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SHORT COMMUNICATION

SYNTHESIS OF KOKUSAGININE*

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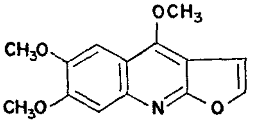
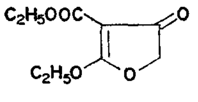
Abstract—A total synthesis of kokusaginine (I), a furoquinoline alkaloid of the dictamnine group, is reported.

As we recently reported,[1] kokusaginine (4,6,7-trimethoxyfuro[2,3-b]quinoline)(I) was obtained in very small amounts from *Haplophyllum suaveolens* (DC) G. Don., a rutaceous species endemic in Romania. Since the overall yield of the total synthesis performed by Kuwayama[2] is also very poor, we decided to investigate other ways to obtain this alkaloid, for which significant physiological activity has been described.[3]

In this connection, we tried to prepare kokusaginine (I) by the method elaborated by Tuppy and Böhm[4] for the preparation of related furoquinoline alkaloids. Thus, by condensing 4-aminoveratrole with 2-ethoxy-3-carbethoxy-4-oxo-4,5-diydrofuran (II), we obtained 2-(3′,4′-dimethoxyanilino)-3-carbethoxy-4-oxo-4,5-dihydrofuran (III), which on heating was cyclized to 3,4-dioxo-6,7-dimethoxy-2,3,4,9-tetrahydrofuro[2,3-b]quinoline (IV). Formation of the 5,6-dimethoxy isomer was not observed. Our numerous attempts to convert the compound IV into its 4-*O*-methyl derivative, by prolonged action of diazomethane (according to the original route of Tuppy and Böhm), was not successful and the starting material was recovered in all cases.†


(I)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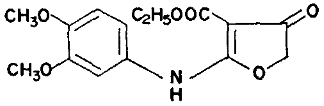
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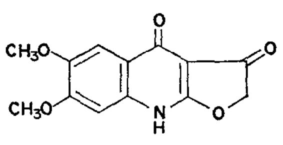
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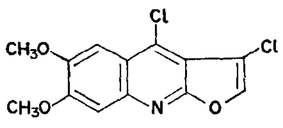
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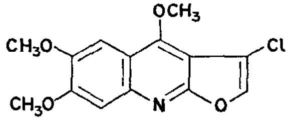
(VI)

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* Part III in series "Alkaloids of *Haplophyllum suaveolens* (DC) G. Don.". For Part II see *Phytochem.* 9, 1137 (1970).

† We noted also, that compound IV has a 4-oxo structure in the solid state, as shown by the IR spectrum: ν_{CO} from the dihydrofuran ring at 1715 cm^{-1} and ν_{CO} from 4-quinolone at 1648 cm^{-1}.

[1] M. Ionescu, I. Mester and M. Vlassa, *Rev. Roumaine Chim.* 13, 1641 (1968).

[2] Y. Kuwayama, *Yakugaku Zasshi* 82, 703 (1962); *Chem. Abs.* 58, 5741e (1963).

[3] I. Novák, G. Buzás, E. Minker, M. Koltai and K. Szendrei, *Planta Med.* 15, 132 (1967); *ibid. Acta Pharm. Hung.* 37, 225 (1967).

[4] H. Tuppy and F. Bohm, *Monatsh.* 87, 720 and 744 (1956).

We decided therefore to prepare 3,4-dichloro-6,7-dimethoxyfuro[2,3-b]quinoline (V), assuming that the chlorine atom in position 4 of this compound could be selectively substituted by the methoxy group, under the action of sodium methoxide.* By treating compound IV with partially hydrolysed phosphorus oxychloride, we obtained the dichloro derivative V, and the latter was indeed converted to 3-chlorokokusaginine (VI) by a short refluxing with methanolic sodium methoxide. The catalytic dehalogenation of this compound (VI) gave kokusaginine (I).

The alkaloid prepared in this manner is identical in all respects (IR and UV spectra, mixed m.p., R_f on TLC) with an authentic specimen isolated from *Haplophyllum suaveolens* (DC) G.Don.[1]

EXPERIMENTAL

Melting points were determined on a Boetius apparatus. IR spectra were recorded in KBr pellets, and UV spectra in EtOH.

2-(3′,4′-*Dimethoxyanilino*)-3-*carbethoxy*-4-*oxo*-4,5-*dihydrofuran* (*III*). To an ice-cold ethereal suspension of diethyl sodiomalonate (7 g Na, 48 g diethyl malonate, 500 ml ether) 13 ml choloroacetyl chloride were added with stirring, during 10 min. The mixture was kept 30 min at 20°, then refluxed for a further 30 min. Thereafter, 30 g 4-aminoveratrole were added, and the refluxing continued for 3 hr. After cooling, the precipitate was extracted with boiling benzene, and from the hot benzene extract 16 g of the ester III deposited on cooling. After repeated recrystallizations from benzene, the product melted at 150–151°. (Found: C, 58·69; H, 5·64; N, 4·78. $C_{15}H_{17}O_6N$ required: C, 58 63; H, 5·57; N, 4·56%). UV: λ_{max}: 241, 283 and 293sh nm (log ϵ_{max}: 4·25, 4·37 and 4·33 resp.) From the concentrated ethereal filtrate a further 4 g of III separated.

3,4-*Dioxo*-6,7-*dimethoxy*-2,3,4,9-*tetrahydrofuro*[2,3-*b*]*quinoline* (*IV*). The above ester (500 mg) in 25 ml paraffin oil was heated at 270° for 2 min. The product isolated after cooling and dilution with ether, was recrystallized from dimethylformamide to give 258 mg of the compound IV; m.p. 335° (decompn.) (aq. acetic acid). (Found: C, 59·70; H, 4·05; N, 5·36. $C_{13}H_{11}O_5N$ required: C, 59·77; H, 4·25; N, 5·36%.)

The ethereal–paraffin oil filtrate was shaken twice with 10 ml portions of 1 N NaOH, the aqueous phase was acidified with conc. HCl to give 90 mg of the starting ester.

3,4-*Dichloro*-6,7-*dimethoxyfuro*[2,3-*b*]*quinoline* (*V*). A mixture of 1 g 3,4-dioxo derivative IV, 30 ml $POCl_3$ and 1 ml water, was heated under reflux for 3 hr, the solution evaporated to dryness *in vacuo*, and the oily residue poured onto crushed ice. The precipitate was extracted with hot benzene, the benzene removed *in vacuo*, and the residue was recrystallized from Cellosolve to give the dichloro derivative V (870 mg), needles, m.p. 238–239°. (Found: C, 52·34; H, 3·49; N, 4·72; Cl, 23·30. $C_{13}H_9O_3NCl_2$ required: C, 52·37; H, 3·04; N, 4·70; Cl, 23·79%.) UV: λ_{max}: 221·4, 247·3sh, 253·3, 323·4sh, 336 7 and 352 nm (log ϵ_{max}: 4·44, 4·66, 4·71, 4·08, 4·20 and 4·23 resp.).

3-*Chloro*-4,6,7-*trimethoxyfuro*[2,3-*b*]*quinoline* (3-*Chlorokokusaginine*) (*VI*). A solution of 500 mg of dichloro derivative V in 15 ml methanolic NaOMe (42 mg of sodium) was refluxed for 45 min, then evaporated to dryness *in vacuo*. The residue was taken in 50 ml water, then extracted with $CHCl_3$ (3 × 25 ml); the $CHCl_3$ solution was concentrated to 5–6 ml and passed through a short column of neutral alumina (15 g). The product was eluted with $CHCl_3$, yielding 310 mg of colourless needles of 3-chlorokokusaginine; m.p. 174–175° ($CHCl_3$-*n*-hexane). (Found: C, 57·83; H, 4·08; N, 4·75; Cl, 11·95. $C_{14}H_{12}O_4NCl$ required: C, 57·25; H, 4·12; N, 4·77; Cl, 12·07%.) UV: λ_{max}: 232·5, 264 5, 275, 285, 305sh, 318 and 331 nm (log ϵ_{max}, 4·93, 4·07, 4·02, 3 99, 3·93, 4·19 and 4·25 resp.).

Kokusaginine (*I*). 3-Chlorokokusaginine (50 mg) in 40 ml ethanol was hydrogenated in the presence of 50 mg of Pd-$CaCO_3$ (10% Pd) catalyst. After filtration of the catalyst and evaporation of the solvent *in vacuo*, the residue was taken up in 2 ml benzene and chromatographed on a column of neutral alumina (20 g). Elution with benzene–ethyl acetate mixture (4:1) gave 32 mg kokusaginine, m.p. 170–171° (ethanol).

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* Tuppy and Bohm have already indicated that 3-chlorofuro[2,3-b]-quinoline remains unchanged after the prolonged action of sodium methoxide.