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Revised Structure of Isoschizogamine

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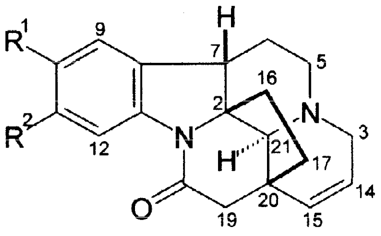
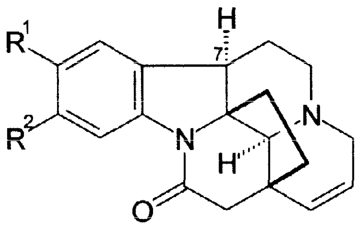
Abstract: Isoschizogamine was isolated from the twigs of *Schizozygia caffaeoides* and its structure revised to **10** on the basis of NMR analysis. It is shown to possess as yet undescribed hexacyclic skeleton of N-acyl 1,2,3,4-tetrahydroquinoline type, the nitrogen atom of which is included in an aminal moiety. The alkaloid is proposed to originate from schizozygane-type intermediates through oxidation, aziridine formation and subsequent ring opening. © 1997 Elsevier Science Ltd. All rights reserved.

Schizozyganes represent a small group of hexacyclic N-acyl indoline alkaloids[1]. With the exception of strempeliopine[2-4], a parent base of this group, all the alkaloids were isolated[5] from the monotypic shrub *Schizozygia caffaeoides* (Boj.) Baill. growing in tropical East Africa. In addition to schizozygine (**1**)[6], the main alkaloid, two pairs of minor alkaloids were reported[7] from the plant, i.e. schizogamine (**2**), schizogaline (**3**), and isoschizogamine (**4**), isoschizogaline (**5**); the differences in physico-chemical properties between the pairs were ascribed to the epimeric stereochemistry at C-7. We wish to report here on the revision of the structure of isoschizogamine[8].



1 $R^1 + R^2 = OCH_2O$
2 $R^1 = R^2 = OMe$
3 $R^1 = H, R^2 = OMe$



4 $R^1 = R^2 = OMe$
5 $R^1 = H, R^2 = OMe$

We have now re-isolated isoschizogamine[9] from the twigs of *Schizozygia caffaeoides*[10] and subjected it to NMR spectral elucidation. The appearance of signals in ^{13}C-NMR spectrum at δ 173.79 (5-membered rather than 6-membered lactam ring), 84.44 (quaternary), 37.66 and 34.95 (both tertiary carbons) was not compatible with structure **4**. In addition, a singlet of hydrogen H-21[11], as well as the spin systems of 4

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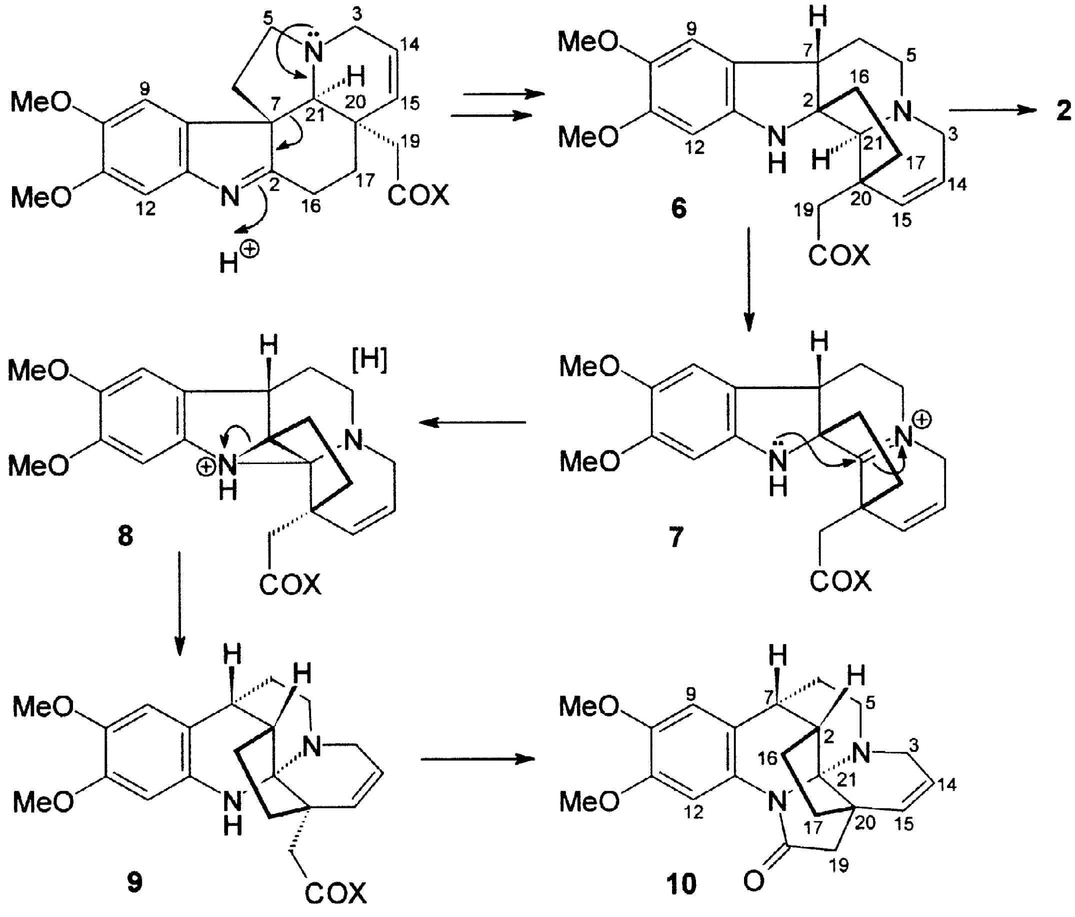
hydrogens on C-16, C-17 and of 5 hydrogens on C-5, C-6, C-7 could not be found in the proton 2D-COSY spectrum; instead, a ten proton spin system, N-CH_2-CH_2-CH-CH-CH_2-CH_2, was identified.

These findings suggest a rearranged structure for isoschizogamine. It is anticipated that the skeleton of the alkaloid could be related biogenetically to that of schizozygane alkaloids, scheme 1. If so, then C-21 dehydrogenation in schizozygane intermediates such as **6**, followed by indoline nitrogen addition to the imminium **7** results in the formation of aziridine **8**. Subsequent reductive opening of the aziridine ring gives rise to the tetrahydro quinoline **9**, and the lactam formation in the latter completes biosynthesis of the isoschizogamine (**10**), manifesting itself by the presence of the 10 hydrogen spin system (vide supra). The peak in the ^{13}C-NMR spectrum at δ 84.44 is now easily recognised as the aminal carbon C-21.



Scheme 1. Biosynthetic proposal for isoschizogamine (**10**)

A combination of proton COSY and NOESY, ^{13}C-APT and ^{1}H-^{13}C-HETCOR spectra, and inspection of the Dreiding stereomodels, allowed complete structural assignment of all carbons and hydrogens, table 1. Important non-trivial NOE-contacts observed in the NOESY spectrum are shown in figure 1. In particular, the NOE effect between hydrogens at δ 3.44 (H-3β) and 2.31 (H-2) confirms the configuration at C-2 as inferred from scheme 1. The spatial arrangement of hydrogens on ring C follows from the NOE effects between H-3β

Table 1. ^{1}H- and ^{13}C-NMR Data for Isoschizogamine (**10**)[a]

Position	δ_C	δ_H		J (H, H)			
2	34.95	2.31	ddd	12.1 (2,16b)	6.9 (2,16a)	2.5 (2,7)	
3 α	47.86	3.28	ddd	17.2 (3α,3β)	4.7 (3α,14)	1.7 (3α,15)	
β		3.44	dt	17.2 (3β,3α)	2.7 (3β,15)	1.9 (3β,14)	
5 α	44.45	2.93	ddd	14.7 (5α,5β)	13.2 (5α,6β)	3.6 (5α,6α)	
β		2.52	dddd	14.7 (5β,5α)	4.5 (5β,6β)	1.6 (5β,6α)	0.5 (5β,7)
6 α	26.77	1.21	ddt	13.2 (6α,6β	3.6 (6α,5α)	3.4 (6α,7)	1.6 (6α,5β)
β		2.21	ddt	13.2 (6β,6α)	13.2 (6β,5α)	4.5 (6β,5β)	3.3 (6β,7)
7	37.66	3.20	bq	3.4 (7,6α)	3.3 (7,6β)	2.5 (7,2)	0.5 (7,5β)
8	117.41	-					
9	111.26	6.60	s				
10	145.34	-					
11	147.66	-					
12	102.61	8.51	s				
13	131.54	-					
14	119.95	5.59	ddd	10.1 (14,15)	4.7 (14,3α)	1.9 (14,3β)	
15	130.98	5.73	ddd	10.1 (15,14)	2.7 (15,3β)	1.7 (15,3α)	
16 a	24.76	1.67	dddd	12.7 (16a,16b)	8.7 (16a,17a)	6.9 (16a,2)	1.7 (16a,17b)
b		1.19	tt	12.7 (16b,16a)	12.1 (16b,2)	9.8 (16b,17a)	9.8 (16b,17b)
17 a	36.57	1.83	ddt	14.0 (17a,17b)	9.8 (17a,16b)	8.7 (17a,16a)	0.6 (17a,19α)
b		1.76	ddd	14.0 (17b,17a)	9.8 (17b,16b)	1.7 (17b,16a)	
18	173.79	-					
19 α	45.96	2.84	bd	16.5 (19α,19β)	0.6 (19α,17a)		
β		2.52	d	16.5 (19β,19α)			
20	44.28	-					
21	84.44	-					
10-MeO	56.11	3.86	s				
11-MeO	56.02	3.92	s				

[a]) in deuteriochloroform, at 500 and 62.5 MHz, respectively; for atom numbering, see fig. 1

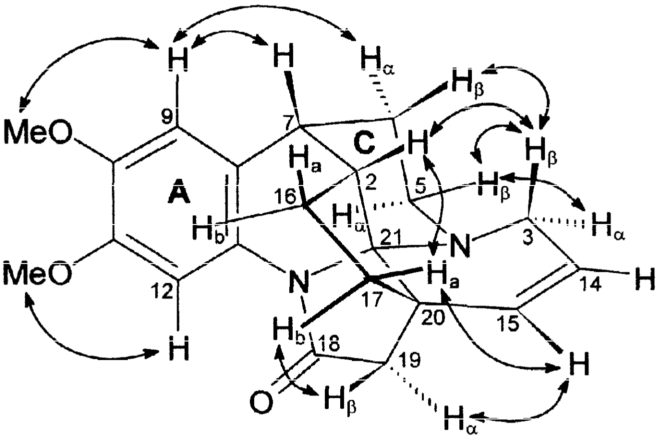


Figure 1. Non-trivial NOE-contacts observed in isoschizogamine (**10**)

and H-6β, between aromatic H-9 and H-7, and finally between both hydrogens on C-3 and H-5β. In combination with the long range (W) coupling between H-7 and H-5β (J ~ 0.5 Hz) these findings allowed us to deduce a chair conformation for the ring C. On the other hand, the hydrogens on C-19 (and on C-17 as well) were easily assigned configuration on the basis of both long range (W) coupling (J = 0.6 Hz) between H-17a and H-19 at δ 2.84 ppm, which is α-oriented, and the cross peak in the NOESY spectrum between H-17b and H-19β.

Isoschizogamine (**10**) is thus the first representative of a new indole alkaloid type manifesting itself by the presence of an aminal moiety. Work is in progress on the isolation and structure elucidation of isoschizogaline.

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References and Notes

1. Saxton, J. E. in *Indoles, Part Four, The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; John Wiley: New York, 1984; Chpt. IX, pp. 439-465
2. Laguna, A.; Novotný, L.; Dolejš, L.; Buděšínský, M. *Planta Med.* **1984**, *50*, 285-288
3. Hájíček, J.; Trojánek, J. *Tetrahedron Lett.* **1981**, *22*, 2927-2928
4. Hájíček, J.; Trojánek, J. *Collect. Czech. Chem. Commun.* **1986**, *51*, 1731-1742
5. Renner, U.; Kernweisz, P. *Experientia*, **1963**, *19*, 244-246
6. Renner, U.; Fritz, H. *Helv. Chim. Acta* **1965**, *48*, 308-317
7. Renner, U. *Lloydia* **1964**, *27*, 406-415
8. Years ago, Dr. U. Renner himself put some doubt on the correctness of the structures **4** and **5**; see reference 20 in ref.[4]
9. M.p. 181,5-184,5°C (AcOEt), $[\alpha]_D$ -241° (c 0.85; $CHCl_3$). Ref.[5,7] m.p. 184-185°C (ether), $[\alpha]_D$ -239° (c 1.0; $CHCl_3$)
10. Twigs and leaves of *Schizozygia caffaeoides* were collected in July 1996 on the seaside of the Mombasa region, Kenya by Sedaherb S.A. (Saint Léger sur Dheune, France).
11. Biogenetic numbering [Le Men, J.; Tailor, W. I. *Experientia* **1965**, *21*, 508-511. Trojánek, J.; Bláha, K. *Lloydia* **1966**, *29*, 149-155], as modified after the biogenetic proposal for the schizozygane alkaloids[4] is used.