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NEW ALKALOIDS FROM *STRYCHNOS ICAJA*

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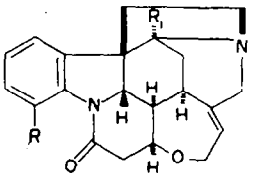
Key Word Index—*Strychnos icaja*; Loganiaceae; indole alkaloids; 4-methoxy-substituted indole alkaloids; 3,4-dimethoxy-substituted indole alkaloids.

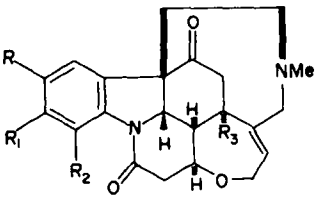
Abstract—The alkaloids of *Strychnos icaja* (Loganiaceae) have been studied. An extract from Zaire leaf material yielded nine alkaloids, comprising novacine, the new base 21,22-α-epoxy-4,14-dihydroxy-3-methoxy-*N*-methyl-*sec*.-pseudostrychnine, and seven others of known structure previously obtained from the plant. Cameroun leaf material gave five alkaloids, of which one, 21,22-α-epoxy-3,4-dimethoxy-*N*-methyl-*sec*.-pseudostrychnine, is new. Fruits from Gabon afforded eight alkaloids; two of them are new and are formulated as 21,22-α-epoxy-4-methoxy-*N*-methyl-*sec*.-pseudostrychnine and the corresponding 14-hydroxy derivative.

INTRODUCTION

Strychnine (**1a**) and 4-hydroxystrychnine (**1b**) are the active principles contained in the roots of the arrow-poison plant *Strychnos icaja* Baill. [1]. From the crude leaf alkaloids of this species, Jaminet [2] isolated three products, which were shown to be compounds related to strychnine and brucine but belonging to different types of the *N*-methyl-*sec*.-pseudo series of bases: a mixture of icajine (**2a**) and vomicine (**2b**) [3], 21,22-α-epoxynovacine (**3d**) [4], and 21,22-α-epoxy-14-hydroxynovacine (**3g**) [5]. Further alkaloids have been obtained from the leaves, which apart from pseudostrychnine (**1c**) [5] are all, like Jaminet's alkaloids, *N*-methyl-*sec*.-pseudo bases of various types (**2e**, **3a–g**) [4,5].

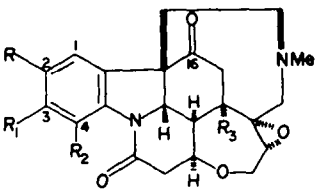


1a R = R_1 = H
1b R = OH, R_1 = H
1c R = H, R_1 = OH



2a R = R_1 = R_2 = R_3 = H
2b R = R_1 = R_3 = H, R_2 = OH
2c R = R_2 = R_3 = H, R_1 = OMe or R = OMe, R_1 = R_2 = R_3 = H
2d R = R_1 = OMe, R_2 = R_3 = H
2e R = R_1 = R_2 = H, R_3 = OH

In the course of the present work, carried out in order to gather information on the variation in alkaloid composition of *S. icaja*, Jaminet's original alkaloid mixture, which came from the leaves of Zaire material [6], has been studied in greater detail. Other products investigated have been the crude alkaloid mixtures from the leaves of Cameroun material [7], from fruits collected in Gabon, and from the samples screened by Bisset and Phillipson [7].



3a R = R_1 = R_3 = H, R_2 = OH
3b R = OMe, R_1 = R_2 = R_3 = H
3c R = R_3 = H, R_1 = OMe, R_2 = OH
3d R = R_1 = OMe, R_2 = R_3 = H
3e R = R_1 = R_2 = H, R_3 = OH
3f R = R_1 = H, R_2 = R_3 = OH
3g R = R_1 = OMe, R_2 = H, R_3 = OH

3h R = R_1 = R_3 = H, R_2 = OMe
3i R = R_3 = H, R_1 = R_2 = OMe
3j R = R_1 = H, R_2 = OMe, R_3 = OH
3k R = H, R_1 = OMe, R_2 = R_3 = OH

RESULTS AND DISCUSSION

Leaf material from Zaire

Fractionation of the $CHCl_3$-soluble bases enabled 8 known alkaloids to be isolated: icajine (**2a**), vomicine (**2b**), novacine (**2d**), 2- or 3-methoxy-*N*-methyl-*sec*.-pseudostrychnine (**2c**), 21,22-α-epoxyvomicine (**3a**), 21,22-α-epoxynovacine (**3d**), 21,22-α-epoxy-4-hydroxy-3-methoxy-*N*-methyl-*sec*.-pseudostrychnine (**3c**), and 21,22-α-epoxy-14-hydroxy-2,3-dimethoxy-*N*-methyl-*sec*.-pseudostrychnine (**3g**). These alkaloids were all identified by comparison of their TLC and spectroscopic properties

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with those of authentic samples. The compounds have previously been obtained from *S. icaja* leaves [5], with the exception of novacine (**2d**) which up until now has been found only in the Asian species *S. nux-vomica* L. [8] and *S. wallichiana* Steud. ex DC. [9].

A ninth alkaloid **3k** is new, but its spectral properties show that it is related to 21,22-α-epoxy-4-hydroxy-3-methoxy-*N*-methyl-*sec.*-pseudostrychnine (**3c**), which has previously been extracted from *S. icaja* [5]. Accurate mass measurement is in agreement with the formula $C_{23}H_{26}N_2O_7$, so that the new base differs only in the occurrence of an extra O atom. This is present as a (second) hydroxyl function—IR band at 3535 cm^{-1} and PMR signal at δ 3.62 disappearing on deuteration. That the function is located at position 14 is suggested by the general similarity of the MS and PMR spectra with those of alkaloids belonging to the 21,22-α-epoxy-14-hydroxy-*N*-methyl-*sec.*-pseudo series (**3e–g**) and more specifically by the peak at *m/e* 316 (M^+–126) and the quartet centred at *ca* δ 2.0—features which have been shown to characterize these bases [5]. The new alkaloid is therefore 21,22-α-epoxy-4,14-dihydroxy-3-methoxy-*N*-methyl-*sec.*-pseudostrychnine (**3k**).

Leaf material from Cameroun (Leeuwenberg 5349)

Five alkaloids were isolated from this material (Table 1), which has previously been screened by Bisset and Phillipson [7]. Four of the component bases were known compounds, while the fifth, which gave a red–violet colour on spraying with $FeCl_3$–$HClO_4$ and heating, was shown to be a new alkaloid (**3i**).* Accurate mass measurement indicated the formula $C_{24}H_{28}N_2O_6$. "Indole" peaks in the MS at *m/e* 190, 203, and 204 and two 3-hydrogen singlets at δ 3.84 and 3.93 in the PMR spectrum show that two OMe substituents are present in the indole moiety. The UV spectrum resembles that of N_a-acyldihydroindole bases with OMe groups at positions 3 and 4, such as pyrifolidine of the aspidospermidine series [10]. This is in agreement with the PMR signals for the aromatic hydrogens which are present as an AB system of doublets centred on δ 6.70 and 7.53 (J_o 9 Hz), indicating that the two hydrogens are adjacent to each other. The suggested locations of the two OMe groups are also acceptable on biogenetic grounds, viz. because of the simultaneous presence of 4-hydroxy-3-methoxy bases in the plant and because the alternative possibility, with the OMe at positions 1 and 2, is less likely in view of the fact that no bases with a substituent at the position 1 have so far been discovered in *Strychnos* species. The compound thus belongs to the 3,4-diOMe series and is isomeric with the more commonly encountered brucine or 2,3-diOMe series of bases. The remaining spectral properties of the compound (see Experimental) indicate that it is a member of the epoxy-*N*-methyl-*sec.*-pseudo series (**3a–d**) [5] and it is therefore assigned the structure 21,22-α-epoxy-3,4-dimethoxy-*N*-methyl-*sec.*-pseudostrychnine (**3i**), which means that it is isomeric with 21,22-α-epoxy-2,3-dimethoxy-*N*-methyl-*sec.*-pseudostrychnine (**3d**), the main alkaloid of the mixture.

Table 1. Alkaloids from *Strychnos icaja* leaves (Cameroun material, *Leeuwenberg* 5439)

Alkaloid	% Yield
Icajine (**2a**) + Vomicine (**2b**)	0.30*
21,22-α-Epoxy-4-hydroxy-3-methoxy-*N*-methyl-*sec.*-pseudostrychnine (**3c**)	0.16
21,22-α-Epoxy-2,3-dimethoxy-*N*-methyl-*sec.*-pseudostrychnine (**3d**)	1.46
21,22-α-Epoxy-3,4-dimethoxy-*N*-methyl-*sec.*-pseudostrychnine (**3i**)	0.60

* 0.06% of **2b** alone was also isolated

Fruits from Gabon (ex Colonial Exhibition, Paris, 1889)

The fruits of *S. icaja* have not so far been examined. The present sample was originally collected in Gabon as the fruits of *m'boundou* [cf. 11] and they were exhibited at the Colonial Exhibition held in Paris in 1889. Extraction by the procedure used in screening African *Strychnos* material [7] afforded as much as 7.4% crude alkaloid mixture from the entire fruits. Repeated preparative-TLC enabled 8 products to be isolated (Table 2).

The identities of the previously known alkaloids were verified on the basis of their TLC and spectroscopic properties and by comparison with authentic samples. Two of the alkaloids **3h** and **3j** gave blue–violet colours on spraying with $FeCl_3$–$HClO_4$ and heating.* They are 4-OMe derivatives and their structure determinations are discussed in the following paragraphs. Accurate mass measurement indicated the formula $C_{23}H_{26}N_2O_5$ for **3h**. "Indole" peaks are present in the MS at *m/e* 160, 173, and 174, showing that there is a OMe substituent in the aromatic ring of the indole nucleus; confirmation is provided by the PMR spectrum which has a 3-hydrogen singlet at δ 3.90. The UV spectrum is similar to that of 9-acetyl-8-methoxyhexahydrocarbazole [12], which suggests that the OMe group is located in the 4-position. Additional evidence comes from a study of the aromatic region of the PMR spectrum which has a set of signals for three hydrogens very like that seen in the spectrum of vomicine (**2b**). The signals for the aromatic hydrogens of **3h** are found at δ 6.85–7.57 which is at slightly lower field than is the case with **2b** [5], presumably because the 4-OMe has a smaller shielding effect than the 4-OH group [13]. The remaining spectro-

Table 2. Alkaloids from *Strychnos icaja* fruits (Gabon material, ex Colonial Exhibition, Paris, 1889)

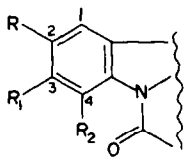
Alkaloid	% Yield
Icajine (**2a**) + Vomicine (**2b**)	0.51
21,22-α-Epoxy-2,3-dimethoxy-*N*-methyl-*sec.*-pseudostrychnine (**3d**)	0.27
21,22-α-Epoxy-4,14-dihydroxy-*N*-methyl-*sec.*-pseudostrychnine (**3f**)	0.18
21,22-α-Epoxy-14-hydroxy-2,3-dimethoxy-*N*-methyl-*sec.*-pseudostrychnine (**3g**)	0.21*
21,22-α-Epoxy-4-methoxy-*N*-methyl-*sec.*-pseudostrychnine (**3h**)	0.39*
21,22-α-Epoxy-14-hydroxy-4-methoxy-*N*-methyl-*sec.*-pseudostrychnine (**3j**)	1.70
21,22-α-Epoxy-4-hydroxy-3-methoxy-*N*-methyl-*sec.*-pseudostrychnine (**3k**)	0.96

* 0.24% of a mixture of **3g** and **3h** was also obtained.

* TLC of the various *S. icaja* extracts previously screened by Bisset and Phillipson [7] after spraying with $FeCl_3$/$HClO_4$ and heating [9] revealed that they all contained component alkaloids giving red- to blue–violet colours with the spray. Evidently, therefore, the occurrence of 4-methoxy- and 3,4-dimethoxy-substituted bases is quite common in the plant. However, Jaminet's alkaloid mixture from Zaire material proved to be an exception and such compounds were not observed to be among its alkaloids.

scopic properties of **3h** show that the alkaloid belongs to the epoxy-*N*-methyl-*sec*.-pseudo series (**3a–d**) [5] and the compound can be formulated as 21,22-α-epoxy-4-methoxy-*N*-methyl-*sec*.-pseudostrychnine.

Accurate mass measurement of the second base **3j**, the major alkaloid obtained from the fruit sample, indicates the formula $C_{23}H_{26}N_2O_6$. It differs from **3h** only in the presence of an additional O, which the IR and PMR spectra reveal is present as an OH function. From the spectral properties of the compound, particularly the MS with the ion at *m/e* 300 (M^+-126), it is clear that it is also a member of the 21,22-α-epoxy-14-hydroxy-*N*-methyl-*sec*.-pseudo series (**3e–g**) [5]; cf. the discussion of **3k** above. The OH group may therefore by placed at position 14, so that **3j** has the structure 21,22-α-epoxy-14-hydroxy-4-methoxy-*N*-methyl-*sec*.-pseudostrychnine.



4a R = R_1 = R_2 = H
4b R = OMe, R_1 = R_2 = H
4c R = R_2 = H, R_1 = OMe
4d R = R_1 = H, R_2 = OH
4e R = R_1 = H, R_2 = OMe
4f R = R_1 = OMe, R_2 = H
4g R = H, R_1 = OMe, R_2 = OH
4h R = H, R_1 = R_2 = OMe

The isolation in recent years of alkaloids from *Strychnos* with new aromatic substitution patterns [5,9] shows that these plants are able to synthesize a wide variety of such alkaloids, **4a–h**. So far, no trisubstituted bases have been isolated, such as are known to occur among the indole alkaloids in species of the related genus *Gardneria* [14] and in species of *Aspidosperma* (Apocynaceae) [15]. Likewise, no bases with a substituent in the 1-position, such as are known to be present in species of *Mitragyna* (Rubiaceae) [16], have yet been found. It is noteworthy that unlike the alkaloids present in the fruits of *S. nux-vomica* [17], which are chiefly bases of the normal series, the greater part of those in the *S. icaja* fruits examined belong to the various *N*-methyl-*sec*.-pseudo series.

EXPERIMENTAL

Mps are uncorrected. PMR spectra were determined in $CDCl_3$ soln at 90 MHz with TMS as internal standard (δ = 0.00). High resolution MS were obtained at 70 eV and at inlet temps between 140° and 260°. The general techniques used in isolating and examining the alkaloids have been described in previous publications [5,17]. For TLC spraying routine use was made of 0.2M $FeCl_3$ in 35% aq. $HClO_4$, rather than Dragendorff reagent, followed by heating at *ca* 90° [9]. Known alkaloids were identified by means of their mp, colour reactions and TLC properties, and by comparison of their UV, IR, and/or MS with those of authentic samples available in our laboratory. Only the data on the new alkaloids are listed.

Zaire leaf material (alkaloid mixture ex Denoël). 21,22-α-*Epoxy*-4,14-*dihydroxy*-3-*methoxy*-N-*methyl*-sec.-*pseudostrychnine* (**3k**). Prisms (EtOAc), mp 255–260°; λ_{max}^{EtOH}: 237 and 270 nm (log ϵ 4.21 and 3.80); $\nu_{max}^{CHCl_3}$: 855, 1255, 1307, 1320, 1400, 1470, 1583, 1605, 1645, 1668, and 3535 cm^{-1}; δ^{CDCl_3}: 1.95 (3-H; *s*; 19-NMe), *ca* 2.0 (*q*; $J_{13,8}$ 12 Hz, $J_{13,12}$ 6 Hz; H-13), 3.62 (1-H; *s*, disappearing on deuteration; 14-OH), 3.81 (3-H; *s*; 3-OMe), 4.06 (1-H; *m*; H-23α), 4.18 (1-H; *d*, $J_{8,13}$ 12 Hz; H-8), 4.80 (1-H; *m*; H-23β), 6.63 (1-H; *d*, J_0 9 Hz; H-2), 7.18 (1-H; *d*, J_0 9 Hz; H-1), and 12.16 (1-H; *s*; 4-OH); [found: M^+ 442.1730, $C_{23}H_{26}N_2O_7$ requires M^+ 442.1740]; MS: *m/e* 442 (M^+, 100%), 383 (6), 371 (6), 316 (6), 271 (6), 272 (3), 256 (9), 255 (9), 190 (12), 189 (12), 176 (6), 72 (19), 71 (39), 70 (19), 58 (66), and 57 (52).

Cameroun leaf material (*Leeuwenberg* 5349) [7]. 21,22-α-*Epoxy*-3,4-*dimethoxy*-N-*methyl*-sec.-*pseudostrychnine* (**3i**). The base was not obtained as crystals, but TLC and GLC examination confirmed that the material was a single entity. λ_{max}^{EtOH}: 226, 256, and 295 nm (log ϵ 4.30, 4.11, and 3.58); $\nu_{max}^{CHCl_3}$: 850, 1130, 1260, 1638, and 1670 cm^{-1}; δ^{CDCl_3}: 2.01 (3-H; *s*; 19-NMe), 3.84 (3-H; *s*; 3-OMe), 3.93 (3-H; *s*; 4-OMe), 4.58 (1-H; *d*, $J_{8,13}$ 12 Hz; H-8), 6.70 (1-H; *d*, J_0 9 Hz; H-2), and 7.53 (1-H; *d*, J_0 9 Hz; H-1); [found: M^+ 440.1944, $C_{24}H_{28}N_2O_6$ requires M^+ 440.1948]; MS: *m/e* 440 (M^+, 100%), 395 (10), 381 (26), 369 (20), 270 (6), 269 (3), 244 (14), 204 (6), 203 (3), 190 (3), 72 (14), 71 (20), 70 (8), 58 (28), and 57 (20).

Gabon fruits (*ex Colonial Exhibition, Paris*, 1889). 21,22-α-*Epoxy*-4-*methoxy*-N-*methyl*-sec.-*pseudostrychnine* (**3h**). The compound was not obtained as crystals. λ_{max}^{EtOH}: 217, 256, and 295 nm (log ϵ 4.29, 4.11, and 3.85); $\nu_{max}^{CHCl_3}$: 850, 1130, 1150, 1175, 1275, 1300, 1385, 1455, 1490, 1605, and 1680 cm^{-1}; δ^{CDCl_3}: 2.01 (3-H; *s*; 19-NMe), 3.90 (3-H; *s*; 4-OMe), 6.92 (1-H; *q*, J_0 7.5 Hz, J_m 1.5 Hz; H-3), 7.13 (1-H; *t*, J_0 7.5 Hz; H-2), and 7.53 (1-H; *q*, J_0 7.5 Hz, J_m 1.5 Hz; H-1); [found: M^+ 410.1857, $C_{23}H_{26}N_2O_5$ requires M^+ 410.1843]; MS: *m/e* 410 (M^+, 100%), 351 (10), 339 (34), 278 (21), 240 (21), 214 (36), 174 (10), 173 (5), 160 (5), 72 (18), 71 (30), 70 (10), 58 (32), and 57 (27).

21,22-α-*Epoxy*-14-*hydroxy*-4-*methoxy*-N-*methyl*-sec.-*pseudostrychnine* (**3j**). The base was not obtained as crystals. λ_{max}^{EtOH}: 217, 256, and 295 nm (log ϵ 4.29, 4.11, and 3.58); $\nu_{max}^{CHCl_3}$: 850, 1130, 1153, 1175, 1273, 1300, 1385, 1456, 1490, 1605, 1680, and 3510 cm^{-1}; δ^{CDCl_3}; 2.04 (3-H; *s*; 19-NMe), 3.53 (1-H; *s*; 14-OH), 3.91 (3-H; *s*; 4-OMe), 6.94 (1-H; *q*, J_0 7.5 Hz, J_m 1.5 Hz; H-3), 7.13 (1-H; *t*, J_0 7.5 Hz; H-2), and 7.53 (1-H; *q*, J_0 7.5 Hz, J_m 1.5 Hz; H-1); [found: M^+ 426.1819, $C_{23}H_{26}N_2O_6$ requires M^+ 426.1792]; MS: *m/e* 426 (M^+, 100%), 367 (4), 355 (7), 300 (14), 240 (10), 230 (24), 174 (24), 173 (10), 160 (14), 72 (21), 71 (38), 70 (21), 58 (59), and 57 (60).

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