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SHORT COMMUNICATION

1′-HEXANOYLNORNICOTINE AND 1′-OCTANOYLNORNICOTINE FROM TOBACCO

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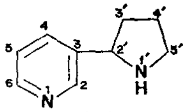
Key Word Index—*Nicotiana tabacum*; Solanaceae; alkaloids; 1′-hexanoylnornicotine; 1′-octanoylnornicotine.

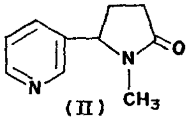
Abstract—Two minor alkaloids, isolated from flue-cured and air-cured tobacco (*Nicotiana tabacum*), have been identified as 1′-hexanoylnornicotine and 1′-octanoylnornicotine.

INTRODUCTION

During a compositional study on the resin fraction of flue-cured tobacco,[1] a minor component of fractions containing duvatriendiols was observed to give a positive reaction with alkaloid reagents. Many minor alkaloids have been identified, together with nicotine, in tobacco and at first there was no reason to suspect that this compound was other than one of these. However, when on gel permeation chromatography the alkaloidal material eluted concurrently with the duvatriendiols (MW 308) and well in advance of reference samples of nornicotine (I; MW 148) and cotinine (II; MW 176), it became apparent that its molecular size was considerably greater than that of any alkaloid previously reported in tobacco and that further investigation was merited.



(I)



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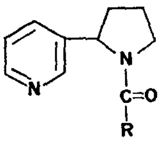

(III) a $R = C_7H_{15}$
b $R = C_5H_{11}$
c $R = CH_3$
d $R = H$

RESULTS AND DISCUSSION

The alkaloidal material was separated from the duvatriendiols and other neutral material by chromatography on silica gel. The 3-pyridyl group, characteristic of the tobacco alkaloids, was clearly represented in its IR spectrum by peaks at 1580, 1030 and 715 cm^{-1} but the spectrum also exhibited inordinately strong C—H absorption and a prominent peak at 1650 cm^{-1} attributable to a tertiary amide carbonyl group.

The MS showed a weak molecular ion peak at *m/e* 274. Precise mass measurement (Obsd. 274·2050; $C_{17}H_{26}N_2O$ requires 274·2045) and the observed fragmentation pattern

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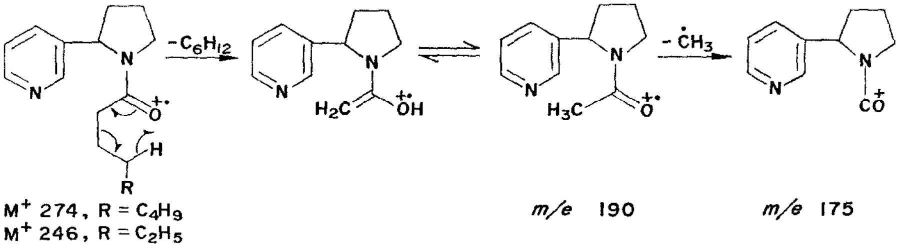
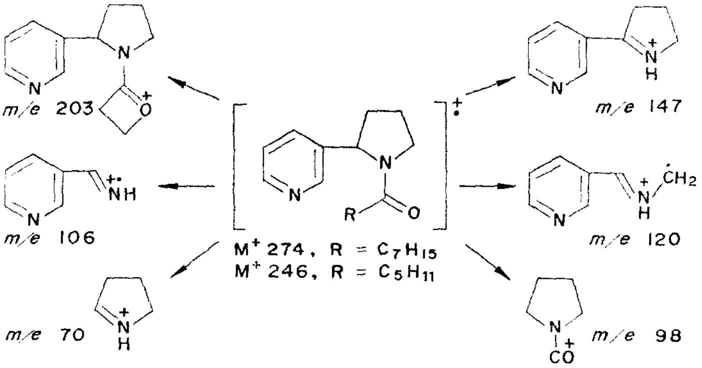
[1] A. J. N. Bolt, *24th Tobacco Chemists Research Conference*, Montreal, Canada (1970).

pointed to the compound being 1′-octanoylnornicotine (IIIa). The base peak at *m/e* 190 results from β-cleavage in the acyl side-chain and γ-hydrogen transfer (McLafferty rearrangement; see Scheme 1). Subsequent α-cleavage with loss of a methyl radical and formation of an *m/e* 175 ion is demonstrated by the appropriate metastable peak at *m/e* 161.



SCHEME 1. FORMATION AND METASTABLE TRANSITION OF THE BASE PEAK ION IN THE MASS SPECTRA OF 1′-OCTANOYLNORNICOTINE AND 1′-HEXANOYLNORNICOTINE.

γ-Cleavage of the molecular ion is also operative and yields a peak at *m/e* 203. Expulsion of the acyl side-chain[2] generates an *m/e* 147 ion which with loss of ethylene[3] yields a peak at *m/e* 120. Proposed structures for these and other major ions are given in Scheme 2.



SCHEME 2. ABUNDANT IONS IN THE MASS SPECTRA OF 1′-OCTANOYLNORNICOTINE AND 1′-HEXANOYLNORNICOTINE.

The above structure assignment was confirmed by inspection of the IR and MS of synthetic 1′-*n*-octanoylnornicotine. A small peak at *m/e* 246 in the MS of the isolated compound was, however, noted to be considerably less prominent in the spectrum of the synthetic material and was construed as representing the molecular ion of a second alkaloidal component, the C6-side-chain homologue, 1′-hexanoylnornicotine (III b). Confirmation for this was obtained subsequently by GLC–MS investigation. The fragmentation pattern of 1′-hexanoylnornicotine is predictably similar to that of 1′-octanoylnornicotine from *m/e* 203 to lower mass.

GLC quantitation indicated that the levels of 1′-octanoylnornicotine and 1′-hexanoylnornicotine in the samples of flue-cured tobacco investigated were approximately 5 and 1·5

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[2] H. BUDZIKIEWICZ, C. DJERASSI and D. H. WILLIAMS, *Mass Spectrometry of Organic Compounds*, p. 348, Holden-Day, New York (1967).

[3] A. M. DUFFIELD, H. BUDZIKIEWICZ and C. DJERASSI, *J. Am. Chem. Soc.* **87**, 2926 (1965).

ppm respectively. These compounds were also found in a sample of air-cured burley tobacco at levels of 3 and 4 ppm respectively. The existence of 1′-acetylnornicotine (IIIc) and 1′-formylnornicotine (IIId) in burley tobacco has been reported[4] but neither these compounds nor other homologues were encountered in the present study.

Established procedures for extracting and purifying tobacco components are known to lead occasionally to artifact formation. Whilst it is very unlikely that 1′-acylnornicotines are formed from known tobacco alkaloids during the work-up procedure, the possibility that they are derived fortuitously from closely related precursors possessing the respective acyl side-chains cannot be entirely dismissed.

EXPERIMENTAL

Materials. The two tobacco types were flue-cured Virginia type tobacco and air-cured Canadian low-nicotine burley. All solvents were re-distilled before use.

Isolation of the 1′-*acylnornicotines.* Tobacco was extracted at near ambient temperatures by percolation with 40–60° light petroleum for 20 hr and the extract was concentrated by rotary evaporation under reduced pressure. Initial column chromatography was carried out on columns (ext. dia., 6·5 cm) of neutral alumina using an adsorbent/sample ratio of 20:1. An extract sample (30 g) was mixed with neutral alumina (90 g; act. grade V) and placed on a neutral alumina column (600 g; act. grade III). Elution was commenced with a 1:1 mixture of ether and light petroleum until elution of solanesol was complete and continued with a 3:1 mixture of these solvents to remove sterols. Fractions containing duvatriendiols and the yellow pigment lutein were eluted with pure ether and monitored for alkaloid content by TLC. The 1′-acylnornicotines were concentrated by further chromatography on alumina columns (ext. dia. 3 cm) using an adsorbent/sample ratio of between 50 and 100:1, and finally separated from neutral material on silica gel columns; neutral material eluting with pure ether and alkaloids with a 20:1 mixture of ether and methanol. The 1′-acylnornicotines were also obtained from methanol extracts of tobacco by conventional alkaloid extraction procedures without recourse to alumina chromatography.

TLC. Duvatriendiol fractions were monitored for alkaloid content by TLC using either basic alumina and EtOAc–MeOH (49:1) or silica gel G and Et_2O–MeOH (99:1). Alkaloids were visualized by spraying with either Dragendorff's or iodoplatinate reagents.

Gel permeation chromatography. Polystyrene beads (Poragel A1; mol. exclusion, 1000) were swollen in benzene and poured into glass columns (ext. dia., 2·5 cm) to a height of 40 cm. Samples (100 mg) were dissolved in benzene (400–500 μl), pipetted on to the columns and eluted with benzene using a constant head device. Fractions (4·4 ml) were collected at a flow rate of *ca.* 1 ml/min and evaporated under nitrogen.

Gas chromatography. The gas chromatograph was a Perkin-Elmer 800 dual column instrument equipped with a flame ionization detector. The 2 m stainless steel columns were packed with 4% UCW-98 on Diatoport S and were programmed from 100 to 250° at 5°/min. The nitrogen carrier flow rate was 40 ml/min. Retention times for 1′-hexanoylnornicotine and 1′-octanoylnornicotine were 19 and 22 min respectively.

MS. Mass spectra were determined on an AEI MS 902 spectrometer by the Physico-Chemical Measurements Unit at Harwell. The following conditions apply; electron energy, 70 eV; ion source temperature, 200°, probe inlet system temperature, 200°. A Perkin–Elmer 881 instrument was used for the GLC–MS studies with 183 cm columns packed with 5% SE-52, a helium carrier flow rate of 30 ml/min and an ion source temperature of 250°. MS data (above *m/e* 40; rel. intensities in parentheses) are listed below. 1′-*Octanoylnornicotine.* (M^+ 274)(11), 245(6), 231(4), 217(6), 204(6), 203(36), 191(12), 190(100), 189(78), 176(9), 175(65), 162(5), 149(8), 148(15), 147(58), 133(7), 132(13), 130(10), 121(9), 120(48), 119(22), 118(13), 117(14), 107(5), 106(36), 105(12), 98(28), 93(12), 92(12), 80(9), 79(7), 78(6), 70(52), 65(7), 57(28), 55(12), 43(30), 42(7), 41(34). 1′-*Hexanoylnornicotine.* (M^+ 246)(12), 217(7), 204(9), 203(17), 191(9), 190(100), 189(67), 176(6), 175(45), 163(6), 162(9), 161(5), 149(5), 148(12), 147(50), 146(9), 134(5), 133(7), 132(8), 130(7), 121(8), 120(36), 119(16), 118(11), 117(10), 107(6), 106(29), 105(10), 98(14), 93(11), 92(9), 80(7), 79(7), 78(7), 71(9), 70(33), 65(6), 56(5), 55(10), 51(5), 43(41), 42(6), 41(9).

Synthesis of 1′-*acylnornicotines.* Reference samples of 1′-*n*-hexanoylnornicotine and 1′-*n*-octanoylnornicotine were prepared by the reaction of (−)-nornicotine with the corresponding acyl chloride. 1′-Formylnornicotine and 1′-acetylnornicotine were prepared by reacting (−)-nornicotine with HCO_2H and a 1:1 mixture of HCO_2H and AC_2O respectively. Purification of the reaction products was achieved by chromatography on silica gel columns.

Acknowledgements—The author is grateful to Miss P. Kington, and Mr. R. Clarke for technical assistance and to the Directors of the Imperial Tobacco Group for permission to publish this paper.

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[4] A. H. Warfield, W. D. Galloway and A. G. Kallianos, *23rd Tobacco Chemists Research Conference*, Philadelphia (1969).