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A Nuclear Magnetic Resonance Study on the Eleven Stereoisomers of Heteroyohimbine-Type Oxindole Alkaloids

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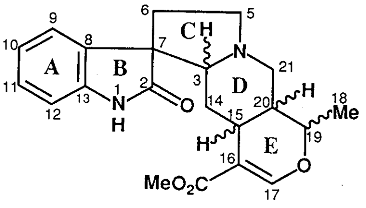
Complete assignments of the proton and carbon signals as well as conformational analysis of eleven basic heteroyohimbine-type oxindole alkaloids were performed by using modern NMR techniques.

Keywords alkaloid; heteroyohimbine-type oxindole; ^{1}H-NMR; ^{13}C-NMR; conformational analysis

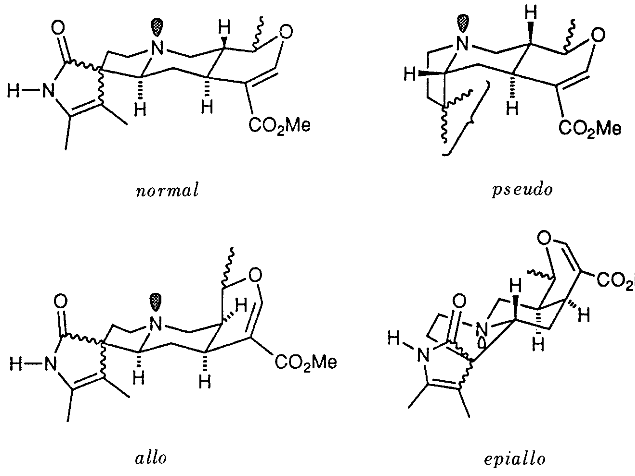
The heteroyohimbine-type oxindole alkaloids represented by the general formula (I) (Fig. 1) have been found in many plants of the genera *Mitragyna* and *Uncaria* plants, certain members of which have been used in traditional folk medicines.[1)] Theoretically, thirty-two stereoisomers of this general formula are possible because the structure contains five asymmetric centers. Biogenetically, the absolute configuration of the asymmetric center at the C-15 position is fixed in (*S*) form.[2)] Therefore, the number of possible isomers of I can be restricted to sixteen. Actually, nine natural heteroyohimbine-type alkaloids and three other semi-synthetic oxindole alkaloids having the basic structure (I) are known.[1,3,4)] However, only a few papers[5)] concerning the high field NMR spectroscopic studies of all the basic heteroyohimbine-type oxindole alkaloids (I) have been published. We describe here the complete assignments of the proton and carbon signals, and detailed conformational analysis of eleven oxindole alkaloids by using 500 MHz NMR equipment.

In 1967, Shamma *et al.*[3)] classified the heteroyohimbine-type oxindole alkaloids into four groups, namely, *normal*-, *pseudo*-, *allo*-, and *epiallo*-types (Table I, Fig. 2). Among them, no *pseudo*-type compound has yet been found in



I

Fig. 1. Heteroyohimbine-Type Oxindole Alkaloids



normal *pseudo*

allo *epiallo*

Fig. 2

TABLE I. Stereoisomers of Heteroyohimbine-Type Oxindole Alkaloids (I)

Type	Configuration of C$_3$-H	Configuration of C$_{20}$-H	D/E ring relationship	Configuration of C$_{19}$-H	Configuration of C$_7$	Alkaloid
normal	*S* (α)	*R* (β)	*trans*	*S* (β)	*S*	Isomitraphylline
					R	Mitraphylline
				R (α)	*S*	Uncarine A (isoformosanine)
					R	Uncarine B (formosanine)
epiallo	*R* (β)	*S* (α)	*cis*	*S* (β)	*S*	Uncarine D (speciophylline)
					R	Uncarine F
				R (α)	*S*	Rauniticine-*epiallo*-oxindole A
					R	Rauniticine-*epiallo*-oxindole B
allo	*S* (α)	*S* (α)	*cis*	*S* (β)	*S*	Uncarine E (isopteropodine)
					R	Uncarine C (pteropodine)
				R (α)	*S*	Rauniticine-*allo*-oxindole A
					R	Rauniticine-*allo*-oxindole B
pseudo	*R* (β)	*R* (β)	*trans*	*S* (β)	*S*	—
					R	—
				R (α)	*S*	—
					R	—

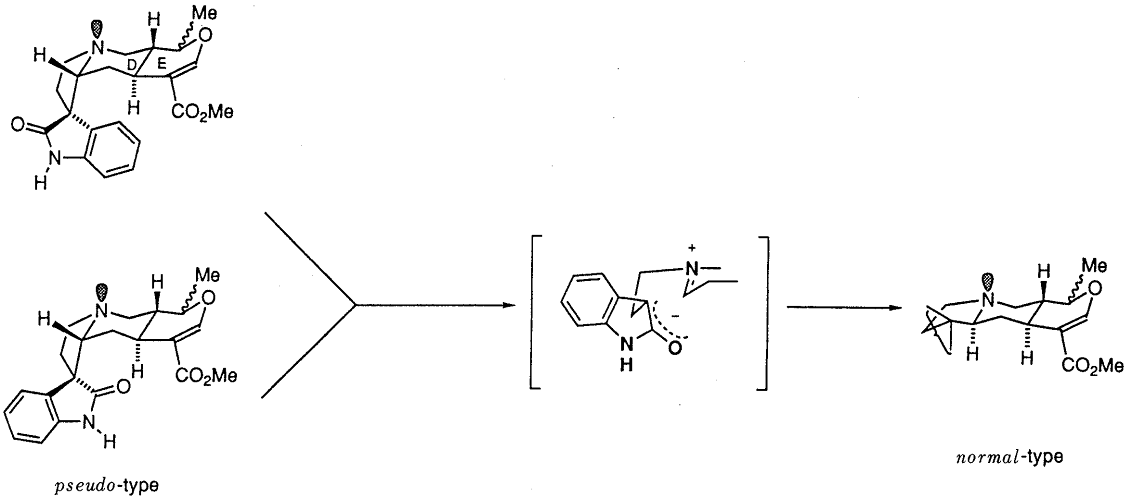


Fig. 3

nature, probably because of the serious steric interference between the oxindole moiety and the underside of the D-ring, as shown in Fig. 3.[1a,3] *pseudo*-Type oxindole alkaloids might easily epimerize to the *normal*-type compounds (*vide infra*) *via* an intermediate illustrated in Fig. 3. Therefore, the number of isomers of I that we need to consider in practice is limited to twelve. Complete assignments of the ^{1}H- and ^{13}C-NMR signals of eleven of these isomers were made.

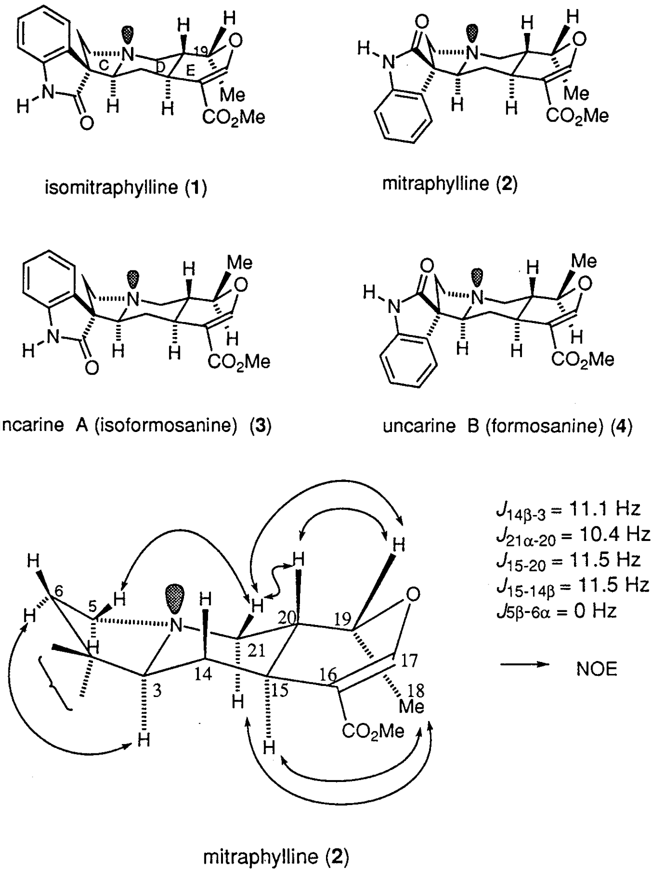


Fig. 4. *normal*-Type Oxindole Alkaloids

***normal*-Type Compounds** Four oxindole alkaloids, isomitraphylline (**1**),[6,7] mitraphylline (**2**),[6,7] uncarine A (isoformosanine) (**3**),[4] and uncarine B (formosanine) (**4**),[4] belong to the *normal*-type group, which is characterized by the *trans* relationships of the C/D and D/E ring junctions. Isomitraphylline (**1**) and mitraphylline (**2**) have 19(*S*) form and uncarine A (**3**) and uncarine B (**4**) have 19(*R*) configuration, and each pair are stereoisomers at the spiro C-7 position. First, unambiguous assignments of the ^{1}H- and ^{13}C-NMR spectra of mitraphylline (**2**) were performed by using HH-correlated spectroscopy (COSY), relayed (R) HH-COSY, nuclear Overhauser and exchange spectroscopy (NOESY), ^{13}C complete proton decoupling (COM), distortionless enhancement by polarization transfer (DEPT), CH-COSY, and correlation spectroscopy *via* long-range coupling (COLOC)[8] experiments and the results are summarized in Tables II and III. In the lowfield region, there are signals of five protons; four of them [δ 7.19 (d, J=7.8 Hz, 9-H), 7.18 (ddd, J=7.8, 7.6, 0.9 Hz, 11-H), 7.03 (ddd, J=7.8, 7.8, 0.9 Hz, 10-H), 6.89 (d, J=7.6 Hz, 12-H)] are due to an indole nucleus and the remaining one at δ 7.43 (d, J=1.3 Hz) is due to olefinic 17-H. An oxygenated 19-H at δ 4.37 showed coupling to overlapped signals at δ 2.10 (br, m) in the RHH-COSY spectrum. The latter signal integrated to two protons, one of which was assigned as 20-H. The remaining proton at δ 2.10 was proved to be 15-H based on the observation of a long-range allylic coupling with 17-H in the RHH-COSY experiment. The severely overlapped signals at δ 2.10 coupled to four protons at δ 1.21, 1.85, 2.38, and 3.22 in the COSY spectrum. The CH-COSY experiment revealed that the signals at δ 2.38 and 1.21 were due to nonequivalent methylene *gem*-protons, as were the two signals at δ 1.85 and 3.22. The former *gem*-protons had connectivity with a signal at δ 2.41 (1H, dd), which correlated with the carbon signal at δ 71.26 in the CH-COSY spectrum. Therefore, the proton at δ 2.41 had to be assigned as H-3 since this was the only position at which a proton could have coupling with an adjacent methylene group (C-14). Of the 14-H$_2$ protons, the one showing a large upfield shift at δ 1.21, caused by the anisotropic effect of the aromatic ring, could be assigned as 14β-H from the observation of the large coupling constants with 15-H (J=11.1 Hz) and 3-H (J=11.1 Hz). The coupling constant between one of the C-21 protons at δ 1.85 and H-20 was 10.4 Hz, a typical axial–axial coupling constant. Therefore, a signal at δ 1.85 was assigned to the α-oriented proton at the C-21 position. The observation of NOEs between this proton and 18-H_3 protons as well as between 19-H and the remaining H-21 proton at δ 3.22 confirmed the assignment of the orientation of C-21 protons. The singals of the C_5–C_6 ethano bridge protons appeared at δ 3.39 (1H), 2.50 (2H), and 2.03 (1H). A geminal pair at δ 2.50 and 3.39 was correlated with the carbon signal at δ 53.32 in the CH-COSY spectrum, and the latter proton signal showed a clear NOE with 21β-H. Therefore, the signal at δ 3.39 can be assigned to 5β-H. Homospin decoupling at δ 2.49, which contains 5α-H and one of the C-6 protons, changed each of the signals at δ 3.39 (5β-H) and at δ 2.03 to a singlet. This indicates that the dihedral angle between 5β-H and a 6-H at δ 2.03 is nearly 90 degrees. Therefore, from a Dreiding model, the proton at δ 2.03 can be assigned as 6α-H. The observed NOE between H-3 and the proton at δ 2.03 also supports this assignment.

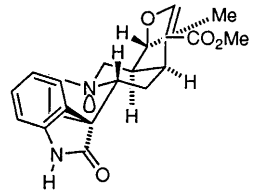
The assignments of the quaternary carbons in **2** were made by means of COLOC experiments, in which the most valuable information could be obtained by using a J-value (8 Hz) for long-range coupling. One of two carbonyl carbons at δ 181.33 had a long-range correlation with H-3 (^3J), showing that this was the amide carbonyl group at the C-2 position. The other carbonyl carbon at δ 167.10 had connectivity with H-17 at δ 7.38. So this was the ester carbonyl carbon. The observation of long-range coupling between H-6 and one of the substituted benzene carbons enabled the distinction of C-8 and C-13. The observed connectivity between a quaternary carbon and the protons attached to C-15 and C-20 (δ 2.10) confirmed the assignment of C-16. A remaining quaternary carbon at δ 55.56 was assignable as C-7 from the chemical shift, and this was confirmed by the long-range connectivities from 5β-H and 3-H.

The NMR assignments of the other three *normal*-type compounds (**1**, **3**, and **4**) were performed by essentially the same procedure.

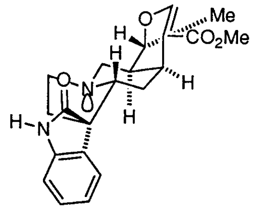
From the coupling constants of the proton on C-3, C-14, C-15, C-20, and C-21 (Table II) as well as the NOE between 19-H and 21β-H, and 15-H and 18-H_3 (Fig. 4), the D-ring is considered to take a chair form.

The following spectroscopic characteristics among the *normal*-type oxindole series should be mentioned. 1) In both the ^{1}H- and ^{13}C-NMR spectra, the C-9 signals of 7(S) isomers [isomitraphylline (**1**) and uncarine A (**3**)] appear at lower field by 0.2 and 2.0 ppm, respectively, compared with those of the 7(R) spiro isomers [mitraphylline (**2**) and uncarine B (**4**)]. A possible deshielding effect of the lone pair electrons on nitrogen has been pointed out in a similar compound.[9)] 2) The signals due to 3-H in the 7(S) isomers (**1** and **3**) are shifted downfield by about 0.2 ppm as compared with those of the 7(R) isomers (**2** and **4**). This phenomenon can be explained by the anisotropic effect of the C-2 carbonyl group.[10)] However, based on ApSimon's concepts,[11)] the proton at the C-3 position is spatially located in the boundary region. Therefore, it seems inadequate to interpret the H-3 behavior in the ^{1}H-NMR spectra only in terms of the anisotropic effect of the C-2 carbonyl function. 3) The signals of the C-14 protons in the 7(S) isomers (**1** and **3**) resonate at higher field (14α-H, Δ 0.2 ppm; 14β-H, Δ 0.8 ppm) than those of the 7(R) isomers (**2** and **4**), owing to the shielding effect of the benzene ring. 4) The NH protons appear at about δ 7.7 in the 7(S) compounds, but at δ 8.4—8.8 in the 7(R) isomers. 5) The signals of the C-19 protons in the 19(S) isomers [isomitraphylline (**1**) and mitraphylline (**2**)] appear at lower field by 0.6 ppm compared with those of the 19(R) isomers [uncarine A (**3**) and uncarine B (**4**)]. On the other hand, the 18-H_3 protons in the 19(S) group are shifted to higher field compared with those of the 19(R) isomers. 6) The coupling constants between 19-H and 20-H are 3.2—3.7 Hz in the 19(S) isomers, but 10.1—12.6 Hz (*trans* diaxial relationship) in the 19(R) isomers. 7) The carbon chemical shifts at C-15 and C-18 in the 19(S) isomers appear at higher field by 6.0 and 3.5 ppm, respectively, than those of 19(R) isomers, due to the γ-steric interaction.[5)] The C-20 carbon chemical shifts in the 19(R) isomers are observed at lower field by 3 ppm than those of the 19(S) isomers. This can be interpreted in terms of 1,3-diaxial alignment[12)] of 20-H and 18-H_3.

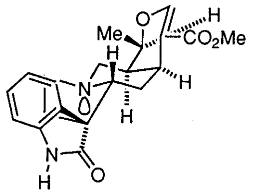
***epiallo*-Type Compounds** Uncarine D (speciophylline) (**5**),[4)] uncarine F (**6**),[4)] rauniticine-*epiallo*-oxindole A (**7**),[3)] and rauniticine-*epiallo*-oxindole B (**8**)[3)] are members of the *epiallo*-type group (Fig. 5). Compounds **7** and **8** were prepared from an indole alkaloid, rauniticine,[13)] by oxidation with *tert*-butyl hypochlorite followed by rearrangement in aqueous acetic acid.[7)] The compounds in this series have 20α-H, so that the D/E ring junction is *cis*.



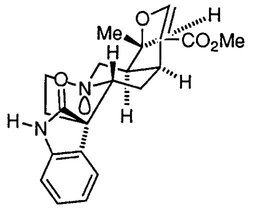
uncarine D (speciophylline) (**5**)



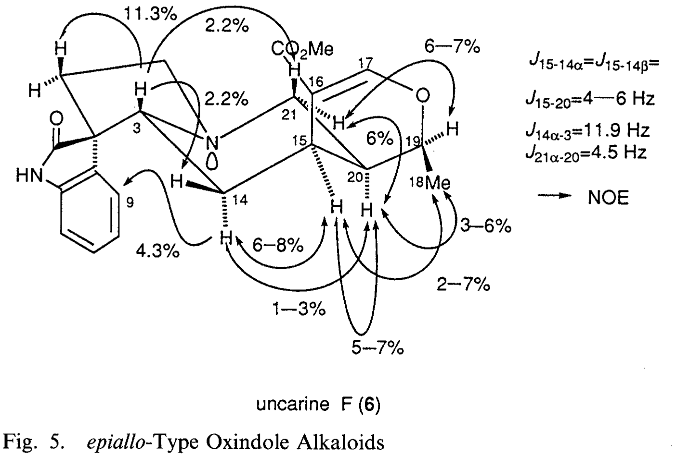
uncarine F (**6**)



rauniticine-*epiallo*-oxindole A (**7**)



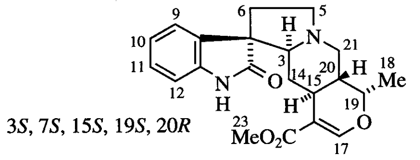
rauniticine-*epiallo*-oxindole B (**8**)



uncarine F (**6**)

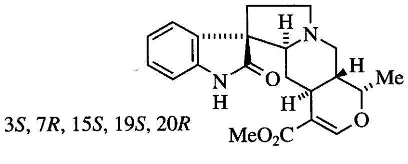
Fig. 5. *epiallo*-Type Oxindole Alkaloids

TABLE II. ^{1}H-NMR Data for the *normal*-Type Compounds **1**, **2**, **3**, and **4**



3*S*, 7*S*, 15*S*, 19*S*, 20*R*

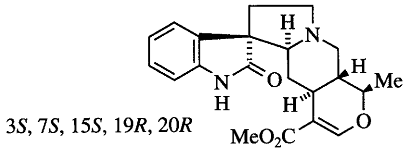
isomitraphylline (**1**)



3*S*, 7*R*, 15*S*, 19*S*, 20*R*

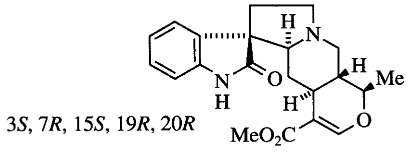
mitraphylline (**2**)

H	**1**			**2**		
	δ		Coupling constant (Hz)	δ		Coupling constant (Hz)
3	2.60	dd	$J_{3-14\beta}=11.5$, $J_{3-14\alpha}=3.0$	2.41	dd	$J_{3-14\beta}=11.1$, $J_{3-14\alpha}=2.4$
5α	2.54	ddd	$J_{5\alpha-5\beta}=8.9$, $J_{5\alpha-6\alpha}=8.9$, $J_{5\alpha-6\beta}=8.9$	2.50	m	
5β	3.30	ddd	$J_{5\beta-5\alpha}=8.9$, $J_{5\beta-6\alpha}=8.6$, $J_{5\beta-6\beta}=2.3$	3.39	m	
6α	2.04	ddd	$J_{6\alpha-6\beta}=13.0$, $J_{6\alpha-5\alpha}=8.9$, $J_{6\alpha-5\beta}=8.6$	2.03	m	
6β	2.41	ddd	$J_{6\beta-6\alpha}=13.0$, $J_{6\beta-5\alpha}=8.9$, $J_{6\beta-5\beta}=2.3$	2.49	m	
9	7.35	d	$J_{9-10}=7.6$,	7.19	d	$J_{9-10}=7.8$
10	7.00	ddd	$J_{10-9}=7.6$, $J_{10-11}=7.6$, $J_{10-12}=0.8$	7.03	ddd	$J_{10-9}=7.8$, $J_{10-11}=7.8$, $J_{10-12}=0.9$
11	7.17	ddd	$J_{11-10}=7.6$, $J_{11-12}=7.6$, $J_{11-9}=1.2$	7.18	ddd	$J_{11-10}=7.8$, $J_{11-12}=7.6$, $J_{11-9}=0.9$
12	6.85	d	$J_{12-11}=7.6$	6.89	d	$J_{12-11}=7.6$
14α	2.21	ddd	$J_{14\alpha-14\beta}=11.5$, $J_{14\alpha-15}=3.0$, $J_{14\alpha-3}=3.0$	2.38	ddd	$J_{14\alpha-14\beta}=11.1$, $J_{14\alpha-15}=2.7$, $J_{14\alpha-3}=2.4$
14β	0.60	ddd	$J_{14\beta-14\alpha}=11.5$, $J_{14\beta-15}=11.5$, $J_{14\beta-3}=11.5$	1.21	ddd	$J_{14\beta-14\alpha}=11.1$, $J_{14\beta-15}=11.1$, $J_{14\beta-3}=11.1$
15	2.18	br ddd	$J_{15-14\beta}=11.5$, $J_{15-20}=11.5$, $J_{15-14\alpha}=3.0$, ($J_{15-17}=1.7$)	2.10	br m	
17	7.38	d	$J_{17-15}=1.7$	7.43	d	$J_{17-15}=1.3$
18(Me)	1.12	d	$J_{18-19}=6.9$	1.11	d	$J_{18-19}=6.6$
19	4.37	qd	$J_{19-18\mathrm{Me}}=6.9$, $J_{19-20}=3.7$	4.37	qd	$J_{19-18\mathrm{Me}}=6.6$, $J_{19-20}=3.2$
20	1.91	m		2.10	br m	
21α	1.94	dd	$J_{21\alpha-20}=11.0$, $J_{21\alpha-21\beta}=11.0$	1.85	dd	$J_{21\alpha-21\beta}=10.5$, $J_{21\alpha-20}=10.4$
21β	3.12	dd	$J_{21\beta-21\alpha}=11.0$, $J_{21\beta-20}=7.3$	3.22	dd	$J_{21\beta-21\alpha}=10.5$, $J_{21\beta-20}=2.2$
23(OMe)	3.57	s		3.58	s	
NH	7.74	br s		8.40	br s	



3*S*, 7*S*, 15*S*, 19*R*, 20*R*

uncarine A (isoformosanine, **3**)



3*S*, 7*R*, 15*S*, 19*R*, 20*R*

uncarine B (formosanine, **4**)

H	**3**			**4**		
	δ		Coupling constant (Hz)	δ		Coupling constant (Hz)
3	2.59	dd	$J_{3-14\beta}=11.5$, $J_{3-14\alpha}=2.2$	2.41	dd	$J_{3-14\beta}=11.8$, $J_{3-14\alpha}=2.5$
5α	2.57	ddd	$J_{5\alpha-5\beta}=8.6$, $J_{5\alpha-6\alpha}=8.6$, $J_{5\alpha-6\beta}=8.6$	2.52	m	
5β	3.31	ddd	$J_{5\beta-5\alpha}=8.6$, $J_{5\beta-6\alpha}=8.6$, $J_{5\beta-6\beta}=2.4$	3.43	m	
6α	2.05	ddd	$J_{6\alpha-6\beta}=13.0$, $J_{6\alpha-5\alpha}=8.6$, $J_{6\alpha-5\beta}=8.6$	2.04	m	
6β	2.42	ddd	$J_{6\beta-6\alpha}=13.0$, $J_{6\beta-5\alpha}=8.6$, $J_{6\beta-5\beta}=2.4$	2.52	m	
9	7.35	d	$J_{9-10}=7.3$	7.18	d	$J_{9-10}=7.2$
10	7.00	ddd	$J_{10-9}=7.3$, $J_{10-11}=7.6$, $J_{10-12}=0.8$	7.02	ddd	$J_{10-9}=7.2$, $J_{10-11}=7.7$, $J_{10-12}=0.8$
11	7.17	ddd	$J_{11-10}=7.6$, $J_{11-12}=7.8$, $J_{11-9}=1.3$	7.17	ddd	$J_{11-10}=7.7$, $J_{11-12}=7.7$, $J_{11-9}=1.1$
12	6.84	d	$J_{12-11}=7.8$	6.89	d	$J_{12-11}=7.7$
14α	2.17	ddd	$J_{14\alpha-14\beta}=11.5$, $J_{14\alpha-15}=3.1$, $J_{14\alpha-3}=2.2$	2.34	ddd	$J_{14\alpha-14\beta}=12.4$, $J_{14\alpha-15}=2.8$, $J_{14\alpha-3}=2.5$
14β	0.56	ddd	$J_{14\beta-14\alpha}=11.5$, $J_{14\beta-15}=11.5$, $J_{14\beta-3}=11.5$	1.19	ddd	$J_{14\beta-14\alpha}=11.8$, $J_{14\beta-15}=11.8$, $J_{14\beta-3}=11.8$
15	2.15	ddd (d)	$J_{15-14\beta}=11.5$, $J_{15-20}=10.8$, $J_{15-14\alpha}=3.1$, ($J_{15-17}=1.4$)	2.05	ddd (d)	$J_{15-14\beta}=11.0$, $J_{15-20}=11.0$, $J_{15-14\alpha}=2.8$ ($J_{15-17}=1.9$)
17	7.42	d	$J_{17-15}=1.4$	7.46	d	$J_{17-15}=1.9$
18(Me)	1.33	d	$J_{18-19}=6.4$	1.31	d	$J_{18-19}=6.3$
19	3.81	qd	$J_{19-18\mathrm{Me}}=6.4$, $J_{19-20}=10.1$	3.81	qd	$J_{19-18\mathrm{Me}}=6.3$, $J_{19-20}=12.6$
20	1.51	m	$J_{20-15}=10.8$, $J_{20-19}=10.1$, $J_{20-21\alpha}=10.8$, $J_{20-21}=3.3$	1.72	m	
21α	1.91	dd	$J_{21\alpha-21\beta}=10.8$, $J_{21\alpha-20}=10.8$	1.82	dd	$J_{21\alpha-21\beta}=10.4$, $J_{21\alpha-20}=10.4$
21β	3.27	dd	$J_{21\beta-21\alpha}=10.8$, $J_{21\beta-20}=3.3$	3.38	dd	$J_{21\beta-21\alpha}=10.4$, $J_{21\beta-20}=3.3$
23(OMe)	3.57	s		3.58	s	
NH	7.73	br s		8.79	br s	

Table III. ^{13}C-NMR Assignments for the *normal*-Type Compounds **1**, **2**, **3**, and **4**

C	Isomitraphylline (**1**)	Mitraphylline (**2**)	Uncarine A (isoformosanine, **3**)	Uncarine B (formosanine, **4**)
2	180.73	181.33	180.89	181.63
3	71.85	74.58	71.26	74.01
5	53.40	54.28	53.32	54.28
6	35.45	35.16	35.37	35.10
7	56.32	55.56	56.38	55.63
8	133.82	133.35	133.83	133.32
9	124.99	122.89	124.93	122.80
10	122.43	122.54	122.36	122.46
11	127.58	128.00	127.54	127.95
12	109.35	109.74	109.40	109.83
13	139.98	140.87	140.04	140.97
14	29.16	28.37	29.17	28.43
15	30.07	30.44	36.00	36.44
16	107.38	106.92	108.66	108.19
17	153.85	154.05	155.26	155.39
18	14.89	14.84	18.36	18.24
19	74.03	73.81	75.58	75.60
20	40.95	40.48	43.61	43.04
21	54.31	54.33	53.40	53.43
22	167.07	167.10	167.08	167.08
23	50.76	50.71	50.76	50.69

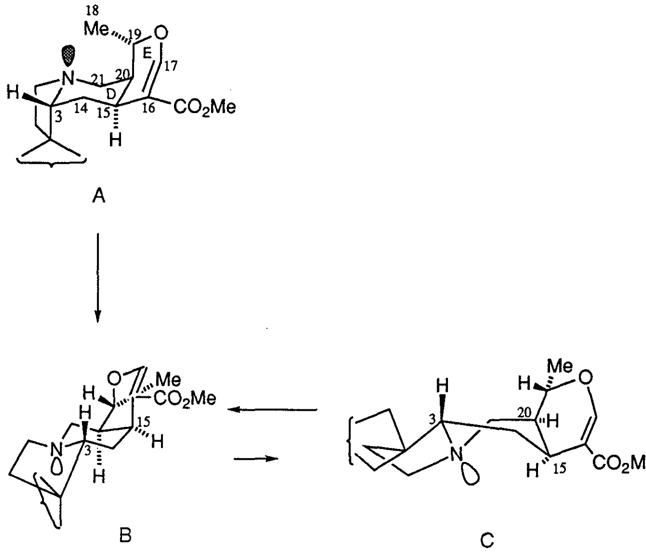


Fig. 6

In the conformer A in Fig. 6, which has a *cis* relationship between 3β-H and the N_b lone pair electrons, the bulky substituent at C-3 is located in the axial position to the D-ring, so that conformer A would transform into the more stable from B by nitrogen flipping. Lounasmaa and Kan[14] claimed that in the case of *epiallo*-type heteroyohimbine indole alkaloids, the D-ring would take a deformed boat conformation such as C. This argument is based on the highfield shift of the C-15 carbon compared with those of other types of heteroyohimbine indole alkaloids.[15] This phenomenon was explained in terms of steric compression between 15-H and the N_b lone pair electrons[16] in a conformer such as C. We investigated the conformation of the *epiallo*-type oxindole alkaloids. The chemical shifts of 3-H (δ 2.12—2.35) in *epiallo*-type compounds are consistent with the *trans* relationship between 3-H and the lone pair of nitrogen,[17] meaning that conformer A can be excluded. The NOEs ($18H_3$ and 15-H, 19-H and 21-H, 14α-H and 20-H, 21β-H and 3-H, 3-H and 14β-H, 3-H and 6β-H) in uncarine F (**6**) (Fig. 5) suggest that the D-ring takes a chair form. Furthermore, the coupling constants ($J_{3-14\alpha}=11.9$ Hz, $J_{3-14\beta}=2.5$ Hz, $J_{15-14\alpha}=$ *ca.* 4.5 Hz, $J_{15-14\beta}=$ *ca.* 4.5 Hz, $J_{15-20}=$ *ca.* 4.5 Hz, $J_{20-21\alpha}=4.5$ Hz, $J_{20-21\beta}=11.6$ Hz), certain values of which could be obtained by using the 1D differential COSY technique,[18] also support the above conclusion.

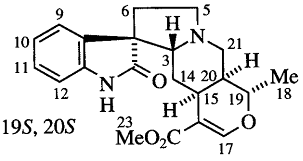
The chemical shifts of C-15 in uncarine D (**5**) and uncarine F (**6**), having 19(*S*) form, appear at relatively higher field (Δ 5 ppm) compared with those of the 19(*R*) isomers (**7**) and (**8**), while those of C-21 in **7** and **8** appear at higher field (Δ 6 ppm) compared with those of **5** and **6**. This can be explained by γ-steric interaction[11] between 15-H and the C-18 methyl group in the 19(*S*) isomers, and between 21-H and the C-18 methyl group in the 19(*R*) isomers.

Owing to the configurational difference at the C-7 position, similar behavior to that in the *normal*-type series is observed in the ^{1}H-NMR signals of 9-H, 3-H, 14α-H, and NH and in the ^{13}C-NMR signals of C-9 and C-3 among the *epiallo*-type compounds (Tables IV and V). In uncarine D (**5**) and rauniticine-*epiallo*-oxindole A (**7**), the signal of the methyl group of the ester function appears at around δ 3.35, relatively high field compared with those of other heteroyohimbine-type oxindole alkaloids. Only in these alkaloids (**5** and **7**) can the methyl groups be placed on the benzene ring.[4]

***allo*-Type Compounds** The *allo*-type compounds, uncarine E (isopteropodine) (**9**),[4] uncarine C (pteropodine) (**10**),[4] rauniticine-*allo*-oxindole A (**11**),[3,9] and rauniticine-*allo*-oxindole B (**12**),[3] are characterized by C/D *trans* and D/E *cis* relationships. Rauniticine-*allo*-oxindole A (**11**) could be obtained by epimerization of **7**, but the isomer (**12**) was not obtained from **7** or **8** in small-scale experiments. The coupling constants observed for the protons on the D-ring, 3-H, 14α, β-H_2, 15-H, 20-H, and 21α, β-H_2, support the chair conformation of the D-ring in the *allo*-type

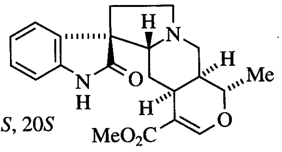
TABLE IV. ^{1}H-NMR Data for the *epiallo*-Type Compounds, **5**, **6**, **7**, and **8**

3*R*, 7*S*, 15*S*, 19*S*, 20*S*



uncarine D (speciophylline, **5**)

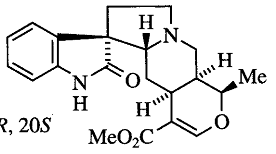
3*R*, 7*R*, 15*S*, 19*S*, 20*S*



uncarine F (**6**)

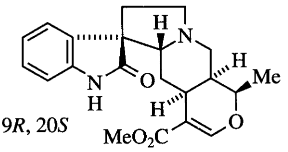
H	**5**			**6**		
	δ		Coupling constant (Hz)	δ		Coupling constant (Hz)
3	2.16	br dd	$J_{3-14\alpha}=12.3$, $J_{3-14\beta}=$ *ca.* 2	2.35	dd	$J_{3-14\alpha}=11.9$, $J_{3-14\beta}=2.5$
5α	3.38	br dd	$J_{5\alpha-5\beta}=7.1$, $J_{5\alpha-6\beta}=7.1$	3.27	ddd	$J_{5\alpha-5\beta}=8.8$, $J_{5\alpha-6\alpha}=8.8$, $J_{5\alpha-6\beta}=2.3$
5β	2.44	m		2.47	ddd	$J_{5\beta-5\alpha}=8.8$, $J_{5\beta-6\alpha}=8.8$, $J_{5\beta-6\beta}=8.8$
6α	2.44	m		2.37	ddd	$J_{6\alpha-6\beta}=12.9$, $J_{6\alpha-5\alpha}=8.8$, $J_{6\alpha-5\beta}=2.3$
6β	2.02	m		2.02	ddd	$J_{6\beta-6\alpha}=12.9$, $J_{6\beta-5\alpha}=8.8$, $J_{6\beta-5\beta}=8.8$
9	7.12	d	$J_{9-10}=7.3$	7.36	dd	$J_{9-10}=7.4$
10	6.99	ddd	$J_{10-9}=7.3$, $J_{10-11}=7.6$, $J_{10-12}=1.0$	7.01	ddd	$J_{10-9}=7.4$, $J_{10-11}=7.7$, $J_{10-12}=1.0$
11	7.17	ddd	$J_{11-10}=7.6$, $J_{11-12}=7.6$, $J_{11-9}=1.2$	7.18	ddd	$J_{11-10}=7.7$, $J_{11-12}=7.7$, $J_{11-9}=1.4$
12	6.90	d	$J_{12-11}=7.6$	6.85	d	$J_{12-11}=7.7$
14α	1.61	ddd	$J_{14\alpha-14\beta}=12.3$, $J_{14\alpha-3}=12.3$, $J_{14\alpha-15}=4.6$	1.04	ddd	$J_{14\alpha-14\beta}=13.2$, $J_{14\alpha-3}=11.9$, $J_{14\alpha-15}=4.8$
14β	2.20	ddd	$J_{14\beta-14\alpha}=12.3$, $J_{14\beta-3}=2.5$, $J_{14\beta-15}=2.5$	2.18	ddd	$J_{14\beta-14\alpha}=13.2$, $J_{14\beta-3}=2.5$, $J_{14\beta-15}=5.8$
15	2.85	br m		2.71	quintet	*ca.* 4—5 ($J_{15-14\alpha}$, $J_{15-14\beta}$, J_{15-20}, J_{15-17})
17	7.37	d	$J_{17-15}=1.9$	7.41	d	$J_{17-15}=1.9$
18(Me)	1.24	d	$J_{18-19}=6.6$	1.21	d	$J_{18-19}=6.6$
19	4.19	br q	$J_{19-18\text{Me}}=6.6$, $J_{19-20}=$ *ca.* 1.0	4.18	qd	$J_{19-18\text{Me}}=6.6$, $J_{19-20}=1.3$
20	2.09	m		1.93	ddd	$J_{20-15}=5.7$, $J_{20-21\alpha}=4.5$, $J_{20-21\beta}=11.6$
21α	3.10	dd	$J_{21\alpha-21\beta}=13.2$, $J_{21\alpha-20}=6.6$	3.00	dd	$J_{21\alpha-21\beta}=11.1$, $J_{21\alpha-20}=4.5$
21β	2.09	m		2.16	dd	$J_{21\beta-21\alpha}=11.1$, $J_{21\beta-20}=11.6$
23(OMe)	3.36	s		3.62	s	
NH	8.79	br s		7.90	br s	

3*R*, 7*S*, 15*S*, 19*R*, 20*S*



rauniticine-*epiallo*-oxindole A (**7**)

3*R*, 7*R*, 15*S*, 19*R*, 20*S*



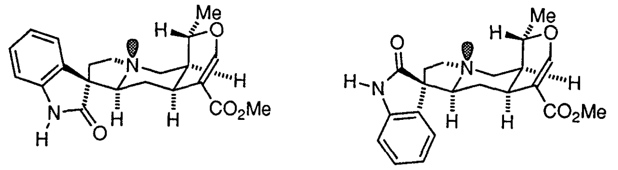
rauniticine-*epiallo*-oxindole B (**8**)

H	**7**			**8**		
	δ		Coupling constant (Hz)	δ		Coupling constant (Hz)
3	2.12	dd	$J_{3-14\alpha}=12.8$, $J_{3-14\beta}=2.6$	2.33	dd	$J_{3-14\alpha}=12.0$, $J_{3-14\beta}=2.1$
5α	3.40	m		3.30	ddd	$J_{5\alpha-5\beta}=8.6$, $J_{5\alpha-6\beta}=8.6$, $J_{5\alpha-6\beta}=2.2$
5β	2.45	m		2.49	ddd	$J_{5\beta-5\alpha}=8.6$, $J_{\beta-\alpha}=8.6$, $J_{5\beta-6\beta}=8.6$
6α	2.45	m		2.38	ddd	$J_{6\alpha-6\beta}=13.1$, $J_{6\alpha-5\alpha}=8.6$, $J_{6\alpha-5\beta}=2.2$
6β	2.04	m		2.05	m	
9	7.12	d	$J_{9-10}=7.0$	7.36	d	$J_{9-10}=7.4$
10	6.99	ddd	$J_{10-9}=7.0$, $J_{10-11}=7.7$, $J_{10-12}=1.1$	7.01	ddd	$J_{10-9}=7.4$, $J_{10-11}=7.7$, $J_{10-12}=0.8$
11	7.17	ddd	$J_{11-10}=7.7$, $J_{11-12}=7.7$, $J_{11-9}=1.3$	7.18	ddd	$J_{11-10}=7.7$, $J_{11-12}=7.7$, $J_{11-9}=1.4$
12	6.88	d	$J_{12-11}=7.7$	6.83	d	$J_{12-11}=7.7$
14α	1.64	ddd	$J_{14\alpha-14\beta}=12.7$, $J_{14\alpha-3}=2.7$, $J_{14\alpha-15}=4.5$	1.07	ddd	$J_{14\alpha-14\beta}=12.6$, $J_{14\alpha-3}=12.0$, $J_{14\alpha-15}=5.2$
14β	2.12	d like		2.08	m	
15	2.90	m	*ca.* 2.4	2.78	quintet	*ca.* 2.5
17	7.43	d	$J_{17-15}=1.8$	7.48	d	$J_{17-15}=1.6$
18(Me)	1.31	d	$J_{18-19}=6.6$	1.33	d	$J_{18-19}=6.6$
19	4.19	qd	$J_{19-18\text{Me}}=6.6$, $J_{19-20}=1.5$	4.09	br q	$J_{19-18\text{Me}}=6.6$, $J_{19-20}=$ *ca.* 1.2
20	2.23	m		2.03	m	($J_{20-21\beta}=12.2$)
21α	3.26	dd	$J_{21\alpha-21\beta}=11.4$, $J_{21\alpha-20}=4.4$	3.16	dd	$J_{21\beta-21\alpha}=10.3$, $J_{21\beta-20}=3.2$
21β	1.99	dd	$J_{21\beta-21\alpha}=11.4$, $J_{21\beta-20}=11.4$	2.08	m	
23(OMe)	3.35	s		3.63	s	
NH	8.46	br s		7.06	br s	

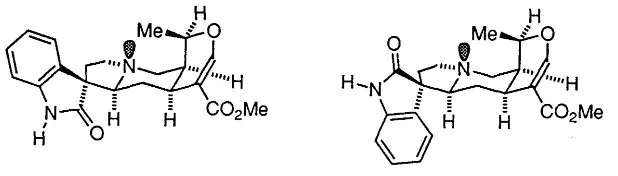
TABLE V. ^{13}C-NMR Assignments for the *epiallo*-Type Compounds **5**, **6**, **7**, and **8**

C	Uncarine D (speciophylline, **5**)	Uncarine F (**6**)	Raunitícine-*epiallo*-oxindole A (**7**)	Rauniticine-*epiallo*-oxindole B (**8**)
2	181.63	181.02	181.46	180.85
3	70.45	67.38	70.04	67.11
5	54.90	53.93	55.11	54.31
6	34.06	34.79	34.09	34.93
7	55.71	56.46	55.66	56.44
8	133.24	133.60	133.10	133.60
9	122.67	125.04	122.74	125.07
10	122.30	122.11	122.35	122.17
11	127.79	127.55	127.82	127.58
12	109.61	109.35	109.52	109.30
13	140.93	140.23	140.85	140.16
14	26.22	26.91	26.66	27.44
15	25.01	24.98	31.54	31.56
16	104.86	104.97	106.41	106.65
17	153.65	153.78	156.05	156.34
18	18.74	18.59	17.32	17.41
19	74.77	74.68	75.50	75.38
20	36.38	36.86	36.51	37.12
21	53.36	53.35	47.63	47.56
22	167.46	167.31	167.53	167.36
23	50.57	50.87	50.61	50.94

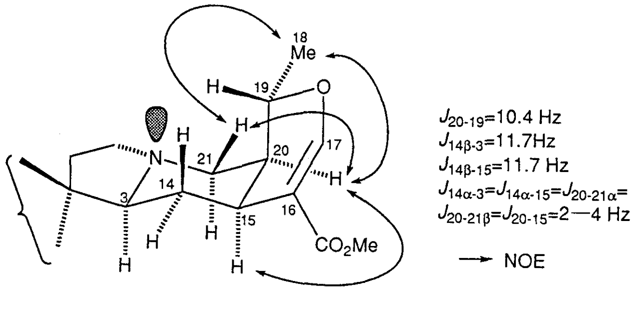
compounds. Interestingly, only in the 19(*S*) isomers (**9** and **10**) among the *allo*-type compounds is allylic long-range coupling between 15-H and 17-H not observed. The 18-H_3 signals in the 19(*R*) isomer (**11**) resonate at lower field by 0.5 ppm compared with those of the 19(*S*) isomers (**9** and **10**), owing to the anisotropic effect of the N_b lone pair electrons. The observed strong NOE between 18-H_3 and 14β-H suggests the presence of a severe steric hindrance in rauniticine-*allo*-oxindole A (**11**). This is supported by the fact that in the oxidation-rearrangement reaction from rauniticine to the corresponding oxindoles, *epiallo*-type compounds (**7** and **8**) are produced predominantly, rather than the *allo*-type compounds (**11** and **12**). In uncarine C (**10**) having the 7(*R*) configuration, a strong NOE between 3-H and 9-H is observed and the proton at the C-14β position appears at relatively highfield (*ca.* δ 0.9) due to the shielding effect of the benzene ring. In the 7(*S*) isomers (**9** and **11**), the signal appeared at lower field by *ca.* 0.2 ppm than that of the 7(*R*) isomer (**10**). The CH-COSY experiment on uncarine E (isopteropodine) (**9**) led to revision of the literature assignments of the proton (9-H and 10-H) and carbon (C-14 and C-15) signals.[5]



uncarine E (isopteropodine) (**9**) uncarine C (pteropodine) (**10**)



rauniticine-*allo*-oxindole A (**11**) rauniticine-*allo*-oxindole B (**12**)



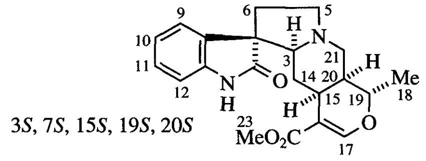
uncarine E (isopteropodine) (**9**)

Fig. 7. *allo*-Type Oxindole Alkaloids

Characteristic Features in the NMR Spectra of *normal*-, *epiallo*-, and *allo*-Type Oxindole Alkaloids 1. In the ^{1}H-NMR spectra, the signals of 15-H appear at δ 2.05—2.2 in *normal*-type, at δ 2.4—2.5 in *allo*-type, and at δ 2.7—2.9 in *epiallo*-type compounds. The coupling constants between 15-H and 14β-H are large (J = 10—11 Hz) in the *normal*- and *allo*-type groups and are small (J = 2.5—5 Hz) in the *epiallo*-series. The long-range coupling constants between 15-H and 17-H in the *normal*- and *epiallo*-type compounds are relatively large (J = 1.3—1.9 Hz), while they are small (J = 0—1.0 Hz) in the *allo*-type alkaloids.

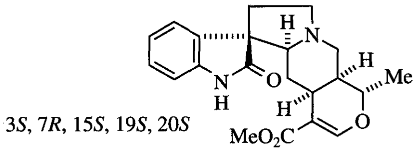
2. In each type of compound, the stereochemistry at the spiro center (C-7) can be distinguished by the chemical shifts of protons and carbons at the C-3 and C-9 positions. Thus, in the *normal*- and *allo*-type compounds, the 3-H signals appear at δ 2.5—2.6 in the 7(*S*) isomers, but at δ 2.3—2.4 in the 7(*R*) isomers. The 9-H signals appear at δ 7.3—7.35 in the 7(*S*) isomers and at around δ 7.2 in the 7(*R*) isomers. In the *epiallo*-series, the behavior observed in the *normal*- and *allo*-type compounds is opposite owing to the conformational change caused by the nitrogen flip. Thus, the C-3 protons appear at δ 2.1—2.2 in the 7(*S*) isomers

TABLE VI. ^{1}H-NMR Data for the *allo*-Type Compounds, **9**, **10**, **11**, and **12**



3*S*, 7*S*, 15*S*, 19*S*, 20*S*

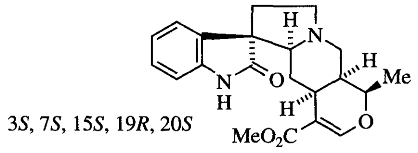
uncarine E (isopteropodine, **9**)



3*S*, 7*R*, 15*S*, 19*S*, 20*S*

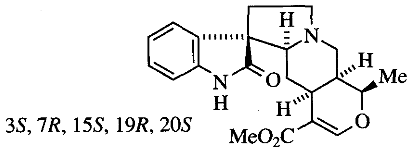
uncarine C (pteropodine, **10**)

H	**9**			**10**		
	δ		Coupling constant (Hz)	δ		Coupling constant (Hz)
3	2.57	dd	$J_{3-14\beta}=11.7$, $J_{3-14\alpha}=2.8$	2.36	dd	$J_{3-14\beta}=12.1$, $J_{3-14\alpha}=4.3$
5α	2.46	ddd	$J_{5\alpha-5\beta}=7.6$, $J_{5\alpha-6\alpha}=7.6$, $J_{5\alpha-6\beta}=7.6$	2.36	m	
5β	3.22	ddd	$J_{5\beta-5\alpha}=7.6$, $J_{5\beta-6\alpha}=7.6$, $J_{5\beta-6\beta}=2.4$	3.30	ddd	$J_{5\beta-5\alpha}=13.0$, $J_{5\beta-6\beta}=8.5$, $J_{5\beta-6\alpha}=2.9$
6α	2.00	ddd	$J_{6\alpha-6\beta}=11.9$, $J_{6\alpha-5\alpha}=7.6$, $J_{6\alpha-5\beta}=7.6$	1.99	m	
6β	2.39	ddd	$J_{6\beta-6\alpha}=11.9$, $J_{6\beta-5\alpha}=7.6$, $J_{6\beta-5\beta}=2.4$	2.40	ddd	$J_{6\beta-6\alpha}=12.5$, $J_{6\beta-5\alpha}=13.0$, $J_{6\beta-5\beta}=7.8$
9	7.27	dd	$J_{9-10}=7.7$, ($J_{9-11}=$ *ca.* 0.7)	7.20	dd	$J_{9-10}=7.3$, ($J_{9-11}=$ *ca.* 0.5)
10	7.02	ddd	$J_{10-9}=7.7$, $J_{10-11}=7.7$, $J_{10-12}=1.1$	7.04	ddd	$J_{10-9}=7.3$, $J_{10-11}=7.6$, $J_{10-12}=1.0$
11	7.19	ddd	$J_{11-10}=7.7$, $J_{11-12}=7.7$, $J_{11-9}=1.3$	7.18	ddd	$J_{11-10}=7.6$, $J_{11-12}=7.6$, $J_{11-9}=1.2$
12	6.89	d	$J_{12-11}=7.7$	6.87	d	$J_{12-11}=7.6$
14α	1.62	ddd	$J_{14\alpha-14\beta}=11.7$, $J_{14\alpha-3}=2.8$, $J_{14\alpha-15}=2.8$	1.72	ddd	$J_{14\alpha-14\beta}=12.1$, $J_{14\alpha-3}=4.3$, $J_{14\alpha-15}=4.3$
14β	0.88	ddd	$J_{14\beta-14\alpha}=11.7$, $J_{14\beta-3}=11.7$, $J_{14\beta-15}=11.7$	1.51	ddd	$J_{14\beta-14\alpha}=12.1$, $J_{14\beta-3}=12.1$, $J_{14\beta-15}=12.1$
15	2.51	ddd	$J_{15-14\beta}=11.7$, $J_{15-14\alpha}=2.8$, $J_{15-20}=2.8$	2.44	ddd	$J_{15-14\beta}=12.1$, $J_{15-14\alpha}=4.3$, $J_{15-20}=4.7$
17	7.41	s		7.41	s	
18(Me)	1.41	d	$J_{18-19}=6.2$	1.40	d	$J_{18-19}=6.1$
19	4.36	qd	$J_{19-18\mathrm{Me}}=6.2$, $J_{19-20}=10.4$	4.55	qd	$J_{19-18\mathrm{Me}}=6.1$, $J_{19-20}=10.5$
20	1.59	br m		1.59	br m	
21α	2.42	dd	$J_{21\alpha-21\beta}=11.9$, $J_{21\alpha-20}=3.8$	2.32	dd	$J_{21\alpha-21\beta}=12.1$, $J_{21\alpha-20}=3.8$
21β	3.29	dd	$J_{21\beta-21\alpha}=11.9$, $J_{21\beta-20}=1.8$	3.32	dd	$J_{21\beta-21\alpha}=12.1$, $J_{21\beta-20}=2.0$
23(OMe)	3.60	s		3.60	s	
NH	8.42	br s		8.52	br s	



3*S*, 7*S*, 15*S*, 19*R*, 20*S*

rauniticine-*allo*-oxindole A (**11**)



3*S*, 7*R*, 15*S*, 19*R*, 20*S*

rauniticine-*allo*-oxindole B (**12**)[a]

H	**11**			**12**		
	δ		Coupling constant (Hz)	δ		Coupling constant (Hz)
3	2.50	(dd)	($J_{3-14\beta}=12.9$, $J_{3-14\alpha}=2.8$)	2.3—2.4	(dd)	$J_{3-14\beta}=$ *ca.* 12, $J_{3-14\alpha}=$ *ca.* 4—5
5α	2.42	m		2.3—2.4	(m)	
5β	3.30	m		*ca.* 3.3	(ddd)	$J_{5\beta-5\alpha}=$ *ca.* 13, $J_{5\beta-6\beta}=$ *ca.* 8—9, $J_{5\beta-6\alpha}=$ *ca.* 3
6α	2.02	m		*ca.* 2.0	(m)	
6β	2.41	ddd	$J_{6\beta-6\alpha}=9.7$, $J_{6\beta-5\alpha}=9.4$, $J_{6\beta-5\beta}=2.2$	*ca.* 2.4	(ddd)	$J_{6\beta-6\alpha}=$ *ca.* 12—13, $J_{6\beta-5\alpha}=$ *ca.* 13, $J_{6\beta-5\beta}=$ *ca.* 8
9	7.25	dd	$J_{9-10}=7.6$, ($J_{9-11}=0.7$)	*ca.* 7.2	(d)	$J_{9-10}=$ *ca.* 7—8
10	6.97	ddd	$J_{10-9}=7.6$, $J_{10-11}=7.6$, $J_{10-12}=1.0$	7.0—7.1	(ddd)	$J_{10-9}=$ *ca.* 7—8, $J_{10-11}=$ *ca.* 7—8, $J_{10-12}=$ *ca.* 1
11	7.19	ddd	$J_{11-10}=7.6$, $J_{11-12}=7.6$, $J_{11-9}=1.2$	*ca.* 7.2	(ddd)	$J_{11-10}=$ *ca.* 7—8, $J_{11-12}=$ *ca.* 7—8, $J_{11-9}=$ *ca.* 1
12	6.82	d	$J_{12-11}=7.6$	6.8—6.9	(d)	$J_{12-11}=$ *ca.* 7—8
14α	1.65	ddd	$J_{14\alpha-14\beta}=12.9$, $J_{14\alpha-15}=5.2$, $J_{14\alpha-3}=2.8$	*ca.* 1.7	(ddd)	$J_{14\alpha-14\beta}=$ *ca.* 12, $J_{14\alpha-15}=$ *ca.* 4—5, $J_{14\alpha-3}=$ *ca.* 4—5
14β	0.91	ddd	$J_{14\beta-14\alpha}=12.9$, $J_{14\beta-15}=12.9$, $J_{14\beta-3}=12.9$	*ca.* 1.5	(ddd)	$J_{14\beta-14\alpha}=$ *ca.* 12, $J_{14\beta-15}=$ *ca.* 12, $J_{14\beta-3}=$ *ca.* 12
15	2.50	(ddd)	($J_{15-14\beta}=12.9$, $J_{15-14\alpha}=5.2$, $J_{15-20}=5.4$)	*ca.* 2.5	(ddd)	$J_{15-14\beta}=$ *ca.* 12, $J_{15-14\alpha}=$ *ca.* 4—5, $J_{15-20}=$ *ca.* 5—6
17	7.44	d	$J_{17-15}=1.0$	7.4—7.5	(d)	$J_{17-15}=$ *ca.* 1
18(Me)	1.45	d	$J_{18-19}=7.1$	1.4—1.5	(d)	$J_{18-19}=$ *ca.* 7
19	4.43	qdd	$J_{19-18\mathrm{Me}}=7.1$, $J_{19-20}=5.4$, $J_{19-15}=1.2$	4.4—4.5	(qdd)	$J_{19-18\mathrm{Me}}=$ *ca.* 7, $J_{19-20}=$ *ca.* 5—6, $J_{19-15}=$ *ca.* 1−1.5
20	2.12	ddd	$J_{20-21\alpha}=5.4$, $J_{20-19}=5.4$, $J_{20-15}=5.4$	2.1—2.2	(ddd)	$J_{20-21\alpha}=$ *ca.* 5—6, $J_{20-19}=$ *ca.* 5—6, $J_{20-15}=$ *ca.* 5—6
21α	2.50	(dd)	($J_{21\alpha-20}=12.2$, $J_{21\alpha-21\beta}=5.4$)	*ca.* 2.5	(dd)	$J_{21\alpha-21\beta}=$ *ca.* 12—13, $J_{21\alpha-20}=$ *ca.* 5—6
21β	3.08	d	$J_{21\beta-21\alpha}=12.2$	3.0—3.1	(d)	$J_{21\beta-21\alpha}=$ *ca.* 12—13
23(OMe)	3.61	s		*ca.* 3.6	(s)	
NH	7.47	br s		7.4—7.5	(br s)	

a) Expected values.

Table VII. ^{13}C-NMR Assignments for the *allo*-Type Compounds **9**, **10**, **11**, and **12**

C	Uncarine E (isopteropodine, **9**)	Uncarine C (pteropodine, **10**)	Rauniticine-*allo*-oxindole A (**11**)	Rauniticine-*allo*-oxindole B (**12**)[a]
2	181.25	181.23	180.72	*ca.* 181
3	71.24	74.43	71.25	74—75
5	54.10	55.18	54.64	*ca.* 55
6	34.83	34.67	34.70	34—75
7	56.92	56.13	56.98	*ca.* 56
8	133.75	133.47	133.75	133—134
9	124.54	123.05	124.85	*ca.* 123
10	122.49	122.60	122.29	122—123
11	127.66	127.92	127.71	*ca.* 128
12	109.62	109.56	109.33	109—110
13	140.21	140.77	139.97	*ca.* 141
14	30.16	29.57	29.28	*ca.* 29
15	30.47	31.00	28.84	*ca.* 29
16	109.94	109.18	107.69	107—108
17	154.94	155.25	153.52	153—154
18	18.62	18.97	19.57	19—20
19	72.13	72.18	76.09	*ca.* 76
20	37.89	37.87	33.33	33—34
21	53.50	53.68	53.65	53—54
22	167.59	167.72	167.79	*ca.* 168
23	50.95	50.89	50.98	*ca.* 51

a) Expected values.

and at δ 2.3—2.4 in the 7(*R*) isomers. Furthermore, the C-9 protons in the 7(*S*) isomers appear at higher field by *ca.* 0.2 ppm compared with those of the 7(*R*) isomers. In the *normal*- and *allo*-type compounds, the C-3 carbon signals appear at δ 71.2—71.8 in the 7(*S*) isomers and at δ 74.0—74.5 in the 7(*R*) isomers. The C-9 chemical shifts also appear at lower field (*ca.* Δ2 ppm) in the 7(*S*) isomers compared with those of the 7(*R*) isomers. In the *epiallo*-type compounds, the C-3 and C-9 chemical shifts in *normal*- and *allo*-type alkaloids also show opposite behavior. Thus, the C-3 signal appears at δ 70.0—80.5 in the 7(*S*) isomers and at δ 67.1—67.4 in the 7(*R*) isomers, and the C-9 signal appears at δ 122.7 in the 7(*S*) isomers and at δ 125.0 in the 7(*R*) isomers.

3. The stereochemistry at the C-19 position in *normal*- and *allo*-type compounds can be easily determined from the coupling constant between 19-H and 20-H, as follows. *normal*-Type: 19(*S*), $J=3$—4 Hz (*cis*); 19(*R*), $J=10$—12 Hz (*trans*-diaxial); *allo*-type: 19(*S*), $J=10.5$ Hz (*trans*-diaxial); 19(*R*), $J=5.5$ Hz (*cis*). In the *epiallo*-type compounds, the C-19 configuration can not be elucidated by using ^{1}H-NMR spectra. However, in the ^{13}C-NMR spectra, a clear difference of the chemical shifts at C-15 and C-21 is observed. Thus, the chemical shift at C-15 in the 19(*S*) isomers was at extraordinarily higher field of around δ 25. The C-21 signals in the 19(*R*) isomers appear at δ 47.6, which is 5.6—5.8 ppm higher than those of the 19(*S*) isomers. To distinguish the configuration of C-19 in *normal*- and *allo*-type compounds, the ^{13}C-NMR technique is also useful. The C-15 signals of the *normal*-type compounds are observed at δ 30—30.5 in the 19(*S*) isomers and at δ 36—36.5 in the 19(*R*) isomers. The C-18, C-19 and C-20 carbons in the 19(*R*) isomers appear at lower field by 2—6 ppm than those of the 19(*S*) isomers. In the *allo*-type compounds, the chemical shifts of C-15 and C-20 in 19(*S*) are observed at lower field by 2—4 ppm than those of the 19(*S*) isomers, while the C-18 and C-19 signals of the 19(*S*) isomers are observed at higher field by 1—4 ppm than those of the 19(*R*) isomers.

On the basis of the NMR spectra of the eleven isomers, we estimated the ^{1}H- and ^{13}C-NMR data for the twelfth alkaloid, rauniticine-*allo*-oxindole B (**12**), as shown in Tables VI and VII.

Experimental

Melting points were determined on a Yamato MP-21 micro melting point apparatus and are uncorrected. UV spectra were recorded with a Hitachi U-3400 spectrometer. MS were measured on a Hitachi M-60 spectrometer, FAB-MS and high resolution (HR)-MS were measured on a JEOL JMS-HX 110 spectrometer. Circular dichroism (CD) spectra were recorded on a JASCO J-500 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on JEOL JNM GSX 500 and A500 spectrometers with tetramethylsilane (TMS) as an internal standard. Chemical shifts are recorded in δ values in ppm and coupling constants (J) are given in hertz (Hz); s, d, t, q, m, and br indicate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. Chloroform-*d* ($CDCl_3$, 99.8 atom% D, Isotec Inc., U.S.A.) was used as the solvent.

Materials Isomitraphylline (**1**), mitraphylline (**2**), uncarine A (isoformosanine) (**3**), and uncarine B (formosanine) (**4**) were isolated from *Uncaria Kawakamii* Hayata in Formosa, and uncarine C (pteropodine) (**10**), uncarine D (speciophylline) (**5**), uncarine E (isopteropodine) (**9**), and uncarine F (**6**) were isolated from *Uncaria florida* Vidal in Formosa.[19,20] Rauniticine-*epiallo*-oxindoles A (**7**) and B (**8**), and rauniticine-*allo*-oxindole A (**11**) were obtained by the transformation of rauniticine[13] as follows.

Preparation of Rauniticine-*epiallo*-oxindoles A (7) and B (8) *tert*-BuOCl (8.2 μl, 0.686 mmol) was added dropwise to a stirred solution of rauniticine (23 mg, 0.0653 mmol) and Et_3N (11 μl, 0.0784 mmol) in dry CH_2Cl_2 (0.5 ml) at -15 °C under argon, and the mixture was stirred at the same temperature for 15 min. The solvent was removed under reduced pressure at 0 °C and the residue was immediately treated with 1 ml of a mixture of MeOH, H_2O and AcOH (1 : 0.5 : 0.05) under reflux for 2.5 h. The reaction mixture was alkalified with aqueous 10% Na_2CO_3 solution to pH 10 and then extracted with $CHCl_3$. The organic extract was washed with brine, dried over $MgSO_4$ and evaporated. The oily residue was separated by medium pressure liquid chromatography (MPLC) (SiO_2, 3% MeOH–$CHCl_3$) to afford 10.5 mg of **7** and 8 mg of **8**. Rauniticine-*epiallo*-oxindole A (**7**): mp 228—230 °C (AcOEt). UV $\lambda_{\max}^{\text{MeOH}}$ nm ($\log\varepsilon$): 208 (4.45), 245.5 (4.06). MS *m*/*z* (%): 368 (M^+, 77), 223 (100), 208 (26). HR-FBMS Calcd for $C_{21}H_{25}N_2O_4$ $(M+H)^+$: 369.1815. Found: 369.1812. CD ($c=0.46\times10^{-3}$, MeOH) $\Delta\varepsilon^{22^\circ}$ (nm): 0 (300), -1.3, (287), 0 (273), $+9.9$ (252), $+0.7$ (232),

+8.6 (218), 0 (205). Rauniticine-*epiallo*-oxindole B (**8**): amorphous powder. UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm (log ε): 207 (4.55), 243.5 (4.22). MS m/z (%): 368 (M^+, 88), 223 (100), 208 (25). HR-FBMS Calcd for $C_{21}H_{25}N_2O_4$ $(M+H)^+$: 369.1815. Found: 369.1809. CD ($c=0.33\times10^{-3}$, MeOH) $\Delta\varepsilon^{22°}$ (nm): 0 (305), +3.2 (282), +2.6 (275), +20.8 (252), 0 (235), −4.3 (225).

Epimerization of Rauniticine-*epiallo*-oxindole A (7) A solution of **7** (10 mg) in dry pyridine (0.5 ml) was heated at 140 °C under argon for 9 h. After removal of pyridine, the residue was separated by MPLC to afford 2.0 mg of **7**, 6.7 mg of **8**, and 1.1 mg of rauniticine-*allo*-oxindole A (**11**). **11**: amorphous powder. UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm (log ε): 207 (4.39), 243 (4.12). MS m/z (%): 368 (M^+, 80), 223 (100). HR-FBMS Calcd for $C_{21}H_{25}N_2O_4$ $(M+H)^+$: 369.1815. Found: 369.1813. CD ($c=0.33\times10^{-3}$, MeOH) $\Delta\varepsilon^{25°}$ (nm): 0 (300), −2.2 (285), −1.8 (275), −12.5 (255), 0 (240), +2.6 (234), 0 (225), +13.0 (209).

Epimerization of Rauniticine-*epiallo*-oxindole B (8) A solution of **8** (15 mg) in dry pyridine (0.5 ml) was heated at 140 °C under argon for 9 h. After removal of pyridine, the residue was separated by MPLC to afford 1.8 mg of **7** and 11.5 mg of **8**.

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