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THE CONSTITUTIONS OF THE CUCURBITACINS

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THE cucurbitacins are an interesting group of bitter principles found in the *Cucurbitaceae*.[1] A constitution (I) was recently proposed[2] for cucurbitacin E. The related cucurbitacin B may be represented as in (II, R = side chain). Cucurbitacins B, D, E and I have all been correlated previously.[3] The position of the ring C ketone group at C_{11} or C_{12} has not hitherto been established. We wish to present proof that the ketone is at C_{11}, to provide independent evidence for the constitution of cucurbitacin B and to propose constitutions for the biogenetically related[1] cucurbitaeins A and C.

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[1] P.R. Enslin, J.M. Hugo, K.B. Norton and D.E.A. Rivett, *J. Chem. Soc.* 4779 (1960); and references there cited.

[2] D. Lavie, Y. Shvo, O.R. Gottlieb and E. Glotter, *Tetrahedron Letters* No. 18, 615 (1961).

[3] D. Lavie, Y. Shvo, D. Willner, P.R. Enslin, J.M. Hugo and K.B. Norton, *Chem. and Ind.* 951 (1959).

The A-nor-ketone[4] (III) from cucurbitacin B affords the tetraketone (IV), m.p. 253 - 258°, $[\alpha]_D$ + 98°, λ_{max} 243 mμ (ε = 11,400), on chromic acid oxidation. The latter was rapidly autoxidised at room temperature in alkaline solution to the diene-dione[5] (V), m.p. 176 - 179°, $[\alpha]_D$ + 377°, λ_{max} 284 mμ (ε = 22,800). The diene-dione character of this compound was confirmed by zinc dust reduction at room temperature (formation of the analogue of (VIII) (see below), m.p. 186 - 191°, $[\alpha]_D$ + 190°, λ_{max} 284 mμ (ε = 1140)) and reoxidation back to starting material. A similar series of compounds was prepared containing the 16(17)-ethylenic linkage. The diene-dione (V; 16(17)-unsaturated) had m.p. 210 - 211°, $[\alpha]_D$ + 438°, $\lambda\lambda_{max}$ 239 and 284 mμ (ε = 13,400 and 21,300 respectively).

Oxidation of cucurbitacin B diacetate with chromic acid affords[3,6] cucurbitone B (VI). With methanolic hydrochloric acid this is converted into another diene-dione[7] (VII), m.p. 236 - 237°, $[\alpha]_D$ + 506°, $\lambda\lambda_{max}$ 238 and 288 mμ (ε = 12,800 and 19,800 respectively). Reduction at room temperature with zinc dust and acetic acid to (VIII), m.p. 222 - 223°, $[\alpha]_D$ + 145°, λ_{max} 238 mμ (ε = 9,400), from which the diene-dione could be regenerated by alkaline autoxidation, confirmed its formulation.

Proof of the position of the unreactive 11-ketone was secured by investigations with cucurbitacins A[1] and C[8]. The nuclear magnetic reson-

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[4] D. Lavie and Y. Shvo, Chem. and Ind. 403 (1960).

[5] This compound is probably identical with a substance obtained by a different route by Lavie and his collaborators.[2]

[6] W. Schlegel, A. Melera and C.R. Noller, J. Org. Chem. 26, 1206 (1961).

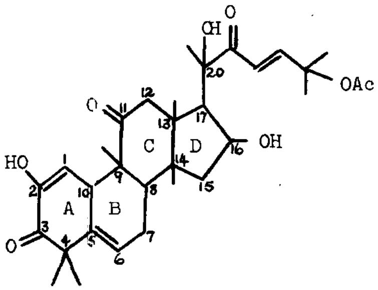
[7] This compound was first prepared by Professor C.R. Noller and his collaborators. We thank Professor Noller cordially for a reference specimen. For analogous rearrangements see R.L. Clarke, J. Amer. Chem. Soc. 82, 4629 (1960).

[8] P.R. Enslin, J.M. Hugo, K.B. Norton and D.E.A. Rivett, J. Chem. Soc. 4787 (1960).

ance spectra of derivatives (see further below) consistently showed only four quaternary methyl groups, whilst acetylated derivatives had a quaternary acetoxymethyl group. Since cucurbitacin A has one more acetylateable hydroxyl group than B, the substitution of this hydroxyl group into one of the (five) quaternary nuclear methyl groups of cucurbitacin B was inferred.

The constitution (IX, R = side chain) for cucurbitacin A was deduced from the following evidence. Cucurbitone A^1 (X) was enol-acetylated with sodium acetate-acetic anhydride under reflux to the enol-acetate (XI), m.p. 88 - 90°, $[\alpha]_D + 594°$, $\lambda\lambda_{max}$ 238 and 357 mμ (ε = 14,400 and 9,200 respectively). With 0.1% aqueous (60%) perchloric acid in acetic acid at room temperature this furnished another diene-dione (XII), m.p. 223 - 224°, $[\alpha]_D + 487°$, $\lambda\lambda_{max}$ 238 and 289 mμ (ε = 13,600 and 19,600 respectively), very similar in its properties to the diene-dione (VII) from cucurbitone B. Now when dihydrocucurbitone A^1 was treated with aqueous alkali under nitrogen it furnished formaldehyde and a nor-compound (XIV), m.p. 242 - 247°, $[\alpha]_D + 187°$, λ_{max} 240 mμ (ε = 9,400) which retained four quaternary methyl groups in its nuclear magnetic resonance spectrum. The ketone in ring C, not that in ring A, must therefore be responsible for the reversed aldol reaction. The diene-dione (XII) behaved similarly and with dilute alkali afforded formaldehyde and the phenolic ketone (XIII), m.p. 248 - 252°, $[\alpha]_D - 31°$, $\lambda\lambda_{max}$ 220, 232, 270 (shoulder) and 337 mμ (ε = 16,300, 14,800, 5,700 and 2,300 respectively).

Cucurbitacin C[8] has three acetylateable hydroxyl groups, four nuclear quaternary methyl groups and an inert ketone group in ring C. Cucurbitacin C is formulated as (XV; R = side chain) on the basis of the following evidence. Acetylated derivatives show the nuclear magnetic resonance bands for a quaternary acetoxymethyl group. This must be α- to a ketone group because cucurbitacin C, like A but unlike B, readily affords formaldehyde with 1N-ethanolic potassium hydroxide at room temperature overnight. Hexa-



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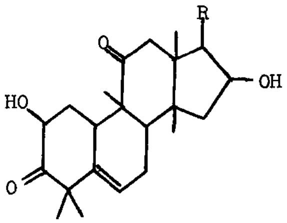

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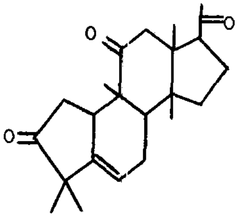

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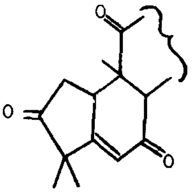

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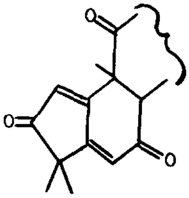

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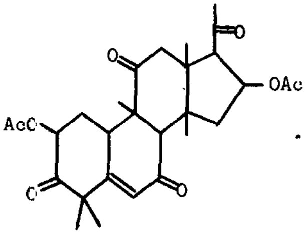

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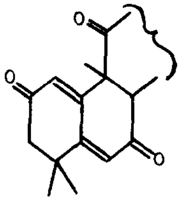

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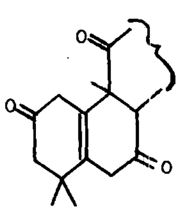

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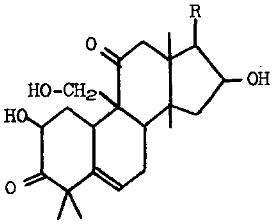

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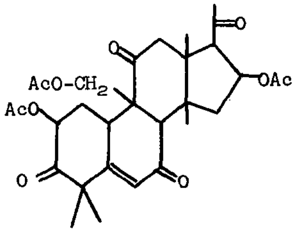

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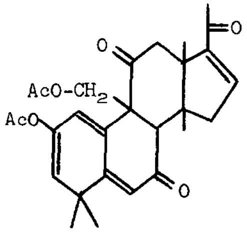

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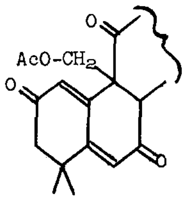

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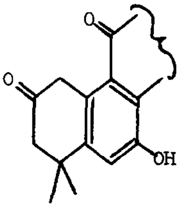

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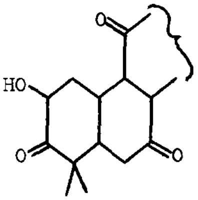

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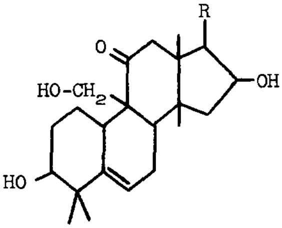

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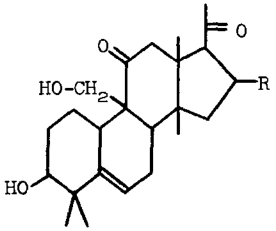

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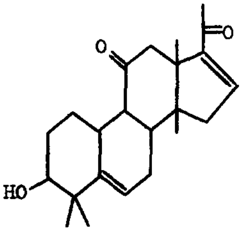

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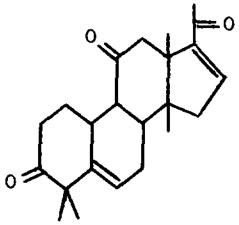

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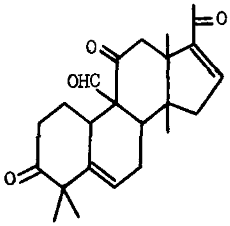

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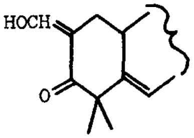

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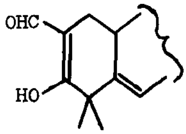

XXI

norcucurbitacin C[8] (XVI; R = OH) and the derived 16-desoxyketone (XVI; R = H) both lost formaldehyde on treatment with base to give heptanor-compounds, (XVII), m.p. 252 - 258°, $[\alpha]_D$ - 191°, λ_{max} 239 mμ (ε = 9,200) and (XVII; 16(17)-saturated), m.p. 197 - 201°, $[\alpha]_D$ - 75° respectively). Chromic acid oxidation gave the triketones (XVIII), m.p. 247 - 250°, $[\alpha]_D$ - 243°, λ_{max} 239 mμ (ε = 9,400) and (XVIII; 16(17)-saturated), m.p. 238 - 243°, $[\alpha]_D$ - 116°. All these compounds had four quaternary methyl groups (nuclear magnetic resonance spectra) and hence the ketone responsible for the loss of formaldehyde must be in ring C (at C_{11}). Compounds (XVI; R = H), (XVII) and (XVII, 16(17)-saturated) gave weak Zimmerman tests. Compounds (XVIII) and (XVIII; 16(17-saturated) gave strongly positive tests. The secondary hydroxyl group must therefore[9] be at C_3.

Oxidation of compounds (XVI; R = H) (XVI; R = H; 16(17)-unsaturated) gave triketo-aldehydes (XIX), m.p. 205 - 207°, $[\alpha]_D$ - 2° (c 1.0), λ_{max} 239 mμ (ε = 9,300) and (XIX; 16(17)-saturated), m.p. 202 - 206°, $[\alpha]_D$ + 100°. Although these compounds could not be enolised under acidic or enol-acetylating conditions (XIX) readily rearranged in alkaline solution to give two isomeric enols, (XX) and (XXI). These compounds had m.p. 214 - 219°, $[\alpha]_D$ - 247°, $\lambda\lambda_{max}$ 241 and 286 mμ (ε = 10,600 and 8,700 respectively) and m.p. 269 - 275°, $[\alpha]_D$ - 245°, $\lambda\lambda_{max}$ 242 and 277 mμ (ε = 10,900 and 11,200 respectively) and showed the appropriate changes in spectra with alkali. This intramolecular formyl transfer is only possible if the ketone group in ring C be at C_{11} and if the B/C ring fusion be *cis*. We shall discuss the full stereochemistry of the cucurbitacins later.

All ultraviolet spectra are in ethanol, all rotations in chloroform with C = approx. 1%. All compounds had the appropriate analytical data

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[9] D.H.R. Barton and P. de Mayo, *J. Chem. Soc.* 887 (1954).

and give infrared spectra in full accord with the assigned structures.

The nuclear magnetic resonance results have been briefly referred to above.[10] We shall give full details later but the following is a brief exposition of the more important features of the spectra.

Proton magnetic resonance spectra at 60 mc/sec were obtained with a Varian DP-60 spectrometer on samples in solution in degassed $CDCl_3$ containing 1/2% tetramethylsilane as a reference. Chemical shifts are reported on Tiers'[11] 'τ-scale.' The most significant first-order assignments in a number of spectra are summarized below:[12]

A-series

Cucurbitone A (X): olefinic proton (C-6) — τ = 3.75; 2 x secondary ester protons — m., τ = 4.37, m., τ = 4.50; $-CH_2-OAc$ — n.e.q., τ = 5.59, 6.02, $|J|$ = 11.0 cps; $-COCH_3$ + 3x -OAc — τ = 7.83, 7.87, 8.02 and 8.10.

Enol-acetate (XI): olefinic protons (on C-16) — m., τ = 3.20, (on C-1) — t., τ = 4.10, (on C-3) — d., τ = 4.35, (on C-6) — d., τ = 3.75, $|J_{1,3}| \sim |J_{3,6}| \sim$ 2.0 cps; $-CH_2OAc$ — n.e.q., τ = 5.49, 6.04, $|J|$ = 10.8 cps; $-COCH_3$ + 2x - OAc — τ = 7.70, 7.83, 8.02; 4x quaternary methyl groups — τ = 8.66, 8.71, 8.89 (area = 6H).

Dienedione (XII): olefinic protons (on C-16) — m., τ = 3.20, (on C-1 and C-6) — n.e.q., τ = 3.62, 3.97, $|J|$ = 2.0 cps; $-CH_2OAc$ — n.e.q., τ = 5.54, 5.88, $|J|$ = 11.2 cps; $-CH_2$ (C-3) — τ = 7.50; $-COCH_3$ — τ = 7.68;

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[10] We thank cordially Dr. J.W. Lown and Mr. R.G. Foster (Imperial College) for some preliminary nuclear magnetic resonance data.

[11] G.V.D. Tiers, J. Phys. Chem. 62, 1151 (1958).

[12] The following abbreviations are used: n.e.q. = non-equivalence quartet; m. = unresolved or not completely analyzed multiplet; d. = doublet; t. = triplet.

-OAc — τ = 7.99; 4x quaternary methyl groups — τ = 8.62, 8.74, 8.89 (area = 6H).

C - series

Cucurbitone C: olefinic proton (C-6) — d., τ = 3.73, $|J_{6,10}|$ = 2.0 cps; secondary ester proton (C-16) — t., τ = 4.32, $|J_{15,16}|$ = 7.2 cps; secondary ester proton (C-3) — m., τ = 5.35; $-CH_2OAc$ — n.e.q., τ = 5.52, 5.98, $|J|$ = 11.4 cps; $-COCH_3$ + 3x - OAc — τ = 7.82, 7.92, 8.00 and 8.08; 4x quaternary methyl groups: τ = 8.72, 8.83 (area = 6H), 9.13.

Triketomonoaldehyde (XIX): aldehyde proton — m.,[13] τ = 0.10; olefinic proton (C-16) — t., τ = 3.25, $|J|$ = 2.5 cps; olefinic proton (C-6) — m., τ = 4.20; $-COCH_3$ — τ = 7.69; 4x quaternary methyl groups — τ = 8.75, 8.79, 8.89 and 9.02.

Anhydroheptanorcucurbitacin C (XVII): olefinic proton (C-16) — t., = 3.20, $|J_{15,16}|$ = 2.5 cps; olefinic proton (C-6) — m., τ = 4.45; $-COCH_3$ — τ = 7.68; 4x quaternary methyl groups — τ = 8.89, 8.93, 8.97 and 9.08.

Triketone (XVIII): olefinic proton (C-16) — t., τ = 3.20, $|J_{15,16}|$ = 2.4 cps; olefinic proton (C-6) — m., τ = 4.43; $-COCH_3$ — τ = 7.72; 4x quaternary methyl groups — τ = 8.72, 8.81, 8.88 and 9.08.

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[13] Small splitting, probably long range: cf.
D.R. Davis, R.P. Lutz, and J.D. Roberts, J. Am. Chem. Soc. **83**, 246 (1961).