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THE STRUCTURE OF CUMANIN, A CONSTITUENT OF *AMBROSIA CUMANENSIS*

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Abstract—Cumanin a constituent of *Ambrosia cumanensis* has been shown to be a sesquiterpene lactone, whose structure is represented by Ia.

FOLLOWING our studies on sesquiterpene lactones, we have undertaken the examination of some Ambrosiae species occurring in the central part of Mexico. The isolation and structure of peruvin,[3] a sesquiterpene lactone isolated from *Ambrosia peruviana* has been described and now the evidence which established the structure Ia for a substance named *Cumanin*, isolated from *Ambrosia cumanensis* is reported.

Cumanin ($C_{15}H_{22}O_4$), m.p. 120°, $[\alpha]_D$ +161°, was obtained from the polar fractions of the chromatogram of the chloroform extract of the plant. Two oxygen atoms of cumanin (Ia) are distributed as hydroxyl groups, as shown by the strong IR band at 3500 cm^{-1} and preparation of a diformate (Ib) and a diacetate (Ic).

The IR bands of cumanin (Ia) at 1755 and 1660 cm^{-1}, indicate that the other oxygen atoms are involved in an α,β-unsaturated-γ-lactone. The presence of an exocyclic methylene group conjugated with the lactone was inferred from the UV maximum (λ_{max} 213 mμ; ε, 9400)[3,4] and confirmed by ozonolysis of cumanin diacetate (Ic), which afforded formaldehyde, characterized as its adduct with dimedone. The formation of the pyrazoline (II) by treatment of cumanin diacetate (Ic) with ethereal diazomethane offered another proof of the presence of this chromophore.

The NMR spectrum[5] of cumanin (Ia) showed a pair of doublets at 6·17 and 5·57, corresponding to the exocyclic methylene protons. In the methyl region, there is a singlet at 0·97, ascribed to a tertiary methyl group. A secondary methyl group is responsible for a doublet centered at 1·04 (partially superimposed on the singlet). Hydrogenation of cumanin (Ia) afforded the dihydroderivative (IIIa), whose NMR spectrum did not exhibit the low field doublets corresponding to the hydrogens of the exocyclic methylene group. A new secondary methyl group is present, since a doublet centered at 1·14 (J = 7 c/s) (intensity six protons) is observed, partially superimposed on a singlet at 1·01, the latter corresponding to the tertiary methyl group. From the hydrogenation of cumanin (Ia) isocumanin (IVa; λ_{max} 219 mμ; ε, 15600) was also obtained as often happens in the hydrogenation of similar lactones.[6] Isocumanin (IVa) exhibited in the NMR spectrum a singlet at 1·8 ascribed to the vinyl methyl group.

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[2] Recipient of a grant from the Instituto Nacional de la Investigación Científica.

[3] P. Joseph-Nathan and J. Romo, *Tetrahedron* **22**, 301 (1966).

[4] W. Herz, K. Ueda and S. Inayama, *Tetrahedron* **19**, 483 (1963).

[5] The NMR spectra were determined by Mr. Eduardo Díaz on a Varian A-60 spectrometer in $CDCl_3$ solution, using tetramethylsilane as internal reference. All chemical shifts are reported in ppm as δ values (c/s/60).

[6] W. Herz, A. Romo de Vivar, J. Romo and N. Viswanathan, *J. Amer. Chem. Soc.* **85**, 19 (1963).

Treatment of cumanin diacetate (Ic) with toluenethiol, followed by desulfuration with Raney nickel,[7,8] furnished 11-epidihydrocumanin diacetate (Vb). Alkaline hydrolysis yielded the diol (Va).

LAH reduction of cumanin (Ia) followed by dehydrogenation with Pd–C, in Nujol solution gave traces of a violet azulene. TLC of this azulene, showed the same R_f as an authentic sample of linderazulene (VI) and their UV spectra were nearly identical. Unfortunately, this azulene could not be characterized due to the small amount obtained.[9] This result combined with the presence of a secondary and a tertiary methyl substituent in cumanin (Ia) indicates that this lactone possesses a pseudoguaiane structure. Furthermore, the complexity of a signal in the NMR spectrum of cumanin (Ia), centered at 4·67, assigned to the hydrogen on the carbon bearing the lactone ether, confirms lactone closure at C-8.

Ozonolysis of cumanin diacetate (Ic) followed by potassium permanganate oxidation, following the method described by Herz *et al.*,[4] afforded in low yield the non-enolized α-diketone (VII; λ_{max}, 282 mμ; ε, 80). It had bands at 1745 cm^{-1} (acetyl groups) and at 1710 cm^{-1} (cycloheptanedione). The NMR spectrum exhibited in the methyl region a singlet at 0·92 (tertiary methyl group) and a doublet centered at 1·06 (secondary methyl group). The acetyl groups are responsible for a singlet at 2·07 (intensity six protons). Treatment of the diketone (VII) with *o*-phenylenediamine, furnished a quinoxaline.

Proof concerning the secondary nature and the relative position of the hydroxyl groups were obtained as follows. Cumanin (Ia) yielded the dimesylate (Id), acetolysis of this derivative (Id) permitted only the substitution of one mesyl group. The NMR spectrum of cumanin diacetate (Ic) showed a complex signal centered at 4·75 (intensity two protons) assigned to the hydrogens of the carbons bearing the acetoxy groupings, which in cumanin (Ia) are displaced to high field. The same displacements are observed in the diacetates (IIIb, IVb, and Vb) as compared with their respective free diols (IIIa, IVa and Va).

Cumanin (Ia) consumed periodic acid. From this reaction the dimethyl ether (VIII) was obtained. Its IR spectrum showed only the carbonyl band at 1772 cm^{-1} of the five membered lactone. A NMR singlet at 3·5 (intensity six protons) indicated the presence of two methoxyl groups. The *cis* position of the glycol system was demonstrated by the formation of the cumanin acetonide (IX) and of the sulfite (X). The acetonide (XI) of 11-epidihydrocumanin (Va) was also prepared. The NMR spectrum of the α-diketone (VII) suggests that the hydroxyl groups of cumanin (Ia) are located at C_3 and C_4, since the signals of the hydrogens attached to the carbons bearing the acetoxy functions are displayed as a doublet (J = 7 c/s) centered at 4·73 and a triplet (J = 7 c/s) centered at 5·34.

Cumanin (Ia) was dehydrated to the ketone (XII) by high vacuum sublimation with potassium bisulfate. This ketone (XII; λ_{max} 212 mμ; ε, 10800) is a cyclopentanone as shown by a strong IR band at 1755 cm^{-1} (five membered ketone and γ-lactone). The exocyclic methylene protons exhibited in the NMR spectrum two low field doublets at 6·3 and 5·7. Lactone ring closure at C-8 is in accord with the multiplicity of a signal

[7] E. Domínguez and J. Romo, *Tetrahedron* **19**, 1415 (1963).

[8] J. Romo, P. Joseph-Nathan and F. Díaz A, *Tetrahedron* **20**, 79 (1964).

[9] Dehydrogenation of pseudoguaianolides afford very poor yields of azulenic material. Pyrolysis of pulchellin, a related lactone (Ref. 4) gave also only traces of linderazulene.

centered at 4·73 (intensity one proton; two lateral doublets and a central triplet). A doublet (J = 7 c/s) centered at 1·13 and a singlet at 1·02 indicated the presence of a secondary and a tertiary methyl group, respectively. Baeyer-Villiger oxidation of the dihydroketone (XIII), obtained by Pd–C catalyzed hydrogenation of XII, afforded the dilactone (XIV). Its IR spectrum had bands at 1772 and 1725 cm^{-1} corresponding to five and six membered lactones, respectively. The position of the keto group at C-4, in XIII, became apparent by observation in the NMR spectrum of its derived dilactone (XIV), of a singlet (at 1·43), whose chemical shift corresponds to a tertiary methyl group, substituted on a carbon bonded to an oxygen atom. The secondary methyl groups are responsible for two doublets centered at 1·16 and 0·98.

LAH reduction of the cycloethylene ketal (XV), of the lactone (XIII), yielded the diol (XVI). Acid hydrolysis of XVI furnished the ketone (XVII), which has an IR band at 1740 cm^{-1} (five membered ketone). Deuterium exchange in the ketone (XVII), indicated that four protons were substituted by deuterium, as shown by comparison of the NMR spectra of XVII, prior to and after substitution. The hydroxyl protons and the methylene hydrogens at position 3 were exchanged, furnishing a further proof concerning the position of the ketone. The lactone (XIII) possesses a *trans* ring junction, since its ORD curve exhibited a positive Cotton effect of the same amplitude as those shown by tetrahydrohelenalin and related lactones.[6] The structure of cumanin (Ia) was fully elucidated when potassium bisulfate dehydration of isocumanin (IVa) gave the ketone (XVIII), identical to a product of known structure, obtained from isoperuvin (XIX), by dehydration followed by hydrogenation.[3] Therefore cumanin possesses structure Ia with the asymmetric centers at 1, 5, 8 and 10 as in peruvin (XX).[3] Biogenetic considerations permit assignment of the beta configuration to the asymmetric center at 7. The following experiments led us to select the beta configuration for the hydroxyl groups of cumanin (Ia). We have found that treatment of an acetic acid solution of cumanin dimesylate (Id) with sodium iodide afforded in good yield the diene (XXI), incidentally, this elimination can be used successfully with other vicinal dimesylates.[10] The NMR spectrum of the diene (XXI) showed signals corresponding to four vinyl protons. The exocyclic methylene protons are responsible for two doublets at 6·12 and 5·52. A complex signal centered at 5·73 (intensity two protons) partially superimposed to one of the doublets, is assigned to the hydrogens of the double bond in the five membered ring. Selective hydroxylation of the cyclopentane double bond of the diene (XXI) with osmium tetroxide, followed by hydrolysis and treatment with acetone in the presence of mineral acid, gave the acetonide (XXII). Acid hydrolysis of XXII yielded the epimer of cumanin (XXIII). A cyclic sulfite was prepared.

Since the intermediary osmic ester must be formed by attack of osmium tetroxide from the opposite side to the beta, angular methyl group, which exerts the most powerful steric effect; the hydroxyl groups of the resulting cumanin epimer (XXIII) must have the alpha configuration. Therefore in cumanin (Ia) and in its derivatives, the hydroxyl groups are beta. For the same reason, to the epoxide (XXIV), prepared by selective oxidation of the diene (XXI) with *m*-chloroperbenzoic acid, the alpha configuration is assigned.

[10] J. Romo and P. Joseph-Nathan unpublished results. A similar method has been previously applied in the steroid field. N. L. Wendler, H. L. Slates and M. Tishler, *J. Amer. Chem. Soc.* **74**, 4894 (1952).

I a, R = H
b, R = HCO
c, R = Ac
d, R = MeSO2
II
III a, R = H
b, R = Ac
IV a, R = H
b, R = Ac
V a, R = H
b, R = Ac
VI
VII
VIII
IX
X
XI
XII
XIII
XIV
XV
XVI
XVII
XVIII
XIX
XX
XXI
XXII
XXIII
XXIV

EXPERIMENTAL[11]

Isolation of cumanin Ia. *Ambrosia cumanensis*[12] was collected in August, 1964, in the neighbourhood of Mexico City. The dried plant (without roots; 10 Kg) was extracted with $CHCl_3$ (35 l.) for 16 hr. The extract was filtered and evaporated to dryness. The residue dissolved in EtOH (4 l.) was treated with a solution of lead acetate (100 g) in water (3·5 l.), left at room temp for 2 hr, filtered, diluted with water (3·5 l.) and extracted with $CHCl_3$. The extract was evaporated to dryness, dissolved in benzene and chromatographed on alumina, The fractions eluted with benzene and ether, left oily residues. The polar fractions eluted with ether and increasing proportions of $CHCl_3$ and with AcOEt gave semicrystalline residues. These fractions were combined and recrystallized from acetone–hexane yielding cumanin (Ia; 24 g), m.p. 83–85°. Further crystallizations from acetone–hexane and acetone–ether afforded prisms m.p. 120°; (cumanin showed erratic m.ps from 85° to 120°), $[\alpha]_D$ +161°; λ_{max} 213 mμ; ε, 9400; IR bands at 3500 cm^{-1} (hydroxyl groups), at 1755 and 1660 cm^{-1} (α,β-unsaturated-γ-lactone). (Found: C, 67·25; H, 8·12. Calc. for $C_{15}H_{22}O_4$: C, 67·64; H, 8·33%.)

Cumanin diformate (Ib). A solution of Ib (200 mg) in 98% HCOOH (6 ml) was heated under reflux for 1 hr, diluted with ice-water, the precipitate collected, washed with water and crystallized from acetone–ether. This yielded needles (160 mg), m.p. 179–181°; $[\alpha]_D$ +82°; λ_{max} 213 mμ; ε 9800; IR bands at 1725 cm^{-1} (formyl groups), at 1758 and 1660 cm^{-1} (α,β-unsaturated-γ-lactone). (Found: C, 63·52; H, 6·97; O, 29·90. Calc. for $C_{17}H_{22}O_6$: C, 63·34; H, 6·88; O, 29·78%.)

Cumanin diacetate (Ic). Acetylation with pyridine–acetic anhydride for 1 hr on the steam bath, furnished the diacetate (Ic), m.p. 105° (needles from acetone–hexane); $[\alpha]_D$ +64°; λ_{max} 213 mμ; ε, 10500; IR bands at 1750 cm^{-1} (strong) (acetyl groups and α,β-unsaturated-γ-lactone) and at 1660 cm^{-1} (C=C double bond). (Found: C, 64·89; H, 7·44; O, 27·70. Calc. for $C_{19}H_{26}O_6$: C, 65·12; H, 7·48; O, 27·40%.)

Pyrazoline of cumanin diacetate (Ic). A solution of Ic (200 mg) in MeOH (4 ml) was treated with 20 ml of an ethereal solution of diazomethane (prepared with 1 g of N-nitrosomethylurea) and left overnight at 4°. The solution was washed with water and concentrated, the crystalline precipitate was collected and recrystallized from acetone–ether; this yielded prisms m.p. 128–129° (dec); $[\alpha]_D$ +235°; λ_{max} 322 mμ; ε, 200. (Found: C, 61·03; H, 7·20; O, 24·26; N, 7·16. Calc. for $C_{20}H_{28}O_6N_2$: C, 61·21; H, 7·19; O, 24·46; N, 7·14%.)

Cumanin dimesylate (Id). A solution of Ia (1 g) in pyridine (8 ml) with external cooling, was treated with methanesulfonyl chloride (2 ml), left at room temp for 3 hr, poured in ice-water and extracted with AcOEt. The organic layer was washed with dil HCl, $NaHCO_3$aq, water, dried and evaporated to dryness *in vacuo*. Crystallization of the gummy residue from acetone–hexane yielded 1·18 g of Id, m.p. 179–183°, $[\alpha]_D$ +91°; λ_{max}, 213 mμ; ε, 9800; IR bands at 1755 and 1660 cm^{-1} (α,β-unsaturated-γ-lactone). (Found: C, 48·46; H, 6·24; O, 30·50; S, 15·09. Calc. for $C_{17}H_{26}O_8S_2$: C, 48·34; H, 6·20; O, 30·30; S, 15·15%.)

Cumanin acetate mesylate. A solution of Id (900 mg) in AcOH (30 ml), containing anh AcONa (2 g), was heated under reflux for 18 hr, concentrated, diluted with water and extracted with AcOEt. The organic layer was washed with 5% NaOH, water and evaporated to dryness. The residue dissolved in benzene was chromatographed on alumina (20 g). The crystalline fractions were combined and crystallized from acetone–hexane; this yielded prisms (310 mg), m.p. 173–174·5°; $[\alpha]_D$ −9°; λ_{max}, 213 mμ; ε, 9800; IR bands at 1755 cm^{-1} (acetyl group and γ-lactone) and at 1660 cm^{-1} (C=C double bond). (Found: C, 55·62; H, 6·84; O, 29·36; S, 8·35. Calc. for $C_{18}H_{26}O_7S$: C, 55·94; H, 6·78; O, 28·98; S, 8·30%.)

Cumanin acetonide (IX). A solution of Ia (200 mg) in anh acetone (6 ml), containing 5 drops conc HCl was left at room temp overnight, evaporated to dryness *in vacuo* and the residue crystallized from acetone–ether. This yielded material m.p. 150–154°; $[\alpha]_D$ +156°; λ_{max} 213 mμ; ε, 9100; IR bands at 1755 and 1660 cm^{-1} (α,β-unsaturated-γ-lactone). The IR spectrum did not exhibit hydroxyl bands. The NMR spectrum showed 2 singlets at 1·33 and 1·49, corresponding to the acetonide methyl groups. (Found: C, 70·39; H, 8·64; O, 20·82. Calc. for $C_{18}H_{26}O_4$: C, 70·56; H, 8·55; O, 20·89%.) Treatment of IX, dissolved in MeOHaq with HCl, afforded Ia, m.p. 85°.

[11] M.ps are uncorrected. Analyses by Dr. Franz Pascher, Bonn, Germany IR spectra and rotations were run in $CHCl_3$; UV spectra in 95% EtOH. The chromatograms were carried out with alumina Alcoa, F-20 (washed with AcOEt).

[12] We are grateful to the late Dr. Faustino Miranda for the identification of the plant.

Cumanin sulfite (X). A solution of Ia (500 mg) in pyridine (6 ml) with external cooling, was treated with $SOCl_2$ (1 ml), left 1 hr at 4°, poured in ice-water and extracted with AcOEt. The organic layer was washed with dil HCl, water, evaporated to dryness and the residue dissolved in benzene was chromatographed on alumina. The crystalline fractions were combined and crystallized from acetone–hexane; this yielded fluffy needles (360 mg), m.p. 169–172°, further crystallizations from acetone–hexane raised the m.p. to 176°; $[\alpha]_D$ +146°; λ_{max} 213 mμ; ε, 10500; IR bands at 1755 and 1660 cm^{-1} (α,β-unsaturated-γ-lactone). (Found: C, 57·89; H, 6·37; O, 25·78; S, 10·20. Calc. for $C_{15}H_{20}O_6S$: C, 57·67; H, 6·45; O, 25·61; S, 10·26%.)

HIO_4 *Oxidation of cumanin* (Ia). A solution of Ia (600 mg) in MeOH (8 ml) was mixed with HIO_4 (800 mg) in water (4 ml), left overnight at room temp and extracted with AcOEt. The organic layer was washed with water, evaporated to dryness and the residue dissolved in benzene, chromatographed on alumina (12 g). The first fractions eluted with benzene crystallized, they were combined and recrystallized from acetone–hexane; this yielded VIII (60 mg) m.p. 129–136°; further crystallizations from acetone–hexane raised the m.p. to 157°; $[\alpha]_D$ +54°, λ_{max} 213 mμ; ϵ, 9500; IR bands at 1772 and 1635 cm^{-1} (α,β-unsaturated-γ-lactone). (Found: C, 65·65; H, 8·14; O, 26·10. Calc. for $C_{17}H_{26}O_5$: C, 65·78; H, 8·44; O, 25·78%.)

Hydrogenation of cumanin (Ia). A solution of Ia (2 g) in AcOEt (70 ml) with 10% Pd–c (200 mg) was hydrogenated until the uptake of H_2 ceased, the catalyst was filtered off and the solution evaporated to dryness. Several crystallizations from acetone–hexane and acetone–ether afforded IVa (540 mg), m.p. 197–203°. The analytical sample showed m.p. 212–213°, (prisms from acetone–ether), $[\alpha]_D$ +8°; λ_{max} 219 mμ; ε, 15600. IR bands at 3550 cm^{-1} (hydroxyl groups) and at 1750 and 1680 cm^{-1}; (α,β-unsaturated-γ-lactone). (Found: C, 67·50; H, 8·42; O, 24·34. Calc. for $C_{15}H_{22}O_4$: C, 67·64; H, 8·33; O, 24·03%.)

The diacetate (IVb) showed m.p. 149–151° (needles from acetone–ether), $[\alpha]_D$ −41°; λ_{max}, 219 mμ; ε, 16200; IR bands at 1740 and 1680 cm^{-1} (α,β-unsaturated-γ-lactone). (Found: C, 65·25; H, 7·51; O, 27·28. Calc. for $C_{19}H_{26}O_6$: C, 65·12; H, 7·48; O, 27·40%.)

From the mother liquors left after the crystallization of IVa, IIIa (380 mg) was obtained, m.p. 178–180° (prismatic needles from acetone–hexane), $[\alpha]_D$ +70°; IR bands at 3640 and 3550 cm^{-1} (hydroxyl groups), and at 1760 cm^{-1} (γ-lactone). (Found: C, 67·28; H, 8·70; O, 24·12. Calc. for $C_{15}H_{24}O_4$: C, 67·13; H, 9·01; O, 23·86%.)

The diacetate (IIIb) showed m.p. 106–107° (needles from acetone–hexane), $[\alpha]_D$ +21°; IR bands at 1740 cm^{-1} (strong) (acetyl groups) with a shoulder at 1770 cm^{-1} (γ-lactone). (Found: C, 64·49; H, 7·81; O, 27·23. Calc. for $C_{19}H_{28}O_6$: C, 64·75; H, 8·01; O, 27·24%.)

11-*Epidihydrocumanin diacetate* (Vb). To a solution of Ic (500 mg) in benzene (60 ml) was added toluenethiol (2 ml) and piperidine (2 ml), heated under reflux for 6 hr, washed with dil HCl, water and evaporated. The residue dissolved in EtOH (100 ml) was treated with freshly prepared Raney Ni (6 g), heated under reflux for 18 hr, filtered and the solution evaporated to dryness. The residue crystallized from acetone–hexane yielded material (280 mg), m.p. 114–115°; $[\alpha]_D$ +86°; (transparent in the UV spectrum); (Found: C, 64·87; H, 7·80; O, 27·19. Calc. for $C_{19}H_{28}O_6$: C, 64·75; H, 8·01; O, 27·24%.)

The diol (Va) was obtained by alkaline hydrolysis of Vb with $KHCO_3$aq. Crystallization from acetone–ether afforded plates m.p. 169–170°; $[\alpha]_D$ +110°. IR bands at 3550 cm^{-1} (hydroxyl groups) and at 1760 cm^{-1} (γ-lactone). (Found: C, 66·87; H, 8·86; O, 23·76. Calc. for $C_{15}H_{24}O_4$: C, 67·13; H, 9·01; O, 23·86%.)

Acetonide (XI). It was prepared following the same method as in IX. It showed m.p. 189–190° (needles from acetone–hexane), $[\alpha]_D$ +137°; IR bands at 1780 cm^{-1} (γ-lactone). (Found: C, 69·84; H, 8·90; O, 21·26. Calc. for $C_{18}H_{28}O_4$: C, 70·10; H, 9·15; O, 20·75%.)

Aromatization of cumanin (Ia). Cumanin (Ia; 2 g) was reduced with excess LAH and THF. The resulting gum (1·8 g) and 10% Pd–C (4 g) in Nujol (20 ml) was heated to 320° for 2 hr. The cool solution was diluted with hexane, filtered and extracted with 85% H_3PO_4. The complex was decomposed with ice-water and the azulene extracted with hexane. Chromatography on alumina gave a pale violet fraction. It was evaporated to dryness. The violet azulene was purified by preparative chromatoplate. It showed in tlc (hexane–benzene 4:1) the same R_f as an authentic sample of linderazulene (VI). λ_{max} (cyclohexane), 227, 278, 289, 293, 298, 321 mμ. (An authentic sample showed λ_{max}, 223, 278, 288, 294, 299, 320 mμ.)

Oxidation of cumanin diacetate (Ic). A stream of O_3 was passed through a solution of Ic (2·8 g) in

AcOEt (60 ml) at −70° until appearance of a violet colour (40 min). The solution was distilled, collecting the distillate in MeOH containing dimedone (50 mg). When 30 ml were collected, the dimedone solution was evaporated to dryness and the residue crystallized from MeOHaq; this yielded 35 mg of formaldehyde–dimedone, m.p. 188–189°, identified with an authentic specimen by the standard methods. The solution containing the product of ozonolysis was evaporated to dryness *in vacuo*, the residue did not crystallize. To a mixture of the above residue and $MgSO_4$ (2 g) in acetone (150 ml), a solution of $KMnO_4$ (2·25 g) in 50% acetone aq (150 ml), with mechanical stirring at 0° was added. The stirring was continued overnight, the precipitate filtered and the solution evaporated to dryness. The oily residue was dissolved in AcOEt and extracted with $NaHCO_3$aq, washed with water and evaporated to dryness. Crystallization from acetone–ether afforded VII as yellow plates (160 mg), m.p. 173–175°; $[\alpha]_D$ +35°, λ_{max}, 282 mμ; ε, 80; IR bands at 1745 cm^{-1} (acetyl groups) and at 1710 cm^{-1} (cycloheptanedione). (Found: C, 61·69; H, 7·12; O, 30·75. Calc. for $C_{16}H_{22}O_6$: C, 61·92; H, 7·15; O, 30·93%.)

The quinoxaline showed m.p. 209–210° (prisms from acetone–hexane); $[\alpha]_D$ −134°. (Found: C, 69·36; H, 6·09; O, 17·21; N, 7·47. Calc. for $C_{22}H_{26}O_4N_2$: C, 69·09; H, 6·85; O, 16·73; N, 7·33%.)

Lactone (XII). An intimate mixture of Ia (500 mg) and $KHSO_4$ (2·5 g) was heated under high vacuum. The ketone (XII) began to sublime at 130°; the mixture was heated at increasing temp until no more sublimate was produced (240°). Crystallization from acetone–hexane afforded plates m.p. 146°; $[\alpha]_D$ +175°; λ_{max}, 212 mμ; ε, 10800; IR bands at 1755 cm^{-1} (double strength) (cyclopentanone and α,β-unsaturated-γ-lactone) and at 1660 cm^{-1} (C=C double bond). (Found: C, 72·51; H, 8·22; O, 19·29. Calc. for $C_{15}H_{20}O_3$: C, 72·55; H, 8·12; O, 19·33%.)

Lactone (XVIII). A mixture of IVa (500 mg) and $KHSO_4$ (2 g) was treated as in the previous case. Crystallization from acetone–hexane yielded needles (85 mg), m.p. 166–169°. Undepressed on admixture with a sample of the product obtained by dehydration of XIX followed by hydrogenation.[3] The IR spectra were superimposable.

Hydrogenation of lactone (XII). A solution of XII (200 mg) in AcOEt (20 ml) was hydrogenated with 10% Pd–C (20 mg) until the uptake of H_2 ceased. The filtered solution was evaporated to dryness. Crystallization of the residue from acetone–hexane furnished brilliant plates of XIII (120 mg), m.p. 147–148°; $[\alpha]_D$ +128°; IR band with 2 peaks at 1760 cm^{-1} (γ-lactone) and at 1738 cm^{-1} (cyclopentanone). Rotatory dispersion (in dioxane); $[\alpha]_{400}$ +238°; $[\alpha]_{325}$ +1743°; $[\alpha]_{320}$ +2324°; $[\alpha]_{317\cdot5}$ +2392°; $[\alpha]_{315}$ +2208°. (Found: C, 71·76; H, 8·62; O, 19·27. Calc. for $C_{15}H_{22}O_3$: C, 71·79; H, 8·86; O, 19·35%.)

Baeyer-Villiger oxidation of the dihydrolactone (XIII). A solution of XIII (350 mg), *m*-chloroperbenzoic acid (600 mg) and *p*-toluenesulfonic acid (200 mg) was heated under reflux for 7 hr, washed with $NaHCO_3$aq, water and evaporated to dryness. The residue dissolved in benzene–hexane 1:1 was chromatographed on alumina (6 g). Crystallization from acetone–isopropylether yielded plates (200 mg) m.p. 169–173°; further crystallizations from acetone–isopropylether raised the m.p. to 184–187°; $[\alpha]_D$ +10°; IR bands at 1772 cm^{-1} (γ-lactone) and at 1725 cm^{-1} (six membered lactone). (Found: C, 67·79; H, 8·47; O, 24·17. Calc. for $C_{15}H_{22}O_4$: C, 67·64; H, 8·33; O, 24·03%.)

Cycloethyleneketal (XV). A mixture of XIII (1·05 g), benzene (50 ml), ethyleneglycol (15 ml) and *p*-toluenesulfonic acid (200 mg) was heated under reflux for 72 hr (water trap), cooled, washed, dried and the benzene removed. The residue was crystallized from acetone–hexane, yield 510 mg, m.p. 144–146°. The analytical sample of XV melted at 146–148°; $[\alpha]_D$ −16°; IR band at 1780 cm^{-1} (γ-lactone). (Found: C, 69·16; H, 8·75; O 21·72. Calc. for $C_{17}H_{26}O_4$: C, 69·36; H 8·90; O, 21·74%.)

LAH reduction of the cycloethyleneketal (XV). A solution of XV (600 mg) in THF (25 ml) was treated with LAH (1·1 g), heated under reflux for 2 hr, cooled, the excess hydride decomposed with AcOEt and 5 ml of water were added. The mixture was filtered, the precipitate washed with $CHCl_3$ and the combined filtrate and washings were dried and evaporated to dryness. Crystallization from acetone–pentane afforded XVI (510 mg), as prisms, m.p. 108–110°, further crystallizations raised the m.p. to 111°; $[\alpha]_D$ −26·5°; IR bands at 3250 cm^{-1} with a shoulder at 3550 cm^{-1} (hydroxyl groups). (Found: C, 68·67; H, 10·04; O, 21·51. Calc. for $C_{17}H_{30}O_4$: C, 68·42; H, 10·13; O, 21·45%.)

Hydrolysis of the cycloethyleneketal (XVI). The XVI (230 mg) was dissolved in MeOH (5 ml) containing conc HCl (0·5 ml) and water (1·5 ml), the solution was left at room temp for 2 hr, heated then for 10 min under reflux, diluted with water and extracted with AcOEt. The organic layer was

washed with $NaHCO_3$aq, water, dried and evaporated to dryness. Crystallization of the residue from acetone–hexane yielded XVII (200 mg), as needles, m.p. 166°; $[\alpha]_D$ +117°; λ_{max}, 291 mμ; ε, 43; bands at 3680 and 3410 cm^{-1} (hydroxyl groups), and at 1740 cm^{-1} (cyclopentanone). (Found: C, 70·58; H, 10·12; O, 19·03. Calc. for $C_{15}H_{26}O_3$: C, 70·82; H, 10·30; O, 18·88%.)

Deuterium exchange in the ketone (XVI). A solution of Na (50 mg) in MeOD (3·5 ml) was prepared. XVI (50 mg) was dissolved in the above solution and left for 4 days at room temp. The volatile components of the mixture were evaporated *in vacuo* and the NMR spectrum was determined with the residue dissolved in $CDCl_3$.

Treatment of cumanin dimesylate (Id) with NaI. A solution of Id (2 g) in AcOH (30 ml), containing NaI (3 g) was heated under reflux for 1·5 hr, diluted with water and extracted with AcOEt. The organic layer was washed with 5% NaOH, water, dried, evaporated to dryness and the residue dissolved in hexane chromatographed on alumina (20 g). Crystallization of XXI from hexane, furnished prisms (720 mg) m.p. 91–93°, $[\alpha]_D$ +126°; λ_{max}, 211 mμ; ε, 10100; IR bands at 1760 and 1660 cm^{-1} (α,β-unsaturated-γ-lactone). (Found: C, 77·42; H, 8·70; O, 13·59. Calc. for $C_{15}H_{20}O_2$: C, 77·55; H, 8·68; O, 13·77%.)

Epoxide (XXIV). A solution of XXI (300 mg) and *m*-chloroperbenzoic acid (250 mg) in $CHCl_3$ (8 ml) was heated under reflux for 2 hr, diluted with ether, washed with $NaHCO_3$aq, water, dried and evaporated to dryness. Crystallization of the residue from ether–hexane yielded plates (250 mg), m.p. 125–128°; $[\alpha]_D$ +85·5°; λ_{max}, 213 mμ; ϵ, 9800; IR bands at 1760 and 1660 cm^{-1} (α,β-unsaturated-γ-lactone). (Found: C, 72·56; H, 8·27; O, 19·62. Calc. for $C_{15}H_{20}O_3$: C, 72·55; H, 8·12; O, 19·33%.)

Epicumanin acetonide (XXII). A solution of XXI (457 mg) in ether (40 ml) was treated with OsO_4 (0·5 g), left at room temp overnight and diluted with MeOH (30 ml). A stream of H_2S was passed for 15 min, left then at room temp for 30 min, filtered and evaporated to dryness *in vacuo*. The residue was dissolved in acetone (10 ml) containing 1 drop of conc HCl, heated under reflux for 15 min, evaporated *in vacuo*, dissolved in benzene–hexane 1:3 and chromatographed on alumina. Crystallization from ether–hexane yielded prisms (265 mg), m.p. 97°, $[\alpha]_D$ +20°; λ_{max} 214 mμ; ε, 9500; IR bands at 1760 and 1660 cm^{-1} (α,β-unsaturated-γ-lactone). (Found: C, 70·29; H, 8·68; O, 20·76; Calc. for $C_{18}H_{26}O_4$: C, 70·56; H, 8·55; O, 20·89%.)

Epicumanin (XXIII). A solution of XXIII (160 mg) in MeOH (6 ml), water (2 ml) and 3 drops conc HCl was heated under reflux for 15 min, diluted with water and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to dryness. Crystallization from ether–hexane afforded prisms (80 mg), m.p. 120–123°; $[\alpha]_D$ +57°; λ_{max} 214 mμ; ε, 9900; IR bands at 3500 cm^{-1} (hydroxyl groups), at 1750 and 1660 cm^{-1} (α,β-unsaturated-γ-lactone). (Found: C, 67·54; H, 8·13; O, 24·17. Calc for $C_{15}H_{22}O_4$: C, 67·64; H, 8·33; O, 24·03%.)

The sulfite crystallized from acetone–hexane as prisms m.p. 154°, $[\alpha]_D$ +15·5°; λ_{max} 212 mμ; ε, 10100; IR bands at 1755 and 1660 cm^{-1} (α,β-unsaturated-γ-lactone). (Found: C, 57·82; H, 6·66; O, 25·81; S, 10·03. Calc. for $C_{15}H_{20}O_5S$: C, 57·67; H, 6·45; O, 25·61; S, 10·26%.)