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FOUR NEW ACRIDONE ALKALOIDS FROM SARCOMELICOPE DOGNIENSIS HARTLEY (RUTACEAE)

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Abstract - Four new acridone alkaloids, 1, 3, 4 and 6 have been isolated from the leaves of Sarcomelicope dogniensis. Their structures have been elucidated by spectroscopic studies and confirmed by their synthesis, using N-desmethylacronycine (2) as starting material.

Sarcomelicope dogniensis Hartley (Rutaceae) is a medium tree upto 12 m high recently described as endemic to the Plateau de Dogny, New Caledonia[1]. In a continuation of our systematic studies of alkaloid containing plants from New Caledonia[2], we wish to report here the structural elucidation of four novel acridones isolated from the leaves of this species[3].

(-)-Cis-1,2-dihydroxy-1,2-dihydro-N-desmethylacronycine (1)[4] has been obtained as a yellow amorphous compound (contents : 0.01 % from the dried plant material) ; $[\alpha]_D^{20} = -2°$ (c = 0.25, MeOH). Its empirical formula has been determined by high resolution mass spectroscopy as $C_{19}H_{19}NO_5$ (Found : 341.1260 ; Calcd. : 341.1263). Its uv spectrum, λ_{max}^{MeOH}nm (log ε) : 228(4.16), 246(sh., 4.31), 260(4.41), 269(4.41), 290(4.07), 320 (sh., 3.65) and 374(3.78) is very close to that of 1,2-dihydroacronycine[5]. The ir spectrum exhibits typical absorptions at ν_{max}.cm^{-1} (KBr) : 775, 1165, 1605, 1625, 1650, 2960, 3005 and 3445, the last of which indicates the presence of free alcoholic groups. The main features of the ^{1}H nmr spectrum

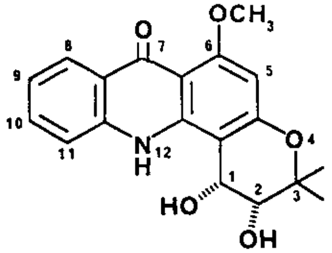
(Table I) are the signal of the NH-10 of a 9-acridone and the series of signals typical to a fused cis-3,4-dihydroxy-2,2-dimethyl-3,4-dihydro-2H-pyran system[6,7]. These elements permitted depicting the structure of this novel alkaloid as 1. Unfortunately, the absolute configurations of the two chiral centers at C-1 and C-2 remain unknown, due to the small amount of natural product isolated. Confirmation of structure 1 could be obtained by partial synthesis. Oxidation[7,8] of N-desmethylacronycine (2) (OsO_4/C_5H_5N/20°C/3 h) leads in 95 % yield to (±)-cis-1,2-dihydroxy-1,2-dihydro-N-desmethylacronycine (1) whose chromatographic and spectral characteristics (tlc, uv, ir, ms, nmr) are identical with those of the natural product.

1-Methoxy-3-(2-methylpropanal-2-oxy)-acridin-9-one-4-carbaldehyde (3) has been obtained as a yellow amorphous solid (contents : 0.01 % from the dried plant material) ; $[\alpha]_D^{20}$= 0°. Its empirical formula could be established by high resolution mass spectrometry as $C_{19}H_{17}NO_5$ (Found : 339.1095 ; Calcd.: 339.1106). The uv spectrum, $\lambda_{max.}^{MeOH}$ (log ε) : 225(4.11), 246(4.47), 260(4.56), 275(sh., 4.38), 285 (sh., 4.37), 309(4.15), 325(sh., 3.89) and 393(4.04) is close to that of acronycine[5] and shows typical absorptions associated with a 9-acridone nucleus bearing two oxygen substitutents at C-1 and C-3 and an unsaturated substitutent at C-4. The ir spectrum, $\nu_{max.}$ cm^{-1} (KBr) : 780, 1160, 1610, 1625, 1640, 1655, 1745, 2950, 3000 and 3430 is consistent with a 9-acridone[9,10] skeleton and with the presence of aliphatic and aromatic aldehyde groups. In good agreement with this statement, the ^1H nmr spectrum (Table I) exhibits one D_2O-exchangeable NH-singlet at 12.95ppm and two 1H-aldehyde singlets at 10.48 and 9.88 ppm. The aromatic signals are typical to a 1,3,4-trisubstituted 9-acridone. One 3H-singlet at 3.98 ppm and one 6H-singlet at 1.68 ppm were assigned to one OMe and one CMe_2 groups. These data suggested a structure of 1-methoxy-3-(2-methylpropanal-2-oxy)-acridin-9-one-4-carbaldehyde (3) for this novel alkaloid. Confirmation of the location of the substitutents on the acridone nucleus was performed by chemical correlation. Periodic oxidation of the diol 1 ($NaIO_4$/MeOH/20°C/2 h) leads in 68 % yield to the dialdehyde 3 identical with the natural product.

(+)-1-Hydroxy-1,2-dihydro-N-desmethylacronycine (4) has been obtained as light yellow prisms from methanol, mp 212-214°C (contents : 0.01 % from the dried plant material) ; $[\alpha]_D^{20}$= +4° (c = 0.25, MeOH). The empirical formula could be established by high resolution mass spectrometry as $C_{19}H_{19}NO_4$ (Found : 325.1301 ;

Calcd. : 325.1313). The uv spectrum, $\lambda_{max.}^{MeOH}$ nm (logε) : 227(4.11), 247(sh., 4.35), 260(4.48), 269(4.49), 291(4.07), 315(sh, 3.68), 321(sh, 3.62) and 374(3.72) is very similar with that of 1,2-dihydroacronycine. The ir spectrum, νmax. cm^{-1} (KBr) : 765, 1165, 1605, 1625, 1650, 2960, 3010 and 3450 shows the characteristic absorptions of a 9-acridone system[9,10] and of a free OH-group. The ^{1}H nmr spectrum (Table I) exhibits in addition to the signals of a 1,3,4-trisubstituted 9-acridone, the signals associated with a fused 4-hydroxy-2,2-dimethyl-3,4-dihydro-2H-pyran system[6]. These elements permitted depicting the structure of this new alkaloid as 4. Nevertheless, the absolute stereochemistry at C-1 remains unknown, due to the small amount of natural product at our disposal. The structure of this alkaloid was finally confirmed by its synthesis from N-desmethylacronycine (2). In a first step, hydroxybromination[8,11] of 2 (N-bromosuccinimide/50 % aqueous THF/0°C/3 h) led in 47 % yield to (±)-trans-hydroxy-1-bromo-2-dihydro-1,2-N-desmethylacronycine (5). This bromohydrin could then be smoothly debrominated using tributyltinhydride-reduction[11,12] (Bu_3SnH/2,2'-Azabis(2-methylpropionitrile)/Toluene/Reflux under Ar/1 h). This latter reaction leads in 80 % yield to (±)-1-hydroxy-1,2-dihydro-N-desmethylacronycine (4) whose chromatographic and spectral characteristics (tlc, uv, ir, ms, nmr) are identical with those of the natural product.

1-Oxo-1,2-dihydro-N-desmethylacronycine (6) has been isolated as a yellow amorphous solid (contents : 0.02 % of the dried plant material) ; $[\alpha]_D^{20} = 0°$. Its empirical formula has been determined by high resolution mass spectrometry as $C_{19}H_{17}NO_4$ (Found : 323.1154 ; Calcd. : 323.1157). The uv spectrum, $\lambda_{max.}^{MeOH}$ nm (logε) : 227(3.71), 245(3.92), 260(4.01), 275(sh., 3.93), 280(3.94), 310(3.59), 326(sh., 3.25) and 384(3.57) and the ir spectrum, ν max. cm^{-1} (KBr) : 780, 1160, 1615, 1630, 1645, 1655, 2940, 3000 and 3415 showed diagnostic absorptions of a 9-acridone nucleus[9]. The ^{1}H nmr spectrum (Table I) exhibits in the aromatic region the signals associated with a 1,3,4-trisubstituted 9-acridone skeleton. In the aliphatic region, one 3H-singlet at 4.06 ppm, one 2H-singlet at 2.83 ppm and one 6H-singlet at 1.56 ppm could be assigned to one OMe and to the protons of a $Ar\text{-}CO\text{-}\underline{\underline{C}}H_2\text{-}C(\underline{\underline{C}}H_3)_2\text{-}O\text{-}Ar$ system. These elements permitted depicting the structure of this novel acridone as 6. Confirmation of this structure was obtained by its synthesis from the benzylic alcohol 4. Chromic oxidation[13,14] of (±)-1-hydroxy-1,2-dihydro-N-desmethylacronycine (4) (Pyridinium chlorochromate/anh. CH_2Cl_2/20°C/3 h) leads in 68 % yield to 1-oxo-1,2-dihydro-N-desmethylacronycine (6) identical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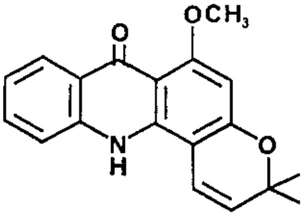
3
OH

1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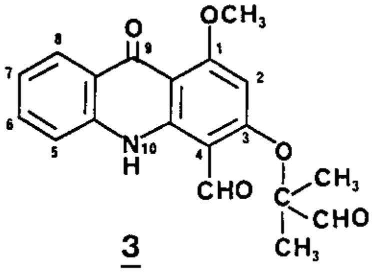
2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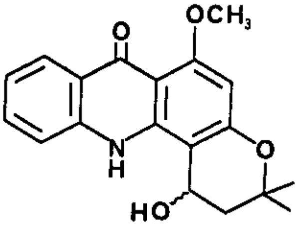
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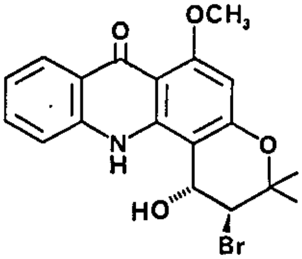
4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H
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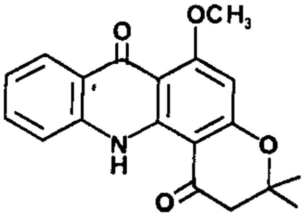
HO
Br

5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H
O
O

6

Table I : ^{1}H nmr spectra of acridones 1, 3, 4 and 6

H	1[a]	4[a]	6[b]	H	3[b]
H-1A	5.02 d: 5	5.08 q:6, tr. to t:6 by D_2O	-	CHO-4	10.48 s
OH-1B	5.33 br.s.D_2O exch.	5.97 d:6, D_2O exch.	-		
H-2A	3.68 d:5	2.14 dd:14,6	2.83 s (2H)	$\text{-OCMe}_2\underline{\text{CHO}}$	9.88 s
H-2B	-	2.04 dd:14,6			
OH-2B	3.40 br.s.D_2O exch.	-	-		
Me-3A	1.32 s	1.43 s	1.56 s(6H)	$\text{-OC}\underline{\text{Me}_2}\text{CHO}$	1.68 s(6H)
Me-3B	1.38 s	1.34 s			
H-5	6.11 s	6.11 s	6.16 s	H-2	5.89 s
OMe-6	3.78 s	3.77 s	4.06 s	OMe-1	3.98 s
H-8	8.09 dd:8,1.5	8.07 dd:8,1.5	8.43 dd:8,1.5	H-8	8.41 dd:8,1.5
H-9	7.17 td:8,1.5	7.17 td:8,1.5	7.30 td:8,1.5	H-7	7.33 td:8,1.5
H-10	7.62 td:8,1.5	7.61 td:8,1.5	7.64 td:8,1.5	H-6	7.66 td:8,1.5
H-11	7.61 dd:8,1.5	7.81 dd:8,1.5	7.37 dd:8,1.5	H-5	7.40 dd:8,1.5
NH-12	10.26 br.s.D_2O exch.	10.35 br.s.D_2O exch.	12.90 br.s.D_2O exch.	NH-10	12.95 br.s.D_2O exch.

a : in CD_3SOCD_3 b : in $CDCl_3$

with the natural product.

All the novel acridone alkaloids isolated from the leaves of *Sarcomelicope dogniensis* result from an oxidation of the dimethylpyran ring of N-desmethylacronycine[15-17]. This latter compound and acronycine itself are the major alkaloids of the plant. From a chemotaxonomic point of view, these results are in full agreement with the recent botanical revision of Hartley[1], since all the *Sarcomelicope* species so far studied are characterized by the presence of acronycine and acronycine-derived alkaloids.

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3. The plant material has been collected on the Plateau de Dogny (New Caledonia) in November 1983. Herbarium samples (Pusset-Chauvière 705) are held in the herbaria of the Centre ORSTOM de Nouméa.
4. The semi-trivial nomenclature used in this paper is that generally used for acronycine derivatives, i.e., 6-hydroxy-3,12-dihydro-3,3,12-trimethyl-7H-pyrano[2,3-c]acridin-7-one is known as noracronycine, whereas 3,12-dihydro-3,3-dimethyl-6-methoxy-7H-pyrano[2,3-c]acridin-7-one is known as N-desmethylacronycine.
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