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FOUR NEW DIMERIC MONOTERPENE ALKALOIDS FROM SCAEVOLA RACEMIGERA DÄNIKER (GOODENIACEAE)

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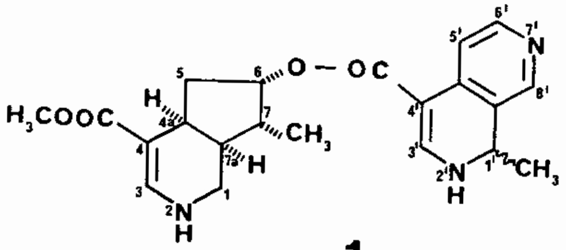
Abstract - Four new dimeric monoterpene alkaloids (1-4) have been isolated from the aerial parts of Scaevola racemigera Däniker. Their structures have been elucidated by spectroscopic studies and chemical correlations.

Scaevola racemigera Däniker (Goodeniaceae) is a tall shrub indigenous to the coastal regions of New Caledonia[1,2]. Various monoterpene alkaloids had been previously isolated from the aerial parts of this species[3]. A thorough search for the more polar constituents of the alkaloid extract has now led to the isolation of four novel dimeric monoterpene alkaloids named scaevodimerines A, B, C and D. The present paper describes their structure determination.

Scaevodimerine A (1) has been obtained as a colourless amorphous solid, $[\alpha]_D^{20}$ +31° (MeOH, c = 1)(contents : 0.02 % from the dried plant material[4]). Its empirical formula has been determined by high resolution mass spectroscopy as $C_{21}H_{25}N_3O_4$ (Found : 383.1831 ; Calcd. : 383.1845). The uv spectrum exhibited characteristic absorptions at $\lambda_{max.}^{EtOH}$ nm (log ε) : 214(4.06), 237(4.00), 269(4.30) and 335(3.70) associated with a pyridine-dihydropyridine chromophore[5,6]. The ir spectrum displayed bands at ν_{max}^{KBr} cm^{-1} : 1715 and 1665 typical to a conjugated carboxylic ester. The ^{1}H nmr spectrum (Table I) exhibited all the characteristic signals of a tetrahydrocantleyine unit[3]. The chemical shift of H-6 (5.38 ppm instead of 4.06 ppm for tetrahydrocantleyine itself) gave evidence for an esterifi-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O — OC
CH$_3$
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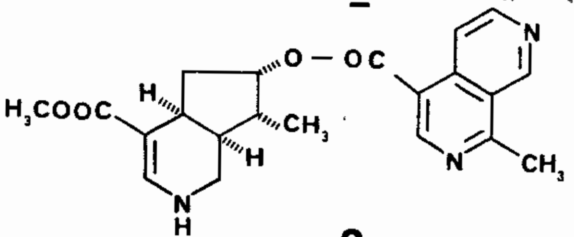
1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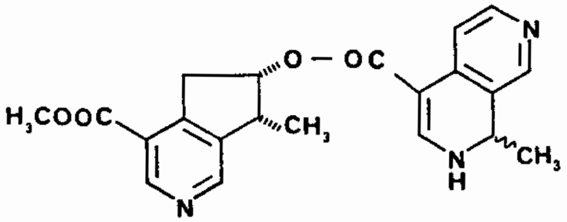
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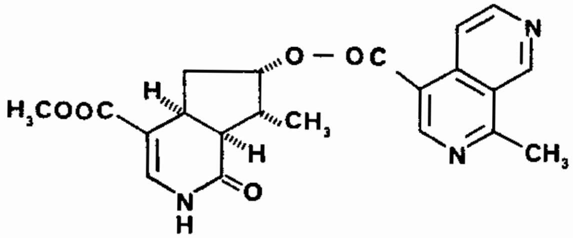
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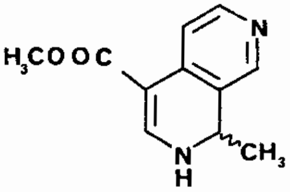
O
N

4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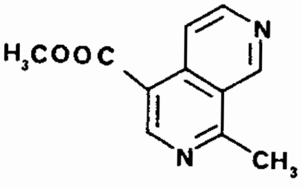
N
CH$_3$
H

5


H$_3$COOC
N
CH$_3$

6

cation by a carboxylic acid at the 6-position[3]. Additional signals on the nmr spectrum permitted depicting the structure of the esterifying unit as 1,2-dihydro-1-methyl-2,7-naphthyridine-4-carboxylic acid. Of particular interest were the coupling constants between Me-1', H-1', NH-2' and H-3' which provided evidence for the 1'-position of the methyl group. Methanolysis of scaevodimerine A (0.25 N MeONa in MeOH/reflux under Ar/72 h) led in 40 % yield to an equimolecular mixture of 1,2-dihydro 4-carbomethoxy-1-methyl-2,7-naphthyridine (5) characterized by its ^{1}H nmr spectrum (Table I) and of tetrahydrocantleyine identical with the natural product (uv, ir, sm, ^{1}H nmr, $[\alpha]_D^{20}$)[3]. This experiment gave evidence for the absolute configuration at C-4a, C-6, C-7 and C-7a. Unfortunately, the absolute configuration at C-1' on the 1,2-dihydro 2,7-naphthyridine moiety of the molecule remains unknown since 5 spontaneously aromatizes by air-oxidation at room temperature within a few hours to the corresponding achiral naphthyridine 6. The uv spectrum of this latter compound exhibited absorptions at λ_{max}^{EtOH} nm (log ε) : 222(3.80) and 290 (3.70) typical to a 2,7-naphthyridine chromophore[7]. The ir spectrum of 6 displayed characteristic bands[8,9] at ν_{max}^{KBr} cm^{-1} : 1725 (ester, c = O), 1605 and 845 (2,7-naphthyridine and its ^{1}H-nmr spectrum (Table I) was very close to that described for 2,7-naphtyridine itself[10], except for the chemical shifts of H-3 and H-5 strongly deshielded by the carbomethoxy group at C-4.

Scaevodimerine B (2) has also been obtained as a colourless amorphous solid, $[\alpha]_D^{20}$ +39° (MeOH, c = 1) (contents : 0.05 % from the dried plant material). The empirical formula could be established by high resolution mass spectrometry as $C_{21}H_{23}N_3O_4$ (Found : 381.1700 ; Calcd. : 381.1688). Its general spectral features were closely related to those of 1. Nevertheless, differences could be noted on its uv spectrum whose typical absorptions : λ_{max}^{EtOH} nm (log ε) : 222(3.99), 283(4.03) were only associated with a pyridine-derivated chromophore. Its ^{1}H nmr spectrum (Table I) exhibited the characteristic signals of tetrahydrocantleyine unit esterified at the 6-position[3] and those previously encountered in the spectrum of naphthyridine 6 with the exception of that associated with the COOMe group. Methanolysis of scaevodimerine B (1N MeONa in MeOH/reflux/2 h) led to tetrahydrocantleyine and to 4-carbomethoxy-1-methyl-2,7-naphthyridine 6 in almost quantitative yield. This experiment provided evidence for both stereochemistry on the tetrahydrocantleyine moiety of the molecule and substitution pattern on the 2,7-naphthyridine unit. The structure of scaevodimerine B could thus be depicted as 2.

In a similar way, the structures of scaevodimerine C (3), $[\alpha]_D^{20}$ -18° (MeOH, c = 1),

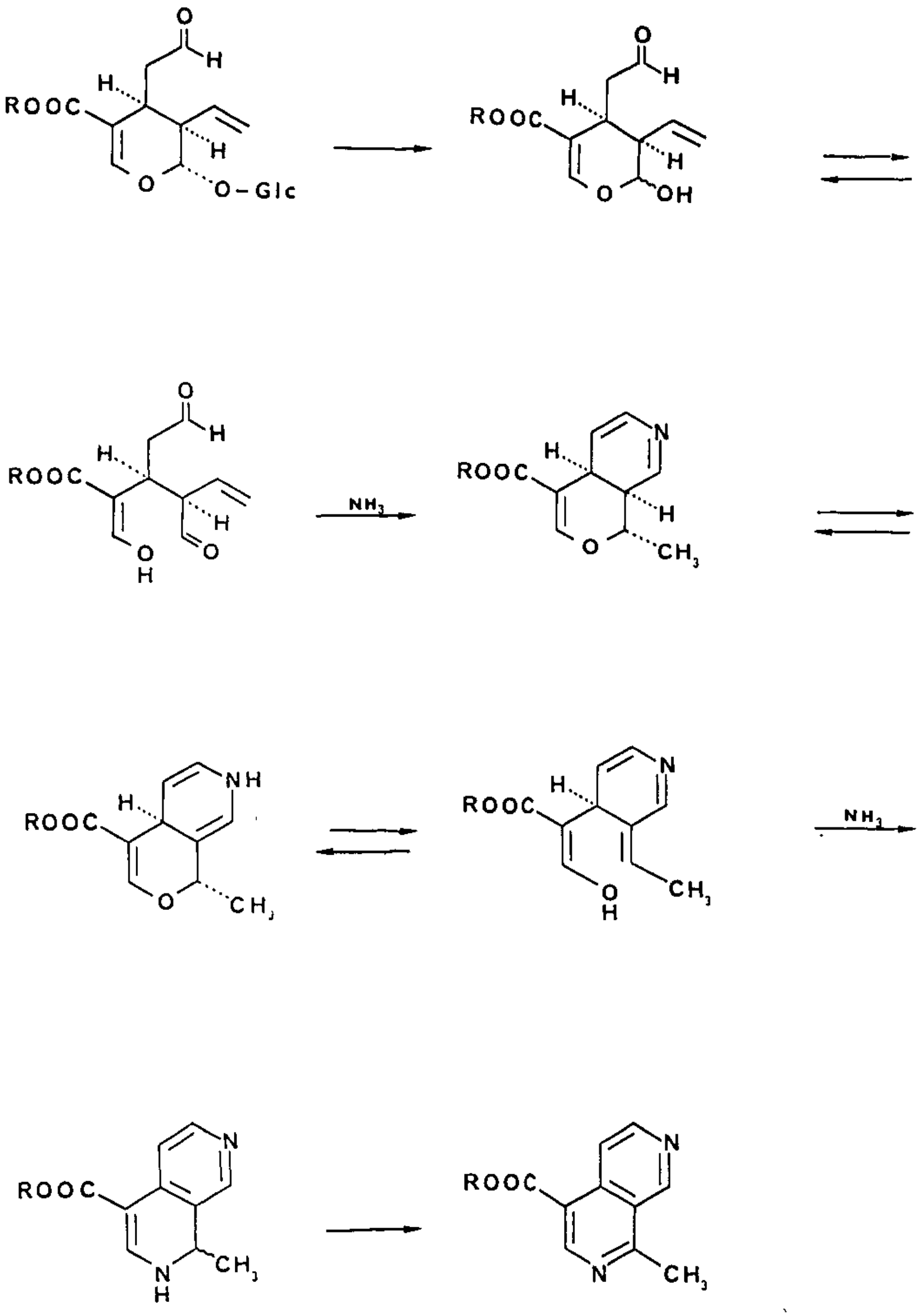
TABLE I

^{1}H N.M.R. spectra of *scaevodimerines* A, B, C, D and of compounds $\underline{5}$ and $\underline{6}$ (270 MHz, δ ppm/TMS , J in Hz).

	$\underline{1}^{a,c}$	$\underline{2}^{a}$	$\underline{3}^{a,c}$	$\underline{4}^{a}$	$\underline{5}^{b}$	$\underline{6}^{b}$
H-1a	2.89 ddd : 13,7,2	2.82 ddd . 13,7,2	8.58	-	-	-
H-1b	3.26 ddd 13,5,2	3.33 ddd : 13,5,2	s	-	-	-
NH-2	4.58 br.s. D_2O exch.	4.48 br.s.D_2O exch	-	7.44 br.s.D_2O exch	-	-
H-3	7.53 d 7,tr.to s by D_2O	7.53 d 7, tr.to s by D_2O	9.07 s	7.22 d.6, tr.to s by D_2O	-	-
COOMe-4	3.67 s	3.68 s	3.96 s	3.73 s	-	-
H-4a	3.11 td 9,7	3.22 td 9,7	-	3.59 ddd 11,9,7	-	-
H-5a	1.71 ddd 15,9,5	1.87 ddd 15,9,5	3.53 m.	1.89 ddd 11,9,7	-	-
H-5b	2.34 ddd 15,7,2	2.52 ddd 15,7,2	3.53 m	2.64 m	-	-
H-6	5.38 ddd 5,4,2	5.56 ddd 5,4,2	5.80 td 5,3	5.55 td 4,2	-	-
H-7	2.00 m	2.15 m	3.53 m	2.64 m	-	-
Me-7	1.04 d 7	1.14 d 7	1.38 d 7	1.34 d 7	-	-
H-7a	2.00 m	2.15 m	-	2.82 dd 11,8	-	-
H-1'	4.96 qd 7,2 tr.to q by D_2O	-	1.89 qd 7,2,tr.to q by D_2O	-	4.74 qd.7,2, tr.to q by D_2O	-
Me-1'	1.49 d 7	3.13 s	1.48 d 7	3.13 s	1.27 d 7	3.03 s
NH-2'	7.52 br.s D_2O exch.	-	7.06 br.s D_2O exch.	-	8.24 br.s.D_2O exch.	-
H-3'	7.94 d 7, tr.to s by D_2O	9.63 s	7.71 d 7,tr.to s by D_2O	9.67 s	7.73 d 7,tr.to s by D_2O	9.71 s
COOMe-4'	-	-	-	-	3.60 s	3.90 s
H-5'	8.20 d 5	8.78 d 5	8.20 d 6	8.81 d 5	7.96 d 5	8.57 d 5
H-6'	8.37 d 5	8.82 d 5	8.38 d 6	8.84 d 5	8.20 d 5	8.82 d 5
H-8'	8.11 s	9.20 s	8.10 s	9.27 s	8.08 s	9.07 s

a : in $CDCl_3$; b : in CD_3SOCD_3 ; c : recorded at 65°C

Scheme 1



$C_{21}H_{21}N_3O_4$ (h.r. ms ; Found : 379.1521 ; Calcd. : 379.1532), (contents : 0.01 % from the dried plant material) and scaevodimerine D (4), $[\alpha]_D^{20}$ +48° (MeOH, c = 0.2), $C_{21}H_{21}N_3O_5$ (h.r. ms ; Found : 395.1465 ; Calcd. : 395.1481), (contents : 0.005 % from the dried plant material) could be determined as 3 and 4. Of particular interest were their ^1H nmr spectra (Table I).which exhibited signals typical to cantleyine[11,12] and 1,2-dihydro-1-methyl-2,7-naphthyridine -4-carboxylic ester units for 3 and to strychnovoline[13] and 1-methyl-2,7-naphthyridine -4-carboxylic ester units for 4.

Scaevodimerines are the first dimeric monoterpene alkaloids and seem related to dimeric iridoid derivatives[14,15]. Their structures involve a 2,7-naphthyridine skeleton which has been previously seldom encountered in higher plants belonging to the families Oleaceae,[16,17] Scrofulariaceae[9] and Valerianaceae[18]. This naphthyridine unit arises most probably from ammonia condensation with a secologanin-derived dialdehyde[19,23] followed by rearrangements[24,25] shown in Scheme 1. Since the alkaloids described in this paper have been extracted by standard means using ammonia as a base, a second alkaloid extraction avoiding the use of a nitrogen-containing alkaline agent and a study of the iridoid contents of the plant seem necessary to understand the exact biogenetic origin and the chemotaxonomic significance of the naphthyridine derivatives.

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