was treated with 35 g. (0.343 mole) of acetic anhydride, added portionwise while vigorously shaking and cooling to keep the temperature below 40°. Precipitation was completed by adding 50 ml. of 6*N* hydrochloric acid. The solids were removed by filtration, dried and taken up in 500 ml. of hot methanol. After filtering off inorganic salts and cooling, 5.8 g. of yellow needles were obtained, m.p. 216–217.5°; concentration of their filtrate to 50 ml. yielded an additional 1.9 g. Recrystallization of these combined crops from methanol gave 6.7 g. (75%) of small yellow needles, m.p. 218–219°.

Anal. Calcd. for $C_{11}H_{10}O_3S$: C, 59.44; H, 4.53; S, 14.43. Found: C, 59.68; H, 4.46; S, 14.16.

p-Thiomyristoxycinnamic acid. p-Thiolcinnamic acid, 11.8 g. (0.066 mole) and 1 g. of potassium hydroxide were dissolved in 200 ml. of dry pyridine and the reaction mixture was stirred for 1 hr. Myristoyl chloride, 22.7 g. (0.092 mole) was added dropwise during 1 hr. below 30°, and stirring was continued for 3 additional hr. The solids obtained upon dilution with 500 ml. of water and 100 ml. of 6*N* hydrochloric acid were removed by filtration and then shaken with 200 ml. methanol to remove excess myristic acid. The residue was recrystallized from benzene with the aid of charcoal, 6.8 g. (27%) light yellow plates, m.p. 166–167°.

Anal. Calcd. for $C_{23}H_{34}O_3S$: C, 70.70; H, 8.77; S, 8.21. Found: C, 70.55; H, 8.88; S, 8.00.

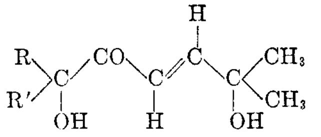
DEPARTMENT OF CHEMISTRY
POLYTECHNIC INSTITUTE OF BROOKLYN
BROOKLYN 1, N. Y.

Structure of the Side Chain of Cucurbitacin B

A. MELERA, W. SCHLEGEL, AND C. R. NOLLER

Received February 2, 1959

In two recent Communications,[1,2] Lavie and his co-workers have proposed the partial structure I

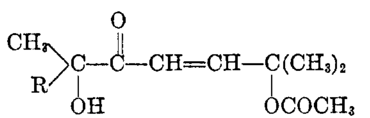


I

RCH(CH_3)COCH=CHC(OH)(CH_3)$_2$

II

for elatericin A and α-elaterin. Structure II was proposed by Rivett and Enslin[3] for elaterin and for cucurbitacins A and C. Still more recently[4] partial structure III has been proposed for elaterin



III

and cucurbitacins A, B, and C. From our work we also have concluded that curcurbitacin B (formerly called fabacein II[5]) has structure III, and we wish to report results which confirm this structure and which clarify the results of catalytic hydrogenation.

Cucurbitacin B has been assigned the molecular formula $C_{32}H_{48}O_8$[6] and is a monoacetate, containing an α,β-unsaturated carbonyl group.[5,7] Analyses of an apparently identical product isolated from the juice of *Echinocystis fabacea* were reported[5,8] to agree with the formulas $C_{30}H_{44-46}O_8$ (Calcd. for $C_{30}H_{44}O_8$: C, 67.64; H, 8.33; for $C_{30}H_{46}O_8$: C, 67.39; H, 8.67. Found: C, 67.38; H, 8.40; average of 12 analyses). However the formulas $C_{32}H_{46-48}O_8 \cdot 0.5\,H_2O$ (Calcd.: C, 67.70; H, 8.34; or C, 67.46; H, 8.67) also are equally satisfactory and agree better with the analyses of derived products.

When cucurbitacin B was hydrogenated in 95% ethanol using 10% palladium on carbon as catalyst, from 1.3 to 1.6 moles of hydrogen was absorbed.[8] The resulting solution contained acetic acid, and titration indicated that 0.3 to 0.6 mole of acetic acid was formed. Evidently hydrogenolysis as well as hydrogenation had occurred. The paper chromatogram of the hydrogenated material showed that two products were present which could be separated readily. One product is dihydrocucurbitacin B (VI) (Calcd. for $C_{32}H_{48}O_8$: C, 68.54; H, 8.63; for $C_{32}H_{50}O_8$: C, 68.30; H, 8.96. Found: C, 68.38; H, 8.80); m.p. 163–164° from acetone-hexane; $[\alpha]_D^{25}$ +57° (c = 0.91 in $CHCl_3$); UV (ethanol) λ_{max} 282 mμ, log ε 2.32; IR ($CHCl_3$): 2.92 (OH), 5.79 w(AcO), 5.85 sh (C=O), 5.89 (C=O), 8.10 (AcO). The other product is dihydrodeacetoxycucurbitacin B (VII) (Calcd. for $C_{30}H_{46}O_6$: C, 71.68; H, 9.22; for $C_{30}H_{48}O_6$: C, 71.39; H, 9.59. Found: C, 71.59; H, 9.37); m.p. 208–210° from ether; $[\alpha]_D^{25}$ +57° (c = 0.93 in $CHCl_3$); UV (ethanol) λ_{max} 279 mμ, log ε 2.46; IR ($CHCl_3$): 2.92 (OH), 5.85 sh (C=O), 5.90 (C=O). In both products the α,β-unsaturated carbonyl system present in cucurbitacin B[5,7] has disappeared.

When cucurbitacin B in acetic acid was treated with zinc dust for 4 hr. at room temperature, a new product was obtained. The ultraviolet and infrared spectra showed that the α,β-unsaturated carbonyl system had disappeared. Although cucurbitacin B gave only a pale yellow color with tetranitromethane, the new compound gave an orange color, indicating the production of a highly alkylated isolated double bond. Analysis showed that the new

---

[1] D. Lavie and Y. Shvo, *Proc. Chem. Soc.*, 220 (1958).

[2] D. Lavie, Y. Shvo, and D. Willner, *Chem. and Ind.*, 1361 (1958).

[3] D. E. A. Rivett and P. R. Enslin, *Proc. Chem. Soc.*, 1958, in press. We wish to thank Dr. Enslin for sending us a copy of this Communication.

[4] Private communication from Dr. P. R. Enslin summarizing a note sent to Chemistry and Industry in December, 1958.

[5] W. O. Eisenhut and C. R. Noller, Abstracts of paper presented at the San Francisco meeting of the American Chemical Society, April 1958.

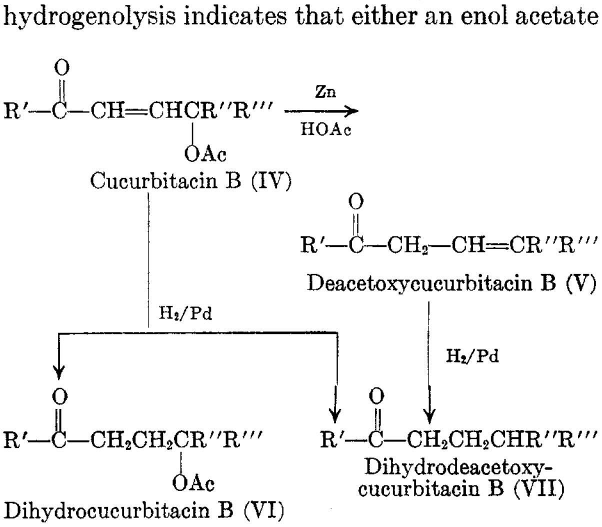
[6] D. E. A. Rivett and F. H. Herbstein, *Chemistry and Industry*, 393 (1957).

[7] P. R. Enslin, S. Rehm, and D. E. A. Rivett, *J. Sci. Food Agr.*, **8**, 673 (1957).

[8] W. O. Eisenhut and C. R. Noller, *J. Org. Chem.*, **23**, 1984 (1958).

compound was a deacetoxycucurbitacin B (V) (Calcd. for $C_{30}H_{44}O_6$: C, 71.97; H, 8.86; for $C_{30}H_{46}O_6$: C, 71.68; H, 9.22. Found: C, 71.72; H, 9.05); m.p. 178–179°; $[\alpha]_D^{25}$ +78° (c = 0.76 in ethanol); UV (ethanol) λ_{max} 292 mμ, log ϵ 2.66; IR ($CHCl_3$) 2.91 (OH), 5.87 (C=O), 5.90 (C=O). Thus, by this reaction not only has the acetoxy group been removed, but the double bond no longer is in conjugation with the carbonyl group. Hydrogenation of this product converted it quantitatively into a single compound which was identical in all respects with dihydrodeacetoxycucurbitacin B (VII).

These results can be explained by partial formula IV for cucurbitacin B. The easy loss of acetic acid from curcurbitacin B by mild saponification[5] or hydrogenolysis indicates that either an enol acetate or allyl acetate grouping is present. The former is excluded by the lack of absorption around 5.68 μ, which is typical of enol acetates. It should be noted that hydrogenation of cucurbitacin B stops completely when considerably less than two moles of hydrogen is absorbed. Thus hydrogenolysis of some molecules takes place previous to hydrogenation of the double bond, and hydrogenation of the double bond without hydrogenolysis occurs simultaneously (VII and VI). Once the double bond is hydrogenated, hydrogenolysis no longer occurs. Facile deacylation of cucurbitacin by reduction with zinc and migration of the double bond out of conjugation with the carbonyl group to give deacetoxycucurbitacin B (V) is analogous to the easy removal by zinc reduction of a hydroxyl or acetoxyl group α to a carbonyl group and undoubtedly occurs by a similar mechanism.[7]



$R'{-}\overset{O}{\overset{\|}{C}}{-}\underset{OAc}{\underset{|}{C}}H{-}CH{=}CHCR''R'''$
Cucurbitacin B (IV)

$R'{-}\overset{O}{\overset{\|}{C}}{-}CH_2{-}CH{=}CR''R'''$
Deacetoxycucurbitacin B (V)

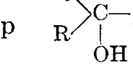
$R'{-}\overset{O}{\overset{\|}{C}}{-}\underset{OAc}{\underset{|}{C}}H{-}CH_2CH_2CR''R'''$
Dihydrocucurbitacin B (VI)

$R'{-}\overset{O}{\overset{\|}{C}}{-}CH_2CH_2CHR''R'''$
Dihydrodeacetoxycucurbitacin B (VII)

Oxidation of dihydrodeacetoxycucurbitacin B (VII) in aqueous dioxane with sodium periodate gave about equal amounts of neutral and acidic products. The latter were converted to the methyl esters with diazomethane and steam distilled. Gas chromatography using a Carbowax-impregnated column identified the chief component of the volatile esters as methyl isocaproate. Methyl isocaproate was obtained also when alkaline hydrogen peroxide was used as an oxidizing agent. Thus the carbon skeleton of isocaproic acid is present as a side chain. The presence of a 1,2-diketo or α-hydroxy keto grouping at the sixth and seventh carbon atoms of the side chain also is indicated.

Acetylation of cucurbitacin B and of its hydrogenation products with acetic anhydride in pyridine gave only amorphous compounds which appeared to be homogeneous on paper. They were purified for analysis by selecting a narrow cut when passed through a chromatographic column. Cucurbitacin B gave a tetraacetate (VIII) (Calcd. for $C_{38}H_{52}O_{11}$: C, 66.65; H, 7.65; O, 25.70; for $C_{38}H_{54}O_{11}$: C, 66.45; H, 7.92; O, 25.63. Found: C, 66.42; H, 7.83; O, 25.38); m.p. 125–130°; $[\alpha]_D^{25}$ +4.4 (c = 0.95 in $CHCl_3$); UV (ethanol) λ_{max} 228 mμ, log ϵ 4.33; IR ($CHCl_3$) 2.90 (OH), 5.80 (AcO), 5.92 (C=O), 6.13 (C=C), 8.10 (AcO). Thus cucurbitacin B contains three acetylatable hydroxyl groups and at least one nonacetylatable hydroxyl group which probably is tertiary.

Dihydrocucurbitacin B also gave a tetraacetate (IX) (Calcd. for $C_{38}H_{54}O_{11}$: C, 66.45; H, 7.92; for $C_{38}H_{56}O_{11}$: C, 66.26; H, 8.19. Found: C, 66.52; H, 8.16); m.p. 120–125°; $[\alpha]_D^{25}$ −16.3 (c = 0.92 in $CHCl_3$); UV (ethanol) λ_{max} 286 mμ, log ϵ 2.28; IR ($CHCl_3$) 2.90 (OH), 5.80 (AcO), 5.90 sh (C=O), 8.10 (AcO). As expected, dihydrodeacetoxycucurbitacin B (VII) gave a triacetate (X). (Calcd. for $C_{36}H_{52}O_9$: C, 68.76; H, 8.34; for $C_{36}H_{54}O_9$: C, 68.54; H, 8.63. Found: C, 68.55; H, 8.46); m.p. ~130°; $[\alpha]_D^{25}$ −20.4° (c = 1.37 in $CHCl_3$); UV (ethanol) λ_{max} 282 mμ, log ϵ 2.44; IR ($CHCl_3$) 2.90 (OH), 5.80 (AcO), 5.90 (C=O), 8.10 (AcO).

Oxidation of all three acetates with chromium trioxide in acetic acid at room temperature gave a mixture of volatile acids and a large neutral fraction. From 0.5 to 1.5 moles of carbon dioxide also was evolved. Examination of the volatile acids by paper chromatography and of their methyl esters by gas chromatography showed that the acetate of dihydrodeacetoxycucurbitacin B (X) gave chiefly isocaproic acid. The acetate of cucurbitacin B (VIII), however, gave chiefly β,β-dimethylacrylic acid. These facts together with the observations concerning the hydrogenation products of cucurbitacin B, prove that its acetoxy group must be in the side chain and that R″ and R‴ are methyl groups. The neutral products of the oxidations appear to be methyl ketones (positive iodoform reaction), which, coupled with the results of periodate oxidation, indicates that R′ in formula IV may be replaced by the group  $\overset{CH_3}{\underset{R}{}}\!\!>\!\underset{OH}{\underset{|}{C}}{-}$, leading to the partial formula III for cucurbitacin B. The formation of β,β-dimethylacrylic acid would

---

(7) *Cf.* R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4225 (1952).

thus involve an allylic shift of the acetoxyl group. An allylic shift of a hydroxyl group previously has been postulated for the formation of senecioaldehyde by oxidation of cucurbitacin B.[3]

The neutral fractions from the oxidations of all of the acetylated compounds appear to be identical and to consist of a mixture of at least six substances. The component present in largest quantity, which for the present is designated as ketone A, appears to have the formula $C_{28}H_{38}O_8$ (Calcd.: C, 66.91; H, 7.62. Found: C, 67.10; H, 7.47); m.p. 219–221° from acetone-hexane; $[\alpha]_D^{25}$ +86.6 (c = 0.96 in $CHCl_3$); UV (ethanol): λ_{max} 243 mμ, log ϵ 4.1; 335 mμ, log ϵ 2.0; IR ($CHCl_3$) 5.77 (AcO), 5.85 (C=O), 6.00, 6.15 (C=C—C=O), 8.12 (AcO). Analyses of the component present in next largest amount, designated as ketone B, indicate the formula $C_{28}H_{36}O_8$ (Calcd.: C, 67.18; H, 7.25; Found: C, 67.09; H, 7.15); m.p. 154–157° from acetone hexane; $[\alpha]_D^{25}$ −84.9 (c = 1.14 in $CHCl_3$); UV (ethanol) λ_{max} 295 mμ, log ϵ 2.37; IR ($CHCl_3$) 5.78 (AcO), 5.91 (C=O), 8.10 (AcO). Both compounds gave a positive iodoform reaction, indicating the possible presence of methyl ketone groups.

The remaining four neutral products, which are present in smaller amounts, have been isolated in a fairly pure state but have not yet been further investigated. Inasmuch as they do not appear when the oxidations are carried out for longer periods, it is possible that they are intermediates in the formation of ketones A and B.

Enslin and Rivett report the isolation of two methyl ketones designated as cucurbitones A and C from the chromic acid oxidation products of the diacetates of cucurbitacins A and C.[3] Their analyses and molecular weight determination on cucurbitone A, m.p. 210°, $[\alpha]_D$ +100° ($CHCl_3$), λ_{max} 245 mμ (log ϵ 4.04), correspond to the molecular formula $C_{30}H_{38}O_{10}$. Their analyses of cucurbitone C, m.p. 246–247°, $[\alpha]_D$ +153 ($CHCl_3$) λ_{max} 241 (log ϵ 4.1), support the molecular formula $C_{30}H_{40}O_9$. The physical constants of our methyl ketone A and cucurbitone A are similar, but the analyses are very different. The other important product of our oxidations, ketone B, is certainly different than any previously reported.

Acknowledgment. This investigation was supported (in part) by a research grant, RG-5076, from the National Institutes of Health, U. S. Public Health Service.

DEPARTMENT OF CHEMISTRY
AND CHEMICAL ENGINEERING
STANFORD UNIVERSITY
STANFORD, CALIF.