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GAMBIRDINE AND ISOGAMBIRDINE, THE ALKALOIDS FROM UNCARIA GAMBIR (HUNT) ROXB.

K.C. CHAN

Department of Chemistry, University of Malaya,
Kuala Lumpur, Malaysia.

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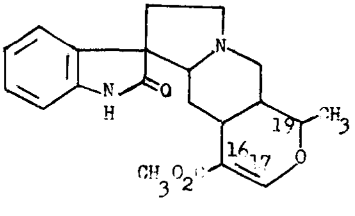
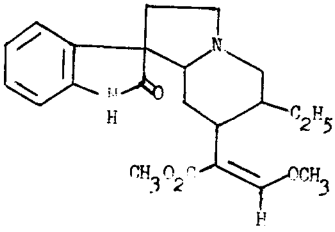
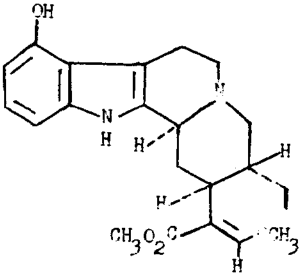
Several *Uncaria* and *Mitragyna* species of the family *Rubiaceae* have yielded a number of oxindole alkaloids having either the mitraphylloid-type (I) or rhyncophylloid-type (II) structure[1]. Merlini, Mendelli, Nasini and Hesse[2] have recently reported the isolation from the leaves of *Uncaria gambier* Roxb. of gambirine whose structure was established (III). We now report the isolation from the stem of *Uncaria gambir* (Hunt) Roxb. of two new alkaloids designated gambirdine and isogambirdine and a known compound, mitraphylline. It will be shown in this communication that the new bases are stereoisomeric with mitraphylline, uncarine-A and -B, pteropodine and isopteropodine, and have the same structure (I).



(I)



(II)



(III)

Examination of the crude methanolic extracts by thin-layer chromatography indicated the presence of five alkaloids. Chromatography of the crude extracts on neutral alumina afforded isogambirdine as an oil which was isolated as its hydrochloride m.p. 179-181° (dec.), gambirdine, m.p. 199-201°, $[\alpha]_D^{21} = +84.8°$ (c 0.02 in $CHCl_3$), and mitraphylline, m.p. 261-263° (dec.), identical in all respects with an authentic sample.

The major alkaloid, isogambirdine, $[\alpha]_D^{21} = +115.5°$ (c 0.02 in $CHCl_3$) was not crystalline but was shown to be homogenous by thin-layer chromatography. Elemental analyses of gambirdine, isogambirdine and their derivatives indicated that the formula is $C_{21}H_{24}N_2O_4$ which was confirmed by mass determinations. Titrations with dilute hydrochloric acid showed them to be monoacidic bases, and both contain one methoxyl but no N-methyl group. Comparison of the ultraviolet and infrared spectra (in $CHCl_3$ and Nujol) with those of mitraphylline[3], uncarine-A and -B[4], pteropodine and isopteropodine[5] showed that gambirdine [uv (EtOH): λ max. 244 mμ and sh. 280 mμ (log ε 4.19 and 3.13 respectively)] and isogambirdine [uv (EtOH): λ max. 244 mμ and sh. 280 mμ (log ε 4.24 and 3.18 respectively)] contain an oxindole chromophore (respective oxindole C=O 1694 and 1702 cm^{-1}) and CH_3O_2C-C=CHOR group (respective ester C=O 1722 and 1722 cm^{-1}). In agreement with this the infrared spectra of gambirdine and isogambirdine showed marked increase in intensity in the respective infrared band at 1617 and 1623 cm^{-1}, attributed by the contribution of a benzene ring and a polarised double bond[3].

TABLE - N.m.r. Spectra in $CDCl_3$ at 60 Mc/sec in p.p.m. from tetramethylsilane

Functional group	Mitra-phylline[6,7]	Uncarine				Pteropodine[5,7]	Isopteropodine[5,7]	Gambirdine	Isogambirdine
		-A[6,7]	-B[6,7]	-C[8]	-D[8]				
$\underline{CH_3}CHO$	1.11	1.30	1.28	1.35	1.22	1.35	1.40	1.32	1.31
$\underline{CH_3}OCO$	3.57	3.51	3.52	3.55	3.32	3.80	3.82	3.56	3.58
C_{19}-H	4.34	3.75	3.73	4.35	4.15	4.49	4.46	3.78	3.82
Aromatic H	-	-	-	-	-	7.30	7.28	7.12	7.08
Olefinic H	7.39	-	7.40	7.41	7.31	7.70	7.72	7.46	7.42
$\overset{H}{-N-}$	-	-	-	-	-	9.47	9.49	8.83	8.32

The n.m.r. spectra of gambirdine and isogambirdine were closely similar to those of known stereoisomers of mitraphylloid-type structure (see TABLE). The signal due to the hydrogen proton at C_{19} was centred at a higher field in gambirdine and isogambirdine (3.78 and 3.82 p.p.m. respectively) as those observed in uncarine-A and -B[7] (3.75 and 3.73 p.p.m. respectively). The aliphatic -NH proton in each case, was indicated by the presence of a singlet which disappeared upon deuteration.

The most convincing verification of the structures of gambirdine and isogambirdine was provided by the fact that the mass spectra of these bases and that of mitraphylline[9] were indistinguishable with only minor differences in relative peak intensities. In particular, peaks at m/e 223, 208, 159, 146-144, 130 and 69 are characteristic of alkaloids having mitraphylloid-type structure (I) as discussed by Djerassi et al[9].

Furthermore, the interconversion of a pair of stereoisomers of mitraphylloid-type or rhyncophylloid-type structure by refluxing in pyridine or aqueous acetic acid has been well studied [5,8,10]. This intriguing feature is also observed in gambirdine and isogambirdine. Thus, the latter on refluxing in aqueous acetic acid led to the formation of 77% of gambirdine while equilibration of gambirdine in pyridine gave a mixture consisting of about 20% isogambirdine.

Biogenetic reasoning[11] as well as the above spectroscopic evidence suggests that gambirdine and isogambirdine are stereoisomeric with mitraphylline, uncarine-A and -B, pteropodine and isopteropodine and they have the same structure (I). Work on the stereochemistry of gambirdine and isogambirdine is being undertaken.

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