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SEPTORINE AND N-METHOXY SEPTORINE,SUBSTITUTED PYRAZINES FROM THE FUNGUS SEPTORIA NODORUM BERK

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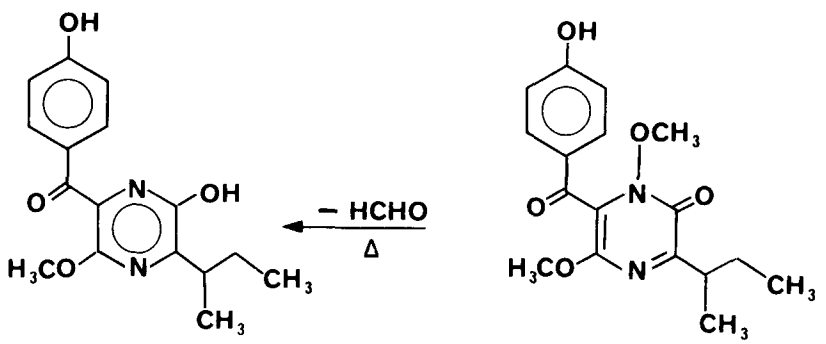
Summary.-On the basis of ^1H nmr correlations with synthetic analogs,structures 1 and 2 are proposed for septorine and N-methoxy septorine,two p-hydroxybenzoyl 1-isobutyl substituted pyrazines obtained from the fungus Septoria nodorum Berk,a parasite of wheat.

A partial structure in which the relative positions of the OH and OCH_3 groups had not been determined,was previously[1] proposed for septorine,a substituted pyrazine isolated from the fungus Septoria nodorum Berk,a common parasite of wheat.Septorine causes a decoupling action on mitochondria isolated from wheat coleoptiles.The septorine induced changes in respiratory activities[2,3] were similar to 2,4-D effects.The culture medium of Septoria nodorum,extracted by ethyl acetate,contains a second pyrazine,isolated through preparative SiO_2 tlc (Schleicher-Schüll fluorescent,$CHCl_3$-methylethylketone 5:1,Rf 1 0.35 and 2 0.55).

Correlations between septorine and N-methoxy septorine with synthetic analogs allow to propose now for these compounds the structures 1 and 2 which are derived from L-isoleucine and tyrosine.



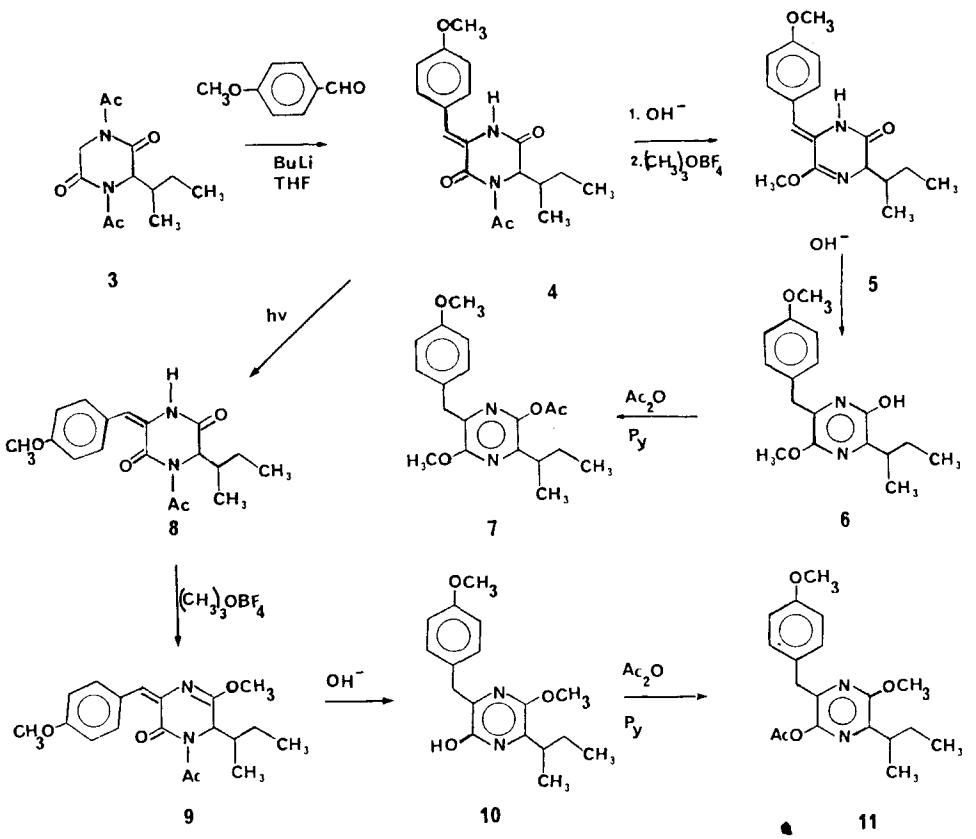
1 2

2:m.p.167° (hexane)$[\alpha]_D^{20}$=+30° ($CHCl_3$); λmax.MeOH,nm,230 ($6.5x10^3$),300 ($9x10^3$), 370 ($4x10^3$);ms,high resolution 332.1398 $(M)^+$ 44%,$C_{17}H_{20}N_2O_5$;302.1242 $(M-HCHO)^+$, $C_{16}H_{18}N_2O_4$,17%;121.0289 ($C_7H_5O_2$,p-OH benzoyl)$^+$,100%;^{1}H nmr,$CDCl_3$,δ,TMS:OH phenolic,1H,s,broad,9.16;N-OCH_3,3H,s,4.04;OCH_3,3H,s,3.82;aromatic protons,2H,d, 7.73,J=9Hz and 2H,d,6.91,J=9Hz;^{13}C nmr,N-OCH_3,64.69;-N-C=O,164.08,both signals missing in the spectrum of 1[1].

The detailed nmr study of the 1-isobutyl side chain gives the following result :H_x,1H,sext.,3.42,J=6Hz;aCH_3,3H,d,1.27,J=6Hz;bCH_3,3H,dd,0.95,J_{HaHbCH_3}=6Hz;HB sept.,1H,1.85,J id.HA;(1a;pyrazine rest in 2).

It is to be noticed that substance 2 is transformed into 1 by refluxing in MeOH (-HCHO) and this is reminiscent of the mycelianamide situation[4,5],but the position of the N-OCH_3 group cannot be formally deduced from this single observation as the isobutyl rest is bulky enough to effect the necessary steric pressure,leading to the elimination of formaldehyde.

Model substances were synthesized from 3 (obtained from BOC-L-isoleucine and glycine methyl ester,HCl[6]) which after acetylation (in boiling Ac_2O),was condensed with p-anisaldehyde (BuLi),leading[7] to the monoacetate 4 (scheme;tlc, SiO_2,ether,yield 48%;mp.135°;ms 330 $(M)^+$,80%,288 $(M-42)^+$,13%,232 $(M-98)^+$,100%;



nmr:OCH_3,s,3H,3.82,aromatic protons 6.90,d,2H;7.42,d,2H;7.12,s,1H (ethylenic), 8.25,s,1H,(NH),2.26,s,3H,CH_3CON;10.2,d,3H;0.96,t,3H;1.80,m,1H (isobutyl substitution).

Saponification of the acetyl group in 4,treatment with $(CH_3)_3OBF_4/CH_2Cl_2/N_2$, 72h at 20°,washing with $NaHCO_3$ and preparative tlc (SiO_2,hexane-AcOEt 3:2 and Al_2O_3,hexane-AcOEt 1:1) afford 5,mp.86° (hexane),ms:302 $(M)^+$,40%,245 $(M-57)^+$ 100%;nmr:new OCH_3 group at 3.96,s,3H;yield 11%.

Aromatisation of 5 (KOH N in $MeOH/H_2O$ 1:1,reflux 1h) gives 6 after extraction by AcOEt and SiO_2 tlc (hexane-AcOEt 3:2);mp.114° (hexane);ms:302 $(M)^+$;nmr:methylen group at 3.95,s,2H;yield 73% ;monoacetate 7 (Ac_2O/Py),ms:344 $(M)^+$,302 $(M-42)^+$

UV irradiation of 4 (MeOH,4h,Q81 100W Hanau lamp) produces the isomerisation of the anisylidene double bond to 8 (SiO_2 tlc,hexane-AcOEt 3:2),amorphous,yield 37%;ms:330$(M)^+$,288 $(M-42)^+$;nmr id.4 but ethylenic proton at 6.57,s,1H,instead of 7.12.

$(CH_3)_3OBF_4/CH_2Cl_2$,20°,20h,treatment of 8 leads to 9 (tlc,hexane-AcOEt 3:2),mp. 84° (hexane);ms:344 $(M)^+$;nmr in agreement with structure 9.

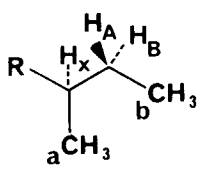
Aromatisation of 9 is performed as above for 5 with KOH,leading to 10,mp. 107° (hexane);ms:302 $(M)^+$;nmr:CH_2 at 3.98,s,2H;monoacetate 11 (Ac_2O/Py) ,amorphous, ms:344 $(M)^+$,302 $(M-42)^+$;nmr in agreement with the expected structure 11.

The acetylation of septorine (Ac_2O/Py) produces an important chemical shift of the 1-isobutyl proton H_x (partial formula 1a),as for the acetylation of the analog 6 to 7 (table),while the acetylation of 10 to 11 results in an opposite variation,and this is clearly establishing the situation 1 for septorine and consequently 2 for N-methoxy septorine.

Proton H_x, δ ,ppm,(1a) :			
1 : 3.31	acetylated 1	:	2.95
6 : 3.17	7	:	2.70
10 : 2.98	11	:	3.02

Table: comparison of the chemical shifts of the proton H_x (1a) between free OH containing derivatives and their acetylated counterparts.

R=substituted pyrazine rest



1a

The comparisons between the $[\alpha]_D$ of septorine (+30°),N-methoxy septorine (+30°) with the synthetic products issued from L-isoleucine (7 :+28°;10 :+25°) indicate that the natural substances 1 and 2 are very likely formed from L-isoleucine and that the biosynthesis proceeds through the condensation of this amino-acid with tyrosine.

Attempts to functionnalise the benzylidene intermediates or to oxidise the benzyl substituted pyrazine obtained in our synthesis,in order to generate benzoyl structures such as in septorine 1,have failed,mainly due to the unstability of the compounds in the reaction conditions.

NMR determinations have been performed on a CAMECA 240 MHz apparatus,MS on an AEI MS 50 spectrometer and HPLC on a Perkin-Elmer Liquid Chromatograph.

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