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FICINE, A NOVEL FLAVONOIDAL ALKALOID FROM FICUS PANTONIANA

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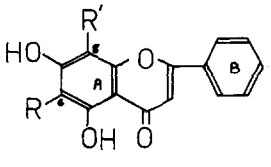
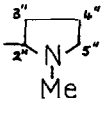
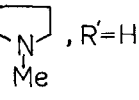
Previously the only alkaloids isolated from Ficus species have been those related to tylocrebrine (1). We now report the isolation from Ficus pantoniana King of the first known flavonoidal alkaloids. The major base, ficine, $C_{20}H_{19}O_4N$, m.p. 235°, is accompanied in small amounts by an isomer, isoficine, m.p. 168°, for which chemical and spectral evidence is consistent only with structures (I) and (II) respectively.



(I) R=H, R'= 

(II) R= 

, R'=H

(III) R=R'=H

Ficine is converted into an equilibrium mixture of ficine and isoficine when heated under reflux with 70% hydrochloric acid, conditions which may be expected to bring about a Wessely-Moser rearrangement in flavones. When treated with 5% aqueous potassium hydroxide or methanolic sodium methoxide solutions at room temperature or when pyrolysed at 250° under high vacuum, ficine is converted into chrysin (III), $C_{15}H_{10}O_4$ (m.p. and mixed m.p. 289-290°, I.R., U.V., and N.M.R. spectra identical with an authentic sample), the $C_5H_{10}N$ fragment is too labile under such conditions to be isolated.

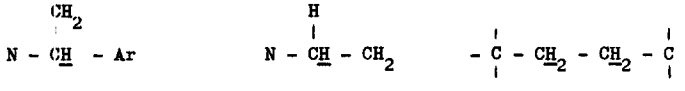
The U.V. spectra of ficine [λmax. 275 mμ (log ε 4.5), λmax. 329 mμ (log ε 4.0] and chrysin [λmax. 268 mμ (log ε 4.5), λmax. 312 mμ (log ε 4.1)], are very similar, hence no chromophore apart from the chrysin moiety is present in ficine. The bathochromic shift is consistent with a saturated alkyl-like substituent in ring A (2). The action of 2,6-dibromobenzoquinone chlorimide (Gibbs reagent) on isoficine at pH 9.2 produces a characteristic absorption at 685 mμ indicative of an unsubstituted CH para to a phenolic hydroxyl group.(3) Chrysin gives a similar absorption at 685 mμ whereas no such absorption is obtained with ficine. The mass spectrum of ficine (inlet temperature 290°) does not show a molecular ion but is equivalent to the sum of the individual spectra of chrysin and N-methylpyrrole (4). It is assumed that pyrolysis at the inlet temperature (290°) takes place prior to bombardment by the electron beam and that the nitrogen-containing pyrolysis product is converted to N-methylpyrrole under such conditions. This evidence indicates that the $C_5H_{10}N$ fragment is N-methylpyrrolidine, the structure of which has been confirmed by nuclear magnetic resonance (N.M.R.) spectroscopy which has also established its point of attachment to the chrysin molecule.

The flavone protons in ficine and isoficine can be readily

identified in the N.M.R. spectra. The ring B aromatic protons resonate as a complex multiplet (5 protons) between δ 7.3 - 8.0 and the olefinic C3 proton appears as a singlet (one proton) at δ 6.60 and 6.55 respectively (5,6). The C5 hydroxyl proton, which is strongly hydrogen bonded to the ketonic oxygen, appears as a singlet (one proton) at δ 12.6 and 13.0 respectively (6). The C7 hydroxyl proton also appears abnormally downfield as a broad band (one proton) at approximately δ 12.0 in ficine and δ 11.0 in isoficine. This indicates that this hydroxyl proton is also hydrogen bonded which can be accounted for in structures (I) and (II) by bonding to the nitrogen lone-pair electrons. The only other signal associated with the flavone moiety appears as a singlet (one proton) at δ 6.25 in ficine and δ 6.33 in isoficine. These peaks are in the region associated with aromatic protons situated between two carbon atoms carrying oxygen substituents. The lack of splitting of these peaks shows that ring A is pentasubstituted and that the $C_5H_{10}N$ moiety is attached to this ring. In reported cases (5-10) in which a C6 and/or a C8 proton occurs in 5,7-dihydroxy- or 5,7-dialkoxy-flavones, the C8 proton is found at lower field than the C6. No direct correlation can be made with a flavone having a nitrogen containing substituent at C6 or C8 but unless such a substituent would influence the chemical shift of one proton relative to the other to such an extent as to reverse this observed difference in chemical shift, ficine, which has the proton at higher field (δ 6.25) can be assigned structure (I) with the proton at C6. Conversely, isoficine with the C8 proton at δ 6.33 would have structure (II), with a CH <u>para</u> to a phenolic hydroxyl group as indicated by the positive Gibbs test.

The remaining peaks in the N.M.R. spectrum of ficine have been assigned as follows: A sharp singlet (3 protons) at δ 2.43 can be attributed to the protons of an N-methyl group. A triplet (one proton)

at δ 4.15 which collapsed to a singlet when irradiated at δ 2.08 can be ascribed to a proton on a carbon atom substituted with a nitrogen, an aromatic ring, and the methylene at δ 2.08 to which the proton is coupled (partial structure IV). An approximate quintuplet (one proton) at δ 3.38 which collapsed to a doublet (J 10.4 c/s) when irradiated at δ 1.99 and to an unresolved triplet when irradiated at δ 2.48 can be attributed to a proton on carbon next to a nitrogen, which is coupled to a geminal proton (J 10.4 c/s) at δ 2.48 and to a methylene δ 1.99 (partial structure V). The geminal proton at δ 2.48 cannot be resolved as the N-methyl protons at δ 2.43 are superimposed upon it. The two methylenes (4 protons) centred at δ 2.08 and δ 1.99 are complex multiplets between δ 1.9 - 2.3 and have chemical shifts indicative of methylenes between saturated carbon atoms (partial structure VI).



IV V VI

This evidence is consistent only with an N-methyl-2-pyrrolidinyl structure for the $C_5H_{10}N$ fragment attached to ring A at C8. The difference in chemical shift between the two C5" protons can be attributed to the different chemical environments (with relation to the aromatic rings A and B and the nitrogen lone-pair electrons) in which they are held due to the strong hydrogen bonding between the C7 hydroxyl proton and the nitrogen lone-pair electrons.

Isoficine has similar peaks in the N.M.R. spectrum to ficine, the N-methyl protons at δ 2.38, the C2" triplet at δ 4.06, the C5" quintuplet at δ 3.38, the other C5" geminal proton under the N-methyl protons at approximately δ 2.4 and the C3" and C4" methylene protons between δ 1.8 - 2.3, which indicate the same N-methyl-2-pyrrolidinyl structure.

Satisfactory analytical figures were obtained for all compounds reported. I.R. spectra were recorded on a UNICAM SP200 spectrophotometer, U.V. on a BECKMAN spectrophotometer. The N.M.R. spectra were recorded on a VARIAN A60 spectrometer (using $CDCl_3$ as solvent). Chemical shifts are reported in δ units with T.M.S. as internal standard. Field-sweep spin-decoupling experiments were carried out on a VARIAN HR100 spectrometer.

REFERENCES

1. J. H. Russel, Naturwissenschaften, 50, 443 (1963).
2. T. A. Geissman, The Chemistry of Flavonoid Compounds, p.111, Macmillan, N.Y., (1962).
3. F. E. King, T. J. King and L. C. Manning, J. Chem. Soc., 563 (1957).
4. H. Budzikiewicz, C. Djerassi, A. H. Jackson, G. W. Kenner, D. J. Newman and J. M. Wilson, J. Chem. Soc., 1949 (1964).
5. T. J. Batterham and R. J. Highet, Aust. J. Chem., 17, 428 (1964).
6. J. Massicot and J. P. Marthe, Bull. Soc. Chem. France, 1962 (1962).
7. C. A. Heinrich, and P. R. Jefferies, Aust. J. Chem., 17, 934 (1964).
8. J. A. Lamberton, Aust. J. Chem., 17, 692 (1964).
9. W. E. Hillis and D. H. S. Horn, Aust. J. Chem., in press.
10. J. Massicot, J. P. Marthe and S. Heitz, Bull. Soc. Chem. France, 2712 (1963).