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ISOLATION, STRUCTURE AND SYNTHESIS OF (±)-RIBALININE(1)

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Previous studies on Balfourodendron riedelianum (Rutaceae) led to the isolation and characterization of many alkaloids belonging to several structural types also occurring in other plants of the same family, especially in the Lunasia genus(2).

The mixture of tertiary bases from the trunk bark of B. riedelianum was subjected to alumina chromatography and the last alkaloidal eluates were rechromatographed through silica-gel.

The fractions with λ_{max} at 237, 314 and 326 mμ were made up and crystallized from absolute ethanol furnishing the new alkaloid ribalinine; m.p. 233-234°(dec.), optically inactive in the range 700-370 mμ (c, 2.90, methanol). Elementary analysis, proton counting by NMR and the molecular ion at m/e 259 in the mass spectrum establish the molecular composition as $C_{15}H_{17}NO_3$.

Functional group analyses of ribalinine reveal one N-methyl and no methoxyl groups. It also contains a secondary alcoholic function as indicated by the following data: infrared band in Nujol at 3170 cm^{-1} while the ultraviolet absorption is not altered on basification; acetylation at room temperature with pyridine-acetic anhydride gives a product with no hydroxyl infrared absorption but an ester band at 1746 cm^{-1}; after acetylation, the NMR spectrum shows a three-proton peak of an acetyl group (δ 2.02 ppm) and a downfield displacement(3) by 1.2 ppm of the triplet originally centred at δ 3.92 ppm (α-proton to alcoholic hydroxyl).

The presence in ribalinine of a 2-alkoxy-4-quinolone moiety is supported by spectroscopic measurements. Its ultraviolet spectra in neutral (λ_{max}

237, 314, 326 mμ, log ε 4.34, 3.83, 3.78; λ_{min} 223, 263, 321 mμ, log ε 4.10, 3.11, 3.74) and acid media (0.3 N in HCl, λ_{max} 236, 300 mμ, log ε 4.41, 3.82; λ_{min} 223, 256 mμ, log ε 4.16, 2.94) are consistent with literature values for these compounds$^{(4)}$. The infrared absorption pattern in the region 1600-1470 cm^{-1} reported for N-methyl-2-alkoxy-4-quinolones$^{(4,5)}$ is also present in the spectrum of ribalinine (in Nujol, ν_{max} 1622, 1604, 1578, 1539, 1507 and 1472 cm^{-1}). The NMR spectrum (Fig. 1) shows four aromatic protons, one of which appears as a quartet (H_5 centred at δ 8.36 ppm) shifted downfield from the centre of gravity of the others by 93 c/s$^{(5,6)}$.

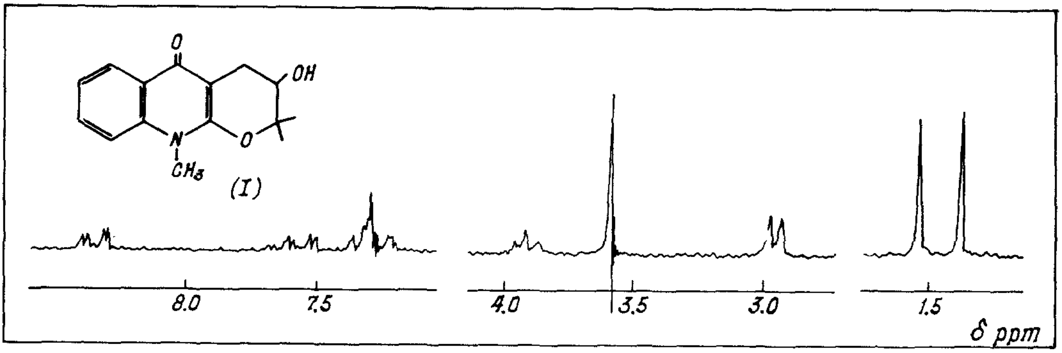

FIG. 1
NMR spectrum of ribalinine (I) in $CDCl_3$ (c, 1.5 %) at 100 Mc/s and internal $SiMe_4$ ($\delta = 0$)

Further structural aspects are also revealed by the NMR spectrum and electronic integration of areas. Ribalinine shows a N-methyl signal at δ 3.58 ppm in agreement with the Herzig-Meyer analysis, and two unsplitted $C-CH_3$ peaks (δ 1.37 and 1.53 ppm) which are 16 and 9.5 c/s apart at 100 and 60 Mc/s respectively; these data indicate two gem-methyls supported by a carbon atom without hydrogen and bonded to an oxygen.

The doublet at δ 2.94 ppm is ascribed to a methylene group adjacent to the secondary alcoholic function (triplet of the α-hydrogen at δ 3.92 ppm); double resonance measurements confirmed these assigments ($\omega_1 - \omega_2$ and the reverse, 96 c/s).

The foregoing results and the fact that the molecular formula of ribalinine requires another ring in addition to the 4-quinolone portion, led to the structure (I) or to the alternative with the alcoholic function located at position-4.

Structure (I) is firmly supported by the chemical shift of the methylene group (δ 2.94 ppm) in comparison with values found in similar compounds. In lunasia-II (8-methoxy derivative of I) the 4-methylene signal appears as a doublet centred at δ 2.88 ppm(7) while the 3-methylene of other pyrano-4-quinolones absorbs at higher field(5,8).

The structure of ribalinine was confirmed by synthesis following the route developped for the synthesis of isobalfourodine(8); the starting 4-hydroxy-1-methyl-3-(3-methyl-but-2-enyl)-2-quinolone, m.p. 162-163°, was obtained boiling a solution of diethyl 3-methyl-but-2-enylmalonate and N-methylaniline in diphenyl ether for 1.5 hr.

The identity of natural and synthetic(9) (±)-ribalinine was proved by mixture m.p. and coincidence of the ultraviolet and infrared curves.

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