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SHORT COMMUNICATION

THE STRUCTURE OF A NEW SESQUITERPENE ISOLATED FROM TOBACCO*

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Abstract—A new eudesmane-type sesquiterpene, 1-keto-α-cyperone (I), has been isolated from domestic tobaccos. The structure and stereochemistry of I have been elucidated from spectroscopic data and from the chemical degradation of I to (+)α-cyperone (IV).

INTRODUCTION

A NUMBER of terpenoids[1–5] have been isolated from tobacco. In this paper we record the characterization of a new eudesmane sesquiterpenoid which has been isolated as a minor component of burley and flue-cured tobaccos (*Nicotiana tabacum*).

Isolation of 1-keto-α-cyperone (I) was accomplished by chloroform extraction of acidified condensate from the steaming of burley tobacco. The acidic material was removed from the chloroform solution by extraction with dilute sodium hydroxide. After careful concentration, neophytadiene and other hydrocarbons were removed from the residue by chromatography on silicic acid. The neophytadiene was removed prior to distillation since it polymerizes on heating. The hydrocarbon-free material then was fractionated by distillation and chromatography to give a small amount of 1-keto-α-cyperone, which on recrystallization from pentane melts at 76–76·5°. The elemental analysis and the mass spectrum showed the compound to be a sesquiterpenoid $C_{15}H_{20}O_2$.

The spectral data on I give significant insight into the functional groups present in the molecule. The IR spectrum indicates the presence of an enolized β-diketone unit[6] as shown by the strong carbonyl band at 1600 cm^{-1}, the broad hydroxyl absorption from 3150 to 2500 cm^{-1}, and the very weak carbonyl absorption at 1670 cm^{-1}. The enolic hydroxyl was confirmed by a positive ferric chloride test. A terminal methylene group was indicated by a strong IR band at 900 cm^{-1}. Three methyl group adsorptions in the NMR spectrum are observed, each on a carbon bearing no hydrogens. The methyl group at τ8·10 is coupled slightly with the methylene protons at τ5·11, thus showing the presence of an isopropenyl

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[1] R. L. ROWLAND, P. H. LATIMER and J. A. GILES, *J. Am. Chem. Soc.* **78,** 4680 (1956); R. L. ROWLAND and J. A. GILES, *Tob. Sci.* **4,** 29 (1960).

[2] R. L. ROWLAND, *J. Am. Chem. Soc.* **79,** 5007 (1957).

[3] D. L. ROBERTS and R. L. ROWLAND, *J. Org. Chem.* **27,** 3989 (1962); R. L. ROWLAND and D. L. ROBERTS, *J. Org. Chem.* **28,** 1165 (1963); R. L. ROWLAND, A. RODGMAN, J. W. SCHUMACHER, D. L. ROBERTS, L. C. COOK and W. E. WALKER, JR., *J. Org. Chem.* **29,** 16 (1964).

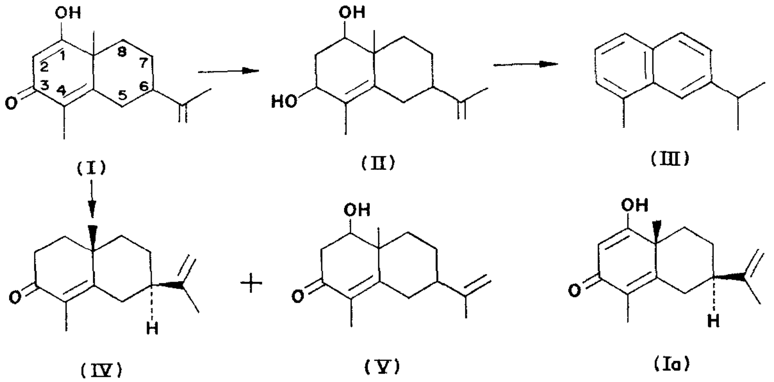
[4] J. R. STEADMAN and L. SEQUEIRA, *Plant Physiol.* **45,** 691 (1970).

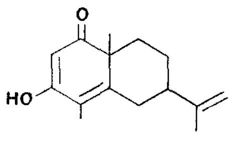
[5] E. DEMOLE and D. BERTHET, *Helv. Chim. Acta* **54,** 681 (1971).

[6] R. G. J. MILLER, H. A. WILLIS and H. J. HEDIGER, *Infrared Structural Correlation Tables*, Heydon, London (1964).

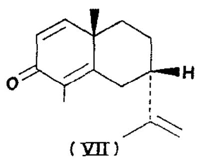
group. The low field position, τ8·02, of one of the methyls shows it to be attached to an α,β-unsaturated carbonyl unit, but it does not distinguish whether the group is α or β to the carbonyl. The sharp olefinic proton absorption at τ3·97 suggests that the double bond is conjugated, and that there are no other hydrogens on adjacent carbons. The assignment of the sharp peak at τ3·60 to the enolic hydrogen was verified by deuterium oxide exchange.

The eudesmane carbon skeleton was established in two ways. Borohydride reduction of I gave diol II which was characterized by its IR and NMR spectra. Selenium dehydrogenation[7] of II gave the hydrocarbon eudalene (III), identified by comparison of its IR and UV spectra with literature spectra.[7,8] Having established the gross carbon skeleton, a selective reduction was carried out. Compound I was reduced with zinc dust in acetic acid, and two products were obtained (IV and V). The major product from the zinc–acetic acid reduction was identified as (+)α-cyperone (IV) by comparison of its IR spectrum with those of (+)α-cyperone and (+)6-epi-α-cyperone.[9] The m.p. and optical rotation of the oxime of IV confirmed the stereochemical assignment. The UV and NMR spectra of IV also agreed with those published for α-cyperone.[10] The IR and NMR spectra of V indicate that it is a hydroxy-α,β-unsaturated ketone. The NMR spectrum is not definitive as to whether the hydroxy group is at positions 1 or 2, but the methine proton resonance at τ5·72 suggests that the hydroxyl is beta rather than alpha to the carbonyl at C-3. The UV spectrum also shows no shift to higher wavelength as would be expected from a compound with a hydroxy group at position 2. Hence, V is assigned the structure 1-hydroxy-α-cyperone which is consistent with presence of a 1,3-dicarbonyl function in I.





(VI)



(VII)

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[8] G. BUCHI, M. S. V. WITTENAU and D. M. WHITE, *J. Am. Chem. Soc.* **81,** 1968 (1959).

[9] R. HOWE and F. J. MCQUILLIN, *J. Chem. Soc.* 2423 (1955).

[10] A. E. BRADFIELD, B. H. HEGDE, B. S. RAO, J. L. SIMONSEN and A. E. GILLAM, *J. Chem. Soc.* 667 (1936).

Using the (+)α-cyperone structure IV as a starting point, the structure of I can be elucidated as 4a,5,6,7-tetrahydro-1,4a-dimethyl-4-hydroxy-7-isopropenyl-2(8H)-naphthalenone (Ia). The requirement of a 1,3-diketone unit places the enolized second carbonyl group at the 1 position (the 4 position according to *Chemical Abstracts* nomenclature). The UV absorption of I at 259 nm supports the cross conjugated structure in I rather than the linear conjugated structure in VI which would absorb at over 300 nm.[11]

Synthesis of I has been initiated and the model compound 1,2-dehydro-epi-α-cyperone (VII) has been prepared from epi-α-cyperone with DDQ. Attempts to selectively epoxidize the 1,2-double bond and open it reductively to the epi structure corresponding to V have been unsuccessful to date. In as much as 1-keto-α-cyperone represents the first identification of a eudesmane-type sesquiterpene from tobacco, it would be expected that additional examples of these compounds will be found in tobacco and tobacco smoke.

EXPERIMENTAL

M.ps are uncorrected and were determined using a Fisher–Johns m.p. apparatus. NMR spectra were obtained on Varian HR-60 and A-60 NMR spectrometers using $CDCl_3$ as the solvent.

Isolation of 1-*keto-α-cyperone* (I). The condensate (*ca.* 330 gal.) from the steaming of about 1500 lb of burley tobacco was acidified with H_2SO_4 to pH 2 and extracted with $CHCl_3$. The extract was concentrated, the final concentration being done by distillation through a fractionating column. The concentrate was washed in hexane solution with 10% aq. NaOH and water; the alkaline solution was back extracted with ether. The residue from the ether–hexane solution was then chromatographed on silicic acid using pentane–ether mixtures as eluents. Eluted material (60·59 g) was vacuum distilled through a 36 in. Nester-Faust spinning band column. Twenty-nine fractions were taken. Chromatography on silicic acid of the fractions boiling at 80–90°/0·2 mm Hg (2·4 g) gave a small amount of colourless crystalline 1-keto-α-cyperone which melted at 76–76·5° after recrystallization from pentane. The material gave a positive $FeCl_3$ colour and had the following properties: optical rotation $[\alpha]_D$ −154° ($CHCl_3$); UV: λ_{max}^{EtOH} 259 nm (ϵ = 17 000). IR: 3150, 2500 (broad), 1670 (small), 1600, 1320, 1300, 1273, 1247, 1220, 1180, 1155, 1050, 1015, 1002, 900, 870 and 787 cm^{-1}. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77·55; H, 8·68; MW 232. Found: C, 77·50; H, 8·49; parent mass 232. A $CHCl_3$ extract of flue-cured tobacco was also shown to contain 1-keto-α-cyperone.

1-*Hydroxy-α-cyperol* (II). A methanolic solution (5 ml) of 1-keto-α-cyperone (177·0 mg) was added to 150 mg $NaBH_4$ in 50% aq. MeOH (5 ml), and the solution was allowed to stand overnight. Cold 5% NaOH (20 ml) was added and the solution was extracted with ether. Concentration of the dried ether solution gave an oil which was identified as 1-hydroxy-α-cyperol (II). IR: 3330, 1640, 1122, 1056, 1025, 970, and 885 cm^{-1}. NMR: τ5·38 (2,CH_2=), 6·23 (2,$C\underline{H}OH$), 7·61 (1,CH), 8·25 (3,CH_3), 8·30 (3,CH_3), and 8·92 (3,CH_3).

Dehydrogenation of 1-*hydroxy-α-cyperol* (II). The 1-hydroxy-α-cyperol (150 mg) from above was heated with 150 mg Se at 180° for 8 hr. Hexane was then added and the filtered solution was passed through an alumina column using pentane as an eluent. The second 100 ml fraction contained an oil which partially crystallized. The IR and UV spectra of the crystalline material agreed completely with those published for eudalene (III).[7,8]

α-Cyperone (IV) *and* 1-*hydroxy-α-cyperone* (V) *from* 1-*keto-α-cyperone* (I). A stirred solution of 300 mg of 1-keto-α-cyperone (I) in 10 ml HOAc was heated to 90°, and Zn dust (1 g) was added over a 2-hr period. The mixture was then cooled, diluted with H_2O and filtered. The filtrate was extracted with ether. The ether extractables (248 mg) were chromatographed on silicic acid, and two materials were eluted with ether–pentane mixtures. The first material (141 mg) was crystallized from hexane and from alcohol-water, and finally purified by trapping from a gas chromatograph using a Dow 710 column. The material was identified as (+)α-cyperone (IV) by its spectra and its oxime. UV: λ_{max}^{EtOH} 250 nm (lit.[10] 251 nm). IR spectrum was identical to literature spectrum of α-cyperone.[9] NMR: τ5·37 (2,CH_2=), 7·36 (2,CH_2), 8·24 (3,CH_3), 8·30 (3,CH_3) and 8·78 (3,CH_3). Parent mass 218; Calcd MW of α-cyperone 218. Oxime: m.p. 155–156° (MeOH), (lit. m.p. 150·5°); Optical rotation $[\alpha]_D^{CHCl_3}$ +103·5° (lit.[9] +133°). The second material (60 mg) was characterized by its spectra and assigned the structure 1-hydroxy-α-cyperone (V). UV: λ_{max}^{EtOH} 250 nm. IR: 3500, 1667, 1610, 1300, 1200, 1121, 1063, 1000, 971, and 887 cm^{-1}. NMR: τ5·25 (2,CH_2=), 5·72 (1, quad, CH), 6·33 (1,OH), 7·26 (1, doublet, CH), 7·48–7·80 (2, multiplet, CH_2), 8·17 (3,CH_3), 8·24 (3,CH_3), and 8·67 (3,CH_3). Parent mass 234; Calcd for $C_{15}H_{22}O_2$, 234.

Preparation of 1,2-*dehydro-epi-α-cyperone*. Epi-α-cyperone, (10 g) was prepared by the method of Howe

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[11] A. I. Scott, *Interpretation of the Ultraviolet Spectra of Natural Products*, Macmillan, New York (1964).

and McQuillin,[9] was dissolved in 500 ml of dry benzene and added to 15 g of 2,3-dichloro-5,6-dicyano benzoquinone (DDQ) in 1000 ml of dry benzene. The solution was refluxed for 96 hr; the mixture was filtered, and the filtrate was chromatographed on basic alumina. Elution with ether-benzene mixtures gave 2·8 g of 1,2-dehydro-epi-α-cyperone (III). IR: 1655, 1640, 1600, 1312, 1086, 885 and 828 cm^{-1}. NMR: τ3·25 (1,J_{AB} = 10·2 Hz), 3·79 (1,J_{AB} = 10·2 Hz), 5·21 (2, CH_2=), 8·10 (3,CH_3), 8·23 (3,CH_3), and 8·76 (3,CH_3).

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Key Word Index—Nicotiana tabacum; Solanaceae; tobacco; sesquiterpene; eudesmane-type 1-keto-α-cyperone.