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STRUCTURE OF VERBENALIN

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VERBENALIN ($C_{17}H_{24}O_{10}$) m.p. 182-183° $[\alpha]_D^{25}$ -173° (H_2O), a glycoside isolated from Verbena officinalis has been the object of several chemical studies and all previous investigators agree that it is a β-D-glucoside. Although the presence of one keto group[1,2] and only one carbon-carbon double bond[1] seemed established, a structure containing a furan ring has been proposed.[3] There was further disagreement concerning the functionalities of the remaining oxygen atoms. One group[3] considered verbenalin to be a methyl ester while others[4,5] preferred a methoxylactone system which was incorporated into the most recent proposal (I)[5]. Catalytic reduction of verbenalin over platinized Raney-Nickel

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1 J. Cheymol, Bull. Soc. Chim. 5, 633, 642 (1938).

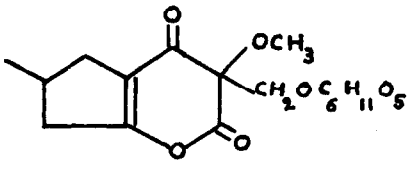
2 W. Hoffmann, Arch. Pharm. 281, 269 (1943).

3 J. Asano, Y. Ueno and Y. Tamaki, J. Pharm. Soc. Japan 62, 7 (1942).

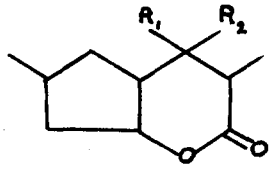
4 A. Chatterjee and L. M. Parks, J. Am. Chem. Soc. 71, 2249 (1949).

5 M. Cohn, E. Vis and P. Karrer, Helv. Chim. Acta 37, 790 (1954); P. Karrer and H. Salomon, Helv. Chim. Acta 29, 1544 (1946).

yields tetrahydroverbenalin m.p. 196-197° [Lit.[5] m.p. 195-196°] $\nu_{max.}^{KBr}$ 3300, 1713 cm^{-1} and desoxyverbanol ($C_{10}H_{16}O_3$) m.p. 139-140° [Lit.[5] m.p. 137-138°], $\nu_{max}^{CHCl_3}$ 3550, 1745 cm^{-1}, two C-Me groups (Kuhn-Roth). We have now oxidized desoxyverbanol with chromium trioxide in pyridine solution to desoxyverbanone m.p. 113-114°, $[\alpha]_D^{26}$ +57° ($CHCl_3$), $\nu_{max}^{CHCl_3}$ 1745 cm^{-1}, λ_{max}^{EtOH} 295 mμ ε 17. The negative ferric test and the infrared spectrum of this substance are inconsistent with III and consequently structures II and I proposed for desoxyverbanol and verbenalin, respectively require modification.



I



II R_1=OH; R_2=H

III R_1=R_2=O=

We assumed that verbenalin, the nepetalactones[6] and the iridomyrmecins[7] contain a common carbon skeleton and this was proved as follows. Desulfurization of desoxyverbanone-ethylene-thioketal m.p. 191-192°, $\nu_{max}^{CHCl_3}$ 1740 cm^{-1} with Raney-Nickel yielded

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[6] R. B. Bates, E. J. Eisenbraun and S. M. McElvain, J. Am. Chem. Soc. 80, 3420 (1958) and earlier papers cited.

[7] G. W. K. Cavill and D. L. Ford, Austräl. J. Chem. 13, 296 (1960) and references given there.

iridomyrmecin (IV) $[\alpha]_D^{26}$ +236° ($CHCl_3$) [Lit. [8,9] $[\alpha]_D^{20}$ +210° (CCl_4)] m.p. 60.5°-61.5° pure and mixed with an authentic specimen[10]. An infrared spectrum in nujol was identical with that of natural iridomyrmecin[9]. We have repeated the previously described hydrolysis of verbenalin with barium hydroxide and obtained verbenalinic acid now formulated as X m.p. 212-214° [Lit.[1] 210-212°] ν_{max}^{KBr} 1735, 1710, 1630 cm^{-1}; λ_{max}^{EtOH} 236 mμ (ε 6000) which however has the composition of $C_{16}H_{22}O_{10}$ rather than $C_{17}H_{26}O_{11}$[1]. In support of the formulation of verbenalin as a methyl ester esterification of X regenerated verbenalin (IX). Since the original glucoside contains one carboxyl function only the lactone grouping in desoxyverbanol (XII) originates from the carbomethoxy function in verbenalin which thus contains part structure V. Its ultraviolet spectrum, λ_{max}^{EtOH} 238 mμ (ε 9600) is similar to those of tetrahydro-desoxyplumieride (VII), λ_{max}^{EtOH} 236 mμ (ε 10000)[11] and bakankosin (VIII), λ_{max}^{EtOH} 236 mμ (ε 11600)[12] and if we accept this analogy an expanded formula (VI) results. Verbenalol (XIV)

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[8] R. Fusco, R. Trave and A. Vercellone, Chim e Industr. 37, 251 (1955).

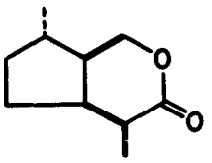
[9] R. H. Jaeger and Sir Robert Robinson, Tetrahedron Letters 15, 14 (1959).

[10] We are indebted to Dr. G. W. K. Cavill for this comparison.

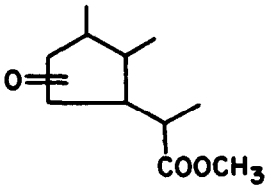
[11] O. Halpern and H. Schmid, Helv. Chim. Acta 41, 1109 (1958).

[12] G. Büchi, unpublished. K. Balenović, H. U. Däniker, R. Goutarel, M. M. Janot and V. Prelog, Helv. Chim. Acta 35, 2519 (1952).

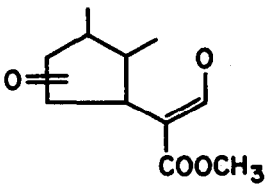
m.p. 125-128° (dec.) [Lit.[5] m.p. 124°], $\nu_{max}^{CHCl_3}$ 3550, 1750, 1710,



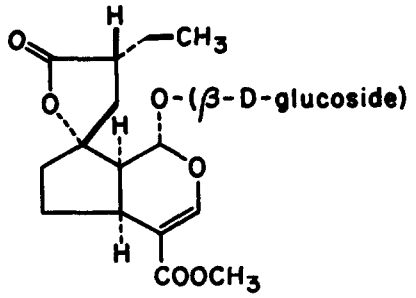
IV



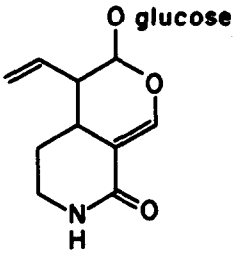
V



VI



VII



VIII

1640 cm^{-1}; λ_{max}^{EtOH} 240 mμ (ε 9050) available by emulsin catalyzed hydrolysis of the glucoside exhibits positive Fehling and Tollens tests. This behavior is explained by XIV and further evidence for the location of the hydroxyl group was provided by the ultraviolet spectrum which has λ_{max}^{EtOH} 271 mμ (ε 19000) in 0.01N sodium hydroxide solution. The bathochromic displacement observed (Δλ 31 mμ) is similar to that of ethyl acetoacetate (Δλ33 mμ)[13] and dihydrobakankogenin (Δλ 38 mμ)[12]. To complete the structure it

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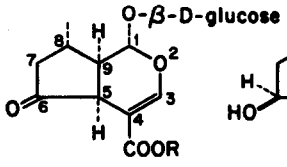
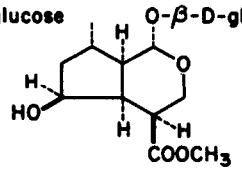
[13] P. Grossmann, Z. physik. Chem. 109, 305 (1924).

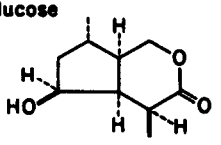
was necessary to place the ketone function which must be located on the cyclopentane ring. We have chosen C_6 for two reasons. (a) The formation of β-methylglutaric acid[5] on oxidation with three moles of ozone can only be rationalized with this alternative and (b) the high intensity n-π^* transition in the ultraviolet spectrum of verbenalin, λ_{max}^{EtOH} 290 mμ (ε 105) is typical for



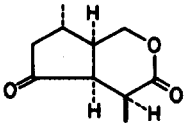
IX R = CH_3
X R = H



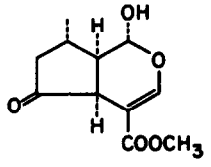
XI



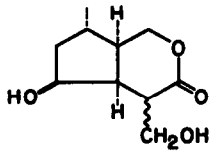
XII



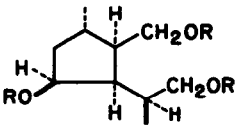
XIII



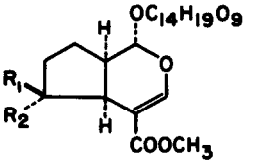
XIV



XV



XVI
R = NO_2
C_6H_4
CO



XVII
R_1 = OAc; R_2 = H

XVIII
R_1 = H; R_2 = OAc

non-planar β,γ-unsaturated ketones[14].

We shall now discuss the stereochemistry of verbenalin. The relative and absolute configuration of (+)-iridomyrmecin is known[7,9,15,16] and desoxyverbanone therefore has the configuration shown in XIII. Since reduction of desoxyverbanone (XIII) with sodium borohydride regenerates desoxyverbanol (XII) no isomerization had occurred during the reverse process and the configuration of XII is established. The previously described reconversion of verbenalinic acid (X) to verbenalin (IX) demonstrates that the natural product already contains a thermodynamically more stable cis-fused ring system. That the $\Delta^{5,6}$-enol was indeed formed during the saponification of IX to X was established in a separate experiment using deuterium oxide as a solvent. The verbenalin (IX) isolated after esterification with diazomethane and recrystallization from methanol contained 2.37 D atoms per molecule. It seems exceedingly unlikely that the configurations at both C_5 and C_9 were inverted in the course of catalytic reduction. The

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[14] R. C. Cookson and N. S. Wariyar, J. Chem. Soc. 2302 (1956); H. Labhart and G. Wagniere, Helv. Chim. Acta 42, 2219 (1959); C. A. Grob and A. Weiss, Helv. Chim. Acta 43, 1390 (1960); G. Büchi and E. M. Burgess, J. Am. Chem. Soc. 82, 4333 (1960).

[15] L. Dolejš, A. Mironov and F. Šorm, Tetrahedron Letters 11, 18 (1960). E. J. Eisenbraun, T. George, B. Riniker and C. Djerassi, J. Am. Chem. Soc. 82, 3648 (1960).

[16] G. W. K. Cavill, personal communication.

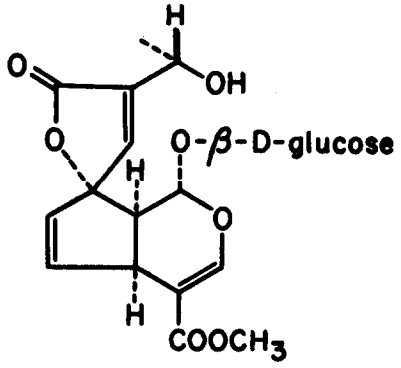
molecular rotation difference $[M]_D$ tetrahydroverbenalin-$[M]_D$ tetrahydroverbenalol is -448° (in water) and that for $[M]_D$ hexahydrodesoxyplumieride - $[M]_D$ of the corresponding aglucone is -325° (in methanol[11]). This tentatively suggests α-configuration for the glucose at C_1.

Catalytic reduction of verbenalol (XIV) takes a different course and yields norverbanol ($C_{10}H_{16}O_4$) (XV) m.p. 97-98.5° [Lit.[5] 95-96°], $\nu_{max}^{CHCl_3}$ 3500, 1750 cm^{-1} containing one C-Me group (Kuhn-Roth). Its monotosylate m.p. 127.5-128° on reduction with lithium aluminum hydride followed by reaction with p-nitrobenzoyl chloride gave the triester XVI m.p. 174-176° which could also be prepared by hydride reduction and esterification of desoxyverbanol (XII).

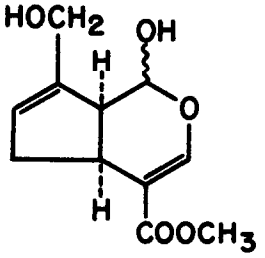
We have also synthesized the two epimeric pentaacetates XVII and XVIII. Treatment of verbenalin with sodium borohydride in absolute methanol produced a crude pentol which was transformed further to XVII m.p. 172-174°, ν_{max}^{KBr} 1735, 1700, 1645 cm^{-1}, λ_{max}^{EtOH} 232 mμ (ε 11200) by acetylation. Tetraacetylverbenalin m.p. 133-134° [Lit.[5] 133°], $\nu_{max}^{CHCl_3}$ 1750, 1710, 1640 cm^{-1}, λ_{max}^{EtOH} 235 mμ (ε 9370) was reduced with sodium borohydride and the resulting pentoltetraacetate transformed to the tetraacetyl monotosylate m.p. 157-158°. Conversion to XVIII m.p. 134-138°, ν_{max}^{KBr} 1750, 1705, 1635 cm^{-1}, λ_{max}^{EtOH} 234 mμ (ε 11500) was achieved by warming the tosylate with tetraethylammonium acetate in acetone solution. Both XVII and XVIII were different from loganinpenta-

acetate[17] m.p. 137-138° (mixed melting points and infrared spectra)[18].

Verbenalin is biogenetically related to (-)-plumieride[11] (XIX) and genipin[19] (XX).



XIX



XX

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17 A. J. Birch and E. Smith, Austral. J. Chem. 9, 234 (1956). K. W. Merz and H. Lehmann, Arch. Pharmaz. 290, 543 (1957).

18 We wish to thank Dr. J. Grimshaw, Manchester, for samples of loganin from Strychnos lucida and its pentaacetate.

19 C. Djerassi, T. Nakano, A. N. James, L. H. Zalkow, E. J. Eisenbraun and J. N. Shoolery, J. Org. Chem. in press.