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FUROQUINOLINE ALKALOIDS FROM HAPLOPHYLLUM VULCANICUM

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Abstract — The new furoquinoline alkaloids (+)-nigdenine (5) and (+)-nkolbisine (7) were obtained from Turkish Haplophyllum vulcanicum Boiss. et Heldr. (Rutaceae).

Haplophyllum vulcanicum Boiss. et Heldr. (Rutaceae) is a perennial herb which grows abundantly in central Anatolia. From the so-called "non-basic" fraction of this plant, the new lignan konyanin (1) was obtained, together with the known (-)-kusunokinin (2) and diphyllin (3), and the known furoquinoline alkaloid kokusaginine (4).[2]

We now report on the study of the "basic" fraction from the same plant, which led to the isolation of the new furoquinoline alkaloids (+)-nigdenine (5) and (+)-nkolbisine (7), which were found to accompany the known kokusaginine (4) and delbine (11)[3] as well as the ubiquitous lignan diphyllin (3). As an extension of the present work, the underground parts of H. vulcanicum were also investigated. But this effort led only to the isolation of the well known alkaloids robustine (12),[4] γ-fagarine (13)[5] and skimmianine (14),[4] together with diphyllin (3).

(+)-Nigdenine (5), $C_{18}H_{21}NO_6$, exhibited λ max (MeOH) 249, 320, 332, 348 sh nm (log ε 4.78, 3.74, 3.73, 3.54), and the spectrum remained unaffected by the addition of alkali. The general pattern of the absorption is typical of furoquinolines in general,[6] and is particularly reminiscent of that for skimmianine (14).[4] Consonant with the presence of at least one hydroxyl function, (+)-nigdenine afforded mono-O-acetyl derivative 6 upon acetylation with acetic anhydride in pyridine.

The 200 MHz NMR spectrum ($CDCl_3$) of (+)-nigdenine, summarized around expression 5, confirmed the furoquinoline nature of the alkaloid. The presence of an $O\text{-}CH_2\text{-}CH(OH)\text{-}C(OH)(CH_3)_2$ side chain was also discernable. The methine proton denoted as H_c which is geminal to an alcohol group, appeared as a doublet of doublets at δ 4.03. This absorption underwent a substantial downfield shift to δ 5.44 upon O-acetylation to 6. The rest of the spectrum of species 5 was almost superimposable on that of skimmianine (14),[4] except that the signal at δ 4.43 in skimmianine due to the C-4 methoxyl was missing in nigdenine. This difference indicated that the alkoxy side chain was located at C-4 in the furo(2,3-b)quinoline system of nigdenine (5).

The mass spectrum of (+)-nigdenine showed molecular ion peak m/z 347 (51). Loss of the five-carbon alkyl side chain from the molecular ion afforded peak m/z 244 (33).

(+)-Nigdenine (5) is of particular interest because it is the first furoquinoline alkaloid with a bulky alkoxyl side chain attached to C-4.

Turning now to (+)-nkolbisine (7), $C_{18}H_{21}NO_6$, which is the second alkaloid of interest found in the plant, it was determined that this base is definitely dextrorotatory, $[\alpha]_D^{25}$ +23° (c 0.5, MeOH) or $[\alpha]_D^{25}$ +7° (c 0.4, $CHCl_3$).

The 200 MHz NMR spectrum ($CDCl_3$) of (+)-nkolbisine bears a distinct similarity to that of the known kokusaginine (4),[7] and has been outlined around expression 7. It will be noted that the alkaloid incorporates the same side chain as (+)-nigdenine (5). Furthermore, in analogy with (+)-nigdenine (5), acetylation of (+)-nkolbisine led to mono-O-acetyl derivative 8 with a resultant downfield shift of H_c from δ 3.83 to δ 5.16.

The presence of the furan ring in (+)-nkolbisine was further ascertained by the catalytic hydrogenation of the compound to (+)-dihydronkolbisine (9), $C_{18}H_{23}NO_6$. Additionally, dehydration of (+)-nkolbisine with dilute hydrochloric acid afforded ketone 10, $C_{18}H_{19}NO_5$, along with some delbine (11).

(+)-Nkolbisine (7) is apparently enantiomeric with (-)-nkolbisine recently obtained from Cameroonian Teclea verdoorniana Exell & Mendonca (Rutaceae),[8] and exhibiting $[\alpha]_D^{25}$ -16.5° (MeOH). Nkolbisine is also present in Brazilian Monnieria trifolia L. (Rutaceae)[3] and in Cameroonian Teclea onabanguiensis Aubrev. & Perr.,[9] but the specific rotations of the alkaloids from these two sources have not been recorded.

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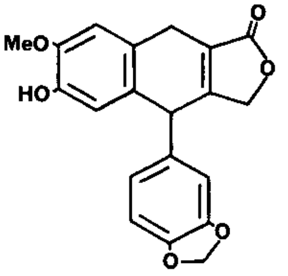

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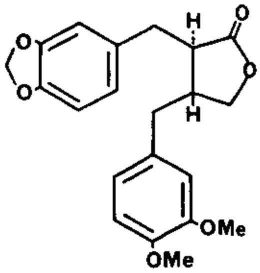

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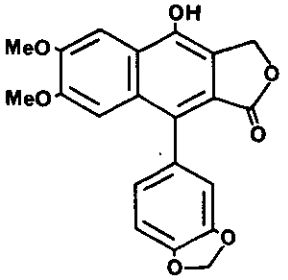

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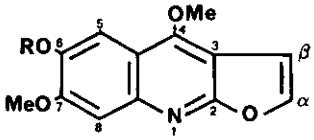

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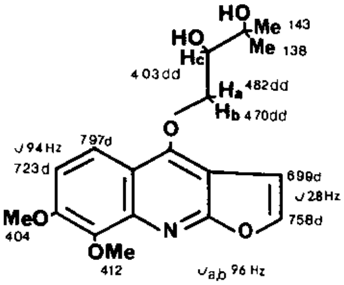

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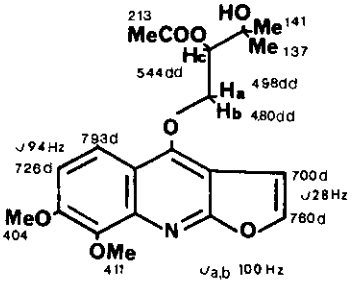

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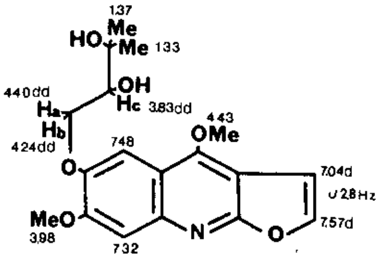

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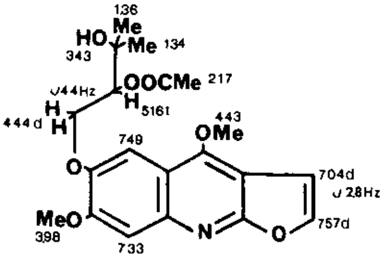

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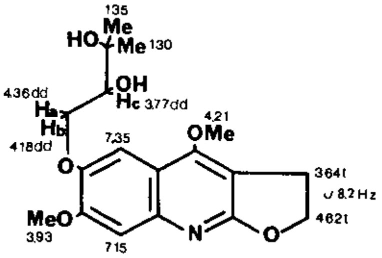

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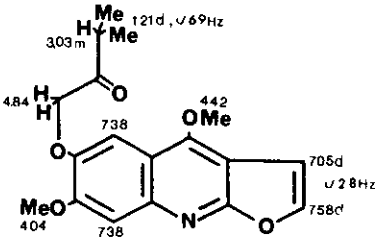

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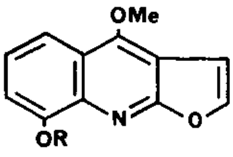

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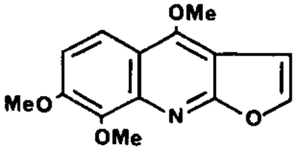

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EXPERIMENTAL

Plant Collection: The plant was collected in Ulukisla, Niğde, south of Konya, at an altitude of 1,450 m in early July, 1982. Its identity was confirmed by Prof. Asuman Baytop, Faculty of Pharmacy, Istanbul University. A voucher specimen No. 634 was deposited in the herbarium of the Department of Pharmacognosy, Faculty of Pharmacy, Ege University, Izmir.

Extraction and Isolation: The air-dried powdered aerial parts (4 kg) was extracted with cold ethanol. The extract was treated with 5% HCl and filtered. The aqueous acidic soln. was extracted with $CHCl_3$. The aqueous layer was basified with NH_4OH and extracted with $CHCl_3$ to supply an alkaloidal fraction of about 3.3 g. This material was placed on a silica gel column. Elution was first with $CHCl_3$ and then with $CHCl_3$-MeOH mixtures of increasing polarity. Earlier $CHCl_3$ fractions gave kokusaginine (4)[7] (300 mg) while later fractions furnished delbine (11)[3] (45 mg). $CHCl_3$-MeOH elution afforded diphyllin (3)[2] (10 mg), nkolbisine (7) (210 mg) and nigdenine (5) (20 mg), successively.

Parallel chemical investigation of the underground parts of the plant afforded robustine (12),[4] γ-fagarine (13) and skimmianine (14), as well as diphyllin (3).

All NMR spectra are at 200 MHz in $CDCl_3$ solution.

(+)-Nigdenine (5): Mp 177-180° C ($CHCl_3$-hexane); $[\alpha]_D^{25}$ +5.3° (c 0.3 , MeOH); λ max (MeOH+HCl) 253, 321, 350 nm (log ε 4.68, 3.71, 3.73); ν max (KBr) 3390 br, 1620, 1580, 1490, 1365, 1270, 1070 cm^{-1}; m/z 347 $(M)^+$ (51), 245 (35), 244 (33), 230 (100), 216 (47), 59 (67).

(+)-Nkolbisine (7): Mp 190-192° C ($CHCl_3$-hexane); λ max (MeOH) 245, 251, 308, 321, 334 nm (log ε 4.83, 4.84, 4.12, 4.13, 3.98); λ max (MeOH+HCl) 217, 251, 335 nm (log ε 4.22, 4.72, 4.23); ν max ($CHCl_3$) 3500, 1620, 1585, 1540, 1487, 1475, 902 cm^{-1}; m/z 347 $(M)^+$ (32), 245 (100), 230 (23), 59 (16).

O-Acetylnigdenine (6): $C_{20}H_{23}NO_7$; $[\alpha]_D^{25}$ 0° (c 0.3, $CHCl_3$); λ max (MeOH) 249, 271 sh, 319, 332, 349 sh nm (log ε 4.71, 4.03, 3.78, 3.77, 3.56); λ max (MeOH+HCl) 253, 276 sh, 322, 351 nm (log ε 4.67, 4.03, 3.74, 3.75); ν max ($CHCl_3$) 3370 br, 1735, 1620, 1610, 1572, 1500, 1487, 902 cm^{-1}; m/z 389 $(M)^+$ (24), 145 (43), 103 (39), 85 (73), 43 (100).

O-Acetylnkolbisine (8): $C_{20}H_{23}NO_7$; was obtained by acetylation of 7 with acetic anhydride in pyridine at room temperature; $[\alpha]_D^{25}$ -28° (c 0.8, $CHCl_3$); λ max (MeOH) 244, 251, 274, 294 sh, 308, 320, 333 nm (log ε 4.76, 4.78, 4.07, 4.03, 4.03, 3.99, 3.86); λ max (MeOH+HCl) 251, 335 nm (log ε 4.69, 4.15); ν max ($CHCl_3$) 3508, 1730, 1622, 1585, 1540, 1500, 1475, 902 cm^{-1}; m/z 389 $(M)^+$ (19), 245 (63), 230 (22), 145 (100), 127 (32), 103 (42), 85 (90), 59 (13), 43 (99).

(+)-Dihydronkolbisine (9): (+)-Nkolbisine (10 mg) in ethanol (10 mL) was hydrogenated for one h in the presence of 5% Pd/C (20 mg). The product (8 mg) was purified by tlc; $[\alpha]_D^{25}$ +25° (c 0.1, MeOH); λ max (MeOH) 233, 252 sh, 264, 273, 288 sh, 305 sh, 317, 331 nm (log ε 4.74, 3.99, 3.89, 3.89, 3.75, 3.70, 3.93, 3.98); λ max (MeOH+HCl) 226, 238 sh, 296, 323 sh, 337 nm (log ε 4.58, 4.49, 3.81, 4.11, 4.17); m/z 349 $(M)^+$ (30), 248 (17), 247 (100), 246 (11), 59 (11).

Dehydration of (+)-Nkolbisine:[8] Alkaloid 7 (10 mg) was refluxed with 4 mL 6N HCl for one h. Work-up, including tlc, provided ketone 10 (3 mg) and delbine (11) (5 mg); ketone 10 exhibited λ max (MeOH) 245, 251, 279, 308, 320, 333 nm (log ε 4.80, 4.81, 4.11, 4.07, 4.05, 3.95), ν max ($CHCl_3$) 1730, 1712, 1622, 1585, 1540, 1500, 1475, 903 cm^{-1}; m/z 329 $(M)^+$ (100), 259 (9), 258 (40), 245 (17), 244 (56), 243 (18), 230 (11). The same products were obtained upon refluxing 7 with 6N H_2SO_4.

REFERENCES AND FOOTNOTES

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