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**Nigritanins: the alkaloids of *Strychnos nigrifera*
Bak: a new example of the biogenetic pathway of
indole alkaloids**

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SEZIONE II

(Fisica, chimica, geologia, paleontologia e mineralogia)

Chimica. — *Nigritanins: the alkaloids of Strychnos nigritana Bak: a new example of the biogenetic pathway of indole alkaloids.* Nota di JAMES UDËNGENE OGUAKWA (*), IRENE MESSANA (**), MARCELLO NICOLETTI (***), CORRADO GALEFFI (**) e GIOVANNI BATTISTA MARINI-BETTÒLO (***), presentata (****) dal Corrisp. G. B. MARINI-BETTÒLO.

RIASSUNTO. — Dalle foglie della *Strychnos nigritana* Bak (Loganiaceae) sono stati isolati quattro nuovi alcaloidi: nigritanina, 10-ossinigritanina, 18-deidronigritanina e 18-deidro-10-ossinigritanina. La loro struttura è stata proposta in base a dati spettroscopici ed a correlazioni chimiche. Il possibile schema biogenetico (unione di una unità corinamica con una triptaminica) è discusso al confronto con quello degli alcaloidi dimeri.

In our systematic survey of *Strychnos* alkaloids we studied the alkaloids of the leaves of *Strychnos nigritana* Bak, an African species which grows especially in Nigeria. Extracts from leaves of *S. nigritana* are known in folk medicine to stimulate the central nervous system.

Alkaloids were extracted, following the usual procedure, from defatted leaves collected in the State of Anambra, identified by A. Ozioko. The yield in alkaloids was about 0.1 % of the dried leaves. TLC assays indicated the presence of two major and two minor alkaloids. Countercurrent distribution between chloroform and buffer at discontinuously decreasing pH made possible the isolation of four new alkaloids which were named nigritanin, 10-hydroxynigritanin, 18-dehydronigritanin and 18-dehydro-10-hydroxynigritanin.

Nigritanin, m.p. 202–4 °C, $C_{30}H_{36}N_4$, $[\alpha]_D^{20} = +61.8$ (c. 0.8, ethanol); NMR ($CDCl_3$, δ): Me-CH₂ (0.93, t), Me-N (2.46, s), CH-3 (3.56, m), 2 NH (6.40 and 7.80, s); MS m/e (%): 452 (M^+ , 82), 437(6), 408(10), 267(8), 253(12), 199(27) and 185(100); $UV_{MeOH} \lambda_{nm}$ (log ϵ) 226(4.76), 282(4.16), 290(4.09).

10-hydroxynigritanin, m.p. 181–3 °C, $C_{30}H_{36}N_4O$, $[\alpha]_D^{20} = +83$ (c. 0.7, ethanol); NMR (pyridine- d_5 , δ): Me-CH₂ (0.72, t), Me-N (2.36, s), CH-3 (3.70, m), 2 NH (10.70 and 11.53, s); MS m/e (%): 468 (M^+ , 86), 453(4), 424(13), 283(8), 269(13), 199(28), 185(100); $UV_{MeOH} \lambda_{nm}$ (log ϵ) 226(4.75), 282(4.17), 290(4.10), 310(3.76); IR_{CHCl_3} 3500 and 3350 cm^{-1} .

18-dehydronigritanin, m.p. 226–8 °C, $C_{30}H_{34}N_4$, $[\alpha]_D^{20} = +45.4$ (c. 0.5, ethanol); NMR ($CDCl_3$, δ): Me-N (2.48, s), CH-3 (3.60, m), $\begin{matrix} C & & H_a \\ & \diagdown & / \\ H_c & -C & =C & -H_b \end{matrix}$

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(H_a 5.10, dd, $J = 1$ and 17 Hz; H_b 5.24, dd, $J = 1$ and 10 Hz; $H_c = 5.65$, dd, $J = 10$ and 17 Hz), 2 NH (6.44 and 7.76), MS m/e (%): 450 (M^+ , 62), 435(3), 406(5), 265(6), 251(9), 199(18) and 185(100); UV_{MeOH} λ_{nm} (log ϵ) 226(4.77), 282(4.16), 290(4.09).

18-dehydro-10-hydroxynigritanin, m.p. 174–6 °C, $C_{30}H_{34}N_4O$, $[\alpha]_D^{20} = +46.8$ (c 0.6, ethanol); NMR (pyridine- d_5 , δ): Me-N (2.42, s), CH-3 (3.90, m), $\begin{matrix} C \\ H_c \end{matrix} \begin{matrix} \diagup \\ \diagdown \end{matrix} C = C \begin{matrix} \diagdown \\ \diagup \end{matrix} \begin{matrix} H_b \\ H_a \end{matrix}$ (H_a 4.95, dd, H_b 5.15, dd, H_c 5.60 dd), 2 NH (10.50 and 11.57); MS m/e (%): 466(55), 451(3), 422(3), 281(6), 267(7), 199(20), 185(100); UV_{MeOH} λ_{nm} (log ϵ) 226(4.74), 281(4.20), 290(4.12), 310(3.76); IR_{CHCl_3} 3500 and 3350 cm^{-1} .

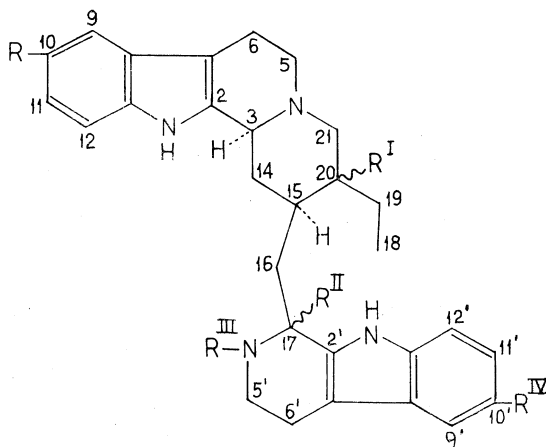


Fig. 1.

	R	R ^I	R ^{II}	R ^{III}	R ^{IV}
I Usambarine.	H	Δ^{19}	u.c.H	Me	H
II Nigritanin	H	u.c.H	α H	Me	H
III 10-hydroxynigritanin	OH	u.c.H	α H	Me	H
IV 18-dehydronigritanin	H	u.c.H	α H	Me	H Δ^{18}
V 18-dehydro-10-hydroxynigritanin	OH	u.c.H	α H	Me	H Δ^{18}
VI Cinchophyllamine	OMe	u.c.H	u.c.H	H	OMe
VII Isocinchophyllamine	OMe	β H	α H	H	OMe
VIII Ochrolifuanin A	H	β H	β H	H	H
IX Ochrolifuanin B	H	β H	α H	H	H

u.c. = undetermined configuration.

Hydrogenation with 5 % Pd(C) of 18-dehydronigritanin and 18-dehydro-10-hydroxynigritanin afforded nigritanin and 10-hydroxynigritanin, respectively.

From the above data and chemical results it was possible to correlate the structure of the four alkaloids, whose skeleton -one corynane moiety linked with one triptamine moiety- was inferred by MS. In particular, the spectrum of 18-dehydronigritanin was similar to that of usambarine (I), an alkaloid isolated from *S. usambarensis* Gilg by Koch and Plat [1].

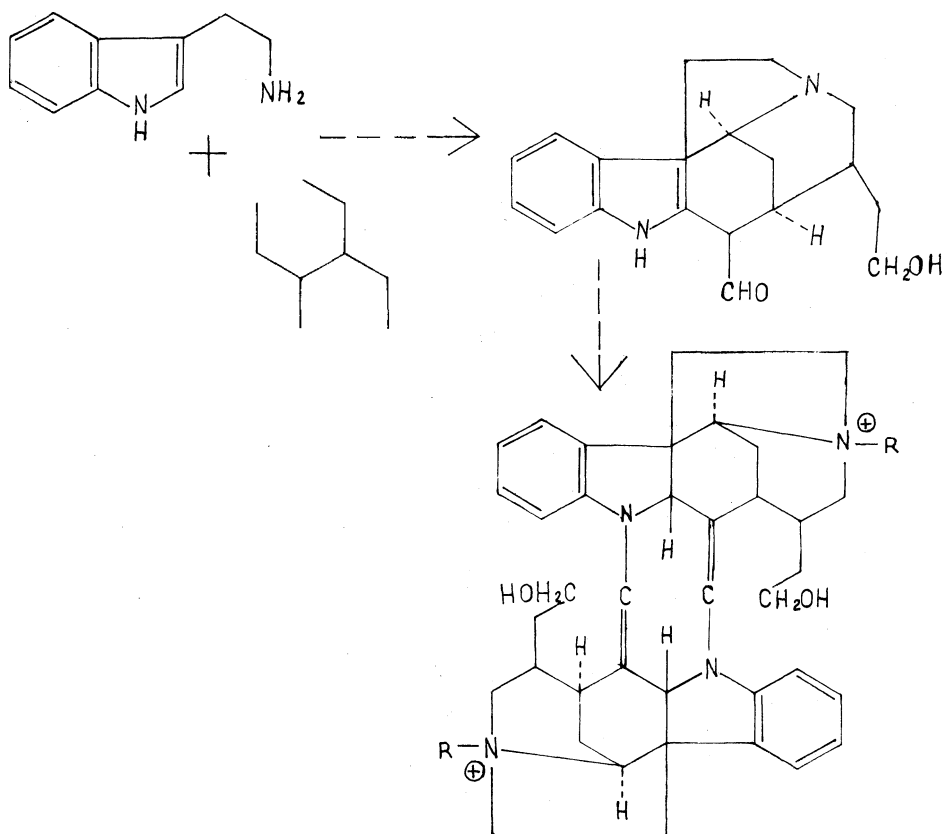


Fig. 2.

Therefore we propose to assign to nigritanin and 10-hydroxynigritanin the formulas II and III, respectively, and to 18-dehydronigritanin and 18-dehydro-10-hydroxynigritanin the formulas IV and V, respectively (fig. 1).

The α configuration of the chiral centers C-3 and C-17 could be inferred from the strong positive Cotton effect at 280 nm [2], whereas the α configuration at C-15 was suggested by biogenetic considerations. The configuration of the chiral center C-20 is still undetermined.

The pathway of the *Strychnos* alkaloid biosynthesis suggested by Schlittler and Taylor [3] and later by Battersby [4] originates from the condensation

or addition of a tryptamine moiety with a C_{10} or C_9 unit (i.e. loganine or a secoiridoid, as proposed by one of us [5]). The synthesis leads to monomeric alkaloids like desacetyldiaboline (W. G. aldehyde) or hemitoxiferine, which may dimerize to the C_{40} alkaloids like curarine (fig. 2). In the present case one tryptamine unit plus one C_9 unit can react to give rise to a corynane type molecule, which reacts further with another tryptamine unit to give nigritanins (fig. 3). A similar mechanism has been demonstrated for the biosynthesis of emetine from phenylalanine [6].

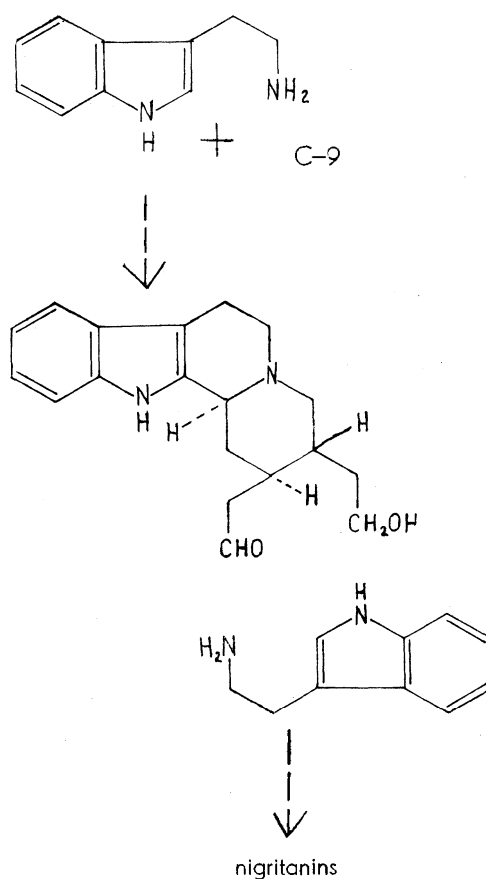


Fig. 3.

Similar alkaloids were isolated from plants of the same order (Gentianaleae). So cinchophyllamine (VI) and isocinchophyllamine (VII) were found in *Cinchona ledgeriana* Moens (Rubiaceae) [7], [8] and ochrolifuanins A and B (VIII and IX, respectively) were found in *Ochrosia lituana* Guill (Apocynaceae) [9], [10].

We wish to stress the fact that all these alkaloids (nigritanins, usambarine, cinchophyllamines, and ochrolifuanins) have been found so far only in the leaves of plants, whereas dimeric alkaloids are present in stem bark and mainly in roots.

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