample; this ketol XVII decomposes to afford XIV with facility near its m.p. and this process is, for an obscure reason, accompanied by a "bubbling" of the sample). The spectral properties and elemental analysis (found: C, 60.12; H, 6.85) of this substance, which amounted to about 20% of the ketol mixture formed under the conditions described above, were the same as those of the previously described sample of bridged ketol, m.p. 173–176°. The melting point of a mixture of originally isolated ketol, m.p. 173–176°, and the presently considered material, m.p. 192–194°, was 173–188°. Recrystallization of the 173–176° material when seeded with 192–194° material gave material melting at 173–178°. Lack of the originally isolated, lower-melting material precluded further attempts to establish the exact relationship between these materials. It is possible that the lower-melting material contained some bridged ketol epimeric at the hydroxyl-bearing carbon to the assumed pure material of m.p. 192–194°, since the spectra of these epimers would be very similar.

When a small sample of the ketol XVII was heated at 185° for 80 min., trituration of the cooled residual oil with ether afforded crystalline material, m.p. 64–65°, which had an infrared spectrum identical with that of the Michael adduct XIV. This uncyclized material was also obtained in good yield when a small sample of XVII was treated with *p*-toluenesulfonic acid in benzene at reflux for 7 hr.

***cis*-9-Acetoxy-10-hydroxydecalin-1,6-dione (XXX).**—The preponderant ketol, present as about 80% of the mixture rechromatographed, was eluted with 3:7 acetone–hexane. Four recrystallizations from acetone–hexane afforded pure XXX, m.p. 192–193° (upon admixture with ketol XVII the m.p. was 171–183°); λ_{max}^{EtOH} 286 mμ (ϵ 59); λ_{max}^{Nujol} 2.95, 5.70, 5.84, 7.93, and 8.10 μ; n.m.r.: (pyridine solution) one sharp peak at 2.16 p.p.m., above subsidiary multiplets (CH_3–COO–).

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.98; H, 6.71. Found: C, 60.08; H, 6.62.

9-Acetoxy-$\Delta^{5,10}$-octalin-1,6-dione (III).—A mixture of 4.00 g. (0.0167 mole) of the ketols XXX and XVII as prepared above, 0.09 g. of *p*-toluenesulfonic acid monohydrate, and 600 ml. of dry benzene was refluxed for 20 min. in a 1-l. round-bottomed flask equipped with a Dean–Stark water separator. The mixture was cooled and poured directly onto a column of 120 g. of acid-washed alumina. Elution with 3:17 acetone–hexane afforded 2.29 g. of oil, λ_{max}^{EtOH} 238 mμ (ϵ 8700; in a later run, ϵ 9300 was obtained). This material, which was shown to consist primarily of the desired dione III by its subsequent reactions, could not be induced to crystallize, and therefore was used directly in the next step. Further elution with 3:17 acetone–hexane yielded 0.160 g. of crystalline material which was shown to be the known **6-hydroxy-1-tetralone**, whose preparation is described below. Elution with 2:3 acetone–hexane afforded 1.283 g. (32%) of recovered ketol mixture, which had an infrared spectrum essentially identical with that of the starting material. The yield of crude 9-acetoxy-$\Delta^{5,10}$-octalin-1,6-dione (III) based on unrecovered starting material was therefore 91%.

9-Hydroxy-$\Delta^{5,10}$-octalin-1,6-dione (XXXV).—From the chromatography of one dehydration reaction there was eluted directly after the oily III 12% of crystalline material, m.p. 112–114°. Recrystallization from acetone–hexane afforded pure hydroxydione XXXV, m.p. 114.5–115.5°; λ_{max}^{EtOH} 233 mμ (ϵ 11,000); $\lambda_{max}^{CHCl_3}$ 2.98, 5.77, 5.96, and 6.12 (w) μ; n.m.r.: 5.82 p.p.m. (H—C=C—).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.63; H, 6.63.

Treatment of a 0.500-g. sample of ketol XXX, m.p. 189–192°, with 0.010 g. of *p*-toluenesulfonic acid monohydrate in 62.5 ml. of refluxing benzene for 25 min. afforded a product from which could be separated by careful chromatography a small amount (*ca.* 0.010 g.) of the hydroxydione XXXV, which was identified by its infrared spectrum, melting point, and the undepressed melting point of a mixture with known XXXV.

***cis*-1-Acetoxy-9-hydroxy-$\Delta^{5,10}$-octalone-6 (XL).**—The dione III was reduced with one equivalent of purified sodium borohydride according to the directions of Boyce and Whitehurst.[31] A magnetically-stirred solution of 2.29 g. (0.0103 mole) of crude dione (as prepared above) in 50 ml. of 95% ethanol was cooled in an ice bath, and 0.100 g. (0.00270 mole) of purified sodium borohydride[37] in 50 ml. of 95% ethanol was added dropwise over a period of 25 min. Stirring was continued for an additional 15 min. at room temperature. The reaction mixture was reduced in volume by distillation *in vacuo*, and the residual mixture was made acid with excess hydrochloric acid. The acidified mixture was partitioned between saturated sodium chloride solution and ether, and the aqueous layer was exhaustively extracted with ether. The ethereal extracts were combined (total volume *ca.* 900 ml.), dried over magnesium sulfate, and evaporated. The residue was chromatographed on 60 g. of acid-washed alumina. Elution with 3:7 acetone–hexane gave 1.91 g. of oil from which crystallized 0.610 g. (25%) of material, m.p. 104.5–105°. Five recrystallizations from acetone–hexane provided an analytical sample of the alcohol XL, m.p. 106.0–106.5°; λ_{max}^{EtOH} 233 mμ (ϵ 12,500); $\lambda_{max}^{CHCl_3}$ 3.0, 5.73, 5.96, 6.13 (w), and 7.95–8.05 μ; n.m.r.: ($CDCl_3$–CS_2 solution) 2.12 (CH_2—COO—), 4.83 (quartet due to H—C—OAc), and 5.89 p.p.m. (H—C=C—).

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.33; H, 7.22.

1,9-*cis*-Diacetoxy-$\Delta^{5,10}$-octalone-6 (XLIII).—The hydroxy compound XL was acetylated by the method of Johnson.[38] To 0.0910 g. (4.06×10^{-4} mole) of XL were added 3 ml. of isopropenyl acetate (redistilled, b.p. 97–98°) and a trace (*ca.* 0.001 g.) of *p*-toluenesulfonic acid monohydrate. The mixture was heated at 86° for 5.5 hr. Most of the excess isopropenyl acetate was evaporated, and the residue was chromatographed on 5 g. of acid-washed alumina. Elution with 1:4 acetone–hexane afforded 0.0835 g. of crude diacetate, which yielded crystals melting at 132–134°. Recrystallization from acetone–hexane afforded the analytical sample, m.p. 134.5–135.0°; λ_{max}^{EtOH} 239 mμ (ϵ 14,000); $\lambda_{max}^{CHCl_3}$ 5.72, 5.98, 6.1 (w), and 8.10 μ; n.m.r.: 2.06 (intense singlet which was resolved on a slow scan into two equally intense peaks due to CH_3—COO—), 4.85 (quartet due to H—C—OAc), and 5.77 p.p.m. (H—C=C—).

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.96; H, 6.87.

The crude sodium borohydride reduction product containing XL was customarily acetylated directly after it was isolated chromatographically. In a typical run, a solution of 1.995 g. (0.00890 mole) of crude hydroxyketone XL (derived from 2.42 g. of crude dione III as described above) and 0.004 g. of *p*-toluenesulfonic acid monohydrate in 15 ml. of isopropenyl acetate was heated at 80° for 2.75 hr., cooled, diluted with 75 ml. of hexane and 25 ml. of benzene, and poured onto a column of 60 g. of acid-washed alumina. Elution with 1:5 acetone–hexane afforded material which crystallized to yield 1.309 g. of the diacetate XLIII, m.p. 129–132°. This 1.309 g. represents a 35% yield based on the mixture of ketols XXX and XVII used in the dehydration step.[25]

N.m.r. Spectra of Model Compounds XLI and XLII.—1β-Hydroxy-9β-methyl-$\Delta^{5,10}$-octalone-6 (XLI) (see Fig. 2) displayed peaks at 1.17 (CH_3—C—) and 5.65 p.p.m. (H—C=C—). 1β-Acetoxy-9β-methyl-$\Delta^{5,10}$-octalone-6 (XLII) (see Fig. 2) displayed peaks at 1.19 (CH_3—C—), 1.93 (CH_3—COO—), 4.46 (quartet due to H—C—OAc), and 5.36 p.p.m. (H—C=C—). The splitting observed in the quartet due to the proton on the acetoxyl-bearing carbon is that expected for an axial proton (as in

(37) H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).

(38) W. S. Johnson, *et al.*, *ibid.*, **78**, 6302 (1956).

XLII, XL, and XLIII) coupling with an axial and an equatorial proton.[18]

Preparation of 6-Hydroxy-1-tetralone (XXXIV) from III.—A solution of 0.52 g. (0.0023 mole) of the crude dione III and 0.004 g. of *p*-toluenesulfonic acid monohydrate in 18 ml. of benzene was refluxed for 4.75 hr., cooled, and poured onto a column of 10 g. of acid-washed alumina. Elution with 1:4 acetone–hexane afforded 0.346 g. (91%) of crude, yellow crystalline phenol, m.p. 142–148.5°. Two recrystallizations from methanol–water raised the melting point to 150.5–152° (lit.[27a] m.p. 150°, lit.[27b] m.p. 149–152°, lit.[27c] m.p. 150–152°); $\lambda_{max}^{CHCl_3}$ 3.05, 5.99, 6.22, and 6.32 μ; λ_{max}^{EtOH} 229 (ϵ 12,000), and 279 mμ (ϵ 16,000) (lit.[27d] λ_{max}^{EtOH} 228 (ϵ 11,400) and 281 mμ (ϵ 17,600)).

The hydrazone derivative was obtained as pale yellow needles, m.p. 194.195.5° dec. (lit.[39] m.p. 195°); λ_{max}^{EtOH} 224 (ϵ 12,000) and 276 mμ (ϵ 17,600); λ_{max}^{Nujol} 3.00, 3.15, 6.19, 6.37, and 6.68 μ. The semicarbazone was prepared as usual and recrystallized from ethanol–water to m.p. 216–216.5° dec. (lit.[27c] m.p. 216.5–217.5°); λ_{max}^{EtOH} 227 (ϵ 12,400) and 288 mμ (ϵ 19,000); λ_{max}^{Nujol} 2.89, 3.15, 5.91, 6.15, 6.32, and 6.65 μ.

Preparation of 6-Hydroxy-1-tetralone from XXX.—A mixture of 0.603 g. (0.00251 mole) of ketol XXX, m.p. 190–192°, and 0.035 g. of *p*-toluenesulfonic acid monohydrate in 30 ml. of dry benzene was refluxed for 1.75 hr., cooled, and chromatographed to yield 0.333 g. (82%) of crystalline 6-hydroxy-1-tetralone (XXXIV), identified by m.p. and infrared spectrum.

Preparation of 6-Hydroxy-1-tetralone from XXXV.—A mixture of 0.061 g. (3.4×10^{-4} mole) of the hydroxydione XXXV, m.p. 114–115.5°, and 0.003 g. of *p*-toluenesulfonic acid monohydrate in 5 ml. of dry benzene was refluxed for 19 hr. After removal of the solvent, the crude product showed λ_{max}^{EtOH} 279 mμ (ϵ 5300). (An aliquot taken after 50 min. of reflux showed no strong absorption at 280 mμ.) Chromatography yielded a small amount (*ca.* 0.005 g.) of crystalline 6-hydroxy-1-tetralone (XXXIV), identified by m.p., m.m.p., and infrared spectrum. The acid-catalyzed aromatization of XXXV thus is much less facile than that of III or its progenitor XXX. It should also be noted that the sodium borohydride reduction product XL survives vigorous acid-catalyzed acetylation conditions without aromatizing, so it seems that both XL and the diacetate XLIII are more resistant to aromatization than III (although XL and XLIII have not been tested with *p*-toluenesulfonic acid in benzene).

Treatment of 2β-Acetoxy-3α-hydroxycholestane with *p*-Toluenesulfonic Acid in Benzene.—A 0.042-g. (9.8×10^{-5} mole) sample of 2β-acetoxy-3α-hydroxycholestane,[40] m.p. 112–114°, was dissolved in 5 ml. of dry benzene containing 6×10^{-4} g. of *p*-toluenesulfonic acid monohydrate and the mixture was refluxed for 25 min. When cool, the mixture was chromatographed on 1.0 g. of acid-washed alumina. There was eluted 0.037 g. of material which was identified as starting material by infrared spectrum and m.p. This substance, however, crystallizes very slowly and poorly, so that recovery of material of m.p. *ca.* 112–114° from the reaction (or upon recrystallization of known pure material) was not good. Accordingly, we cannot exclude the possibility of the presence of a small amount of material other than 2β-acetoxy-3α-hydroxycholestane, which escaped detection in the infrared spectrum. Further experiments were desirable, but were precluded by lack of additional model substance. In any case, in view of the conformational rigidity of hydroxyl and acetoxyl in XXIX as opposed to the more flexible relationship in 2β-acetoxy-3α-hydroxycholestane, the latter is not a completely adequate model.

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Synthesis of the New 5-Phosphomethyl-6-chromanyl Acetate of Vitamin $K_{1(20)}$ by a Novel Cyclization Reaction[1]

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A new type of phosphorylated chromanyl derivative, of current interest in studies of biological oxidative phosphorylation, has been synthesized by a novel cyclization reaction. Treatment of vitamin $K_{1(20)}$ with concentrated sulfuric acid, followed by reaction with water, yields the γ-hydroxy side-chain substituted derivative of vitamin $K_{1(20)}$. On reaction with acetyl chloride, the γ-hydroxy derivative is cyclized to the 5-chloromethyl-6-chromanyl acetate derivative of vitamin $K_{1(20)}$. This compound was converted, in several steps, to the 5-phosphomethyl-6-chromanyl acetate derivative of vitamin $K_{1(20)}$.

In a continuing study of phosphate derivatives of vitamin K in microbial oxidative phosphorylation, we have synthesized the 5-phosphomethyl-6-chromanyl acetate II of vitamin $K_{1(20)}$. This new structural type of phosphorylated chromanol (I) is likely to be more productive than previously reported hydroquinone monophosphates (III) and 6-chromanyl phosphates (IV) for studies of biological oxidative phosphorylation. Related data supporting a mechanism for one step in the synthesis of the 5-phosphomethyl derivative as well as its possible function in the formation of ATP from ADP by way of oxidative phosphorylation will be described in a subsequent publication.[2]

Anaerobic and acetylation techniques were recently introduced[3,4] to study a possible role for vitamin K in electron transport and coupled phosphorylation in light-inactivated, cell-free extracts of *Mycobacterium phlei*. Extension of these initial studies resulted in the isolation and identification of the new 6-chromanyl acetate V and later, the new and unexpected 5-chloromethyl-6-chromanyl acetate VI derivatives of vitamin $K_{1(20)}$ from the enzymic and acetylated reaction mixture.[5,6] Since it appeared likely that the chloro derivative VI was a nonenzymic product, the reaction of vitamin $K_{1(20)}$ with acetyl chloride was studied under a variety of conditions. This study revealed a new facet of vitamin K chemistry and provided the first experimental data to support a new concept[7] of "active phosphate" on the biosynthetic pathway from ADP to ATP.

Vitamin $K_{1(20)}$ and acetyl chloride do not react under strictly anhydrous conditions; in the presence of traces of moisture, however, the chloromethyl derivative VI was formed from these two reactants. Similarly, the

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