SYNTHESIS OF PYRAZOLE ANALOGS FROM ARGENTATIN B*

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Received September 6, 1994
Accepted January 30, 1995

The pyrazole derivatives 3′-(2-R-phenyl)[3,2-*c*]pyrazole-16,24-epoxy-25-hydroxy-9,19-cyclostane *Va – Vf* have been prepared in a three step reaction from argentatin B. The structure of all the compounds synthesized was corroborated by ^{1}H and ^{13}C NMR, IR and mass spectroscopy.

Argentatin B (*I*) is an abundant tetracyclic triterpene obtained[1] from the resin of the Mexican guayule (*Parthenium argentatum* A. GRAY). The skeleton of argentatin B has been found highly similar to steroidal ring and therefore a suitable target for the rational design of potentially useful steroidal-like active molecules. As an extension of our strategy for preparing other argentatin derivatives[2], herein we report the synthesis of pyrazole derivatives of argentatin B as an attempt to pursue possible biologically active compounds. In this regard it has been reported the synthesis of some steroidal-like molecules with pyrazole group fused to the ring A which are currently used as antiinflammatory drugs[3,4]. Our synthetic approach to prepare *Va – Vf* involves a Claisen–Schmidt condensation of argentatin B (*I*) with 2-substituted benzaldehydes *IIa – IIf* under basic medium to give intermediates *IIIa – IIIf* and subsequent condensation with hydrazine to furnish *IVa – IVf*. The final pyrazole derivatives *Va – Vf* were obtained upon treatment of *IVa – IVf* with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (Scheme 1).

The IR data of *IIIa – IIIf* showed a characteristic band between 1 698 – 1 675 cm^{-1} corresponding to α,β-unsaturated ketone in agreement with the expected Claisen–Schmidt condensation product (Table I). The ^{1}H NMR spectrum of *IIIa – IIIf* showed typical signals for the seven methyls[1,5] of argentatin B skeleton, one of them being secondary (δ 0.94 – 0.95, J = 8 Hz, H-20) and six being tertiary (δ 0.95 – 0.93, H-28;

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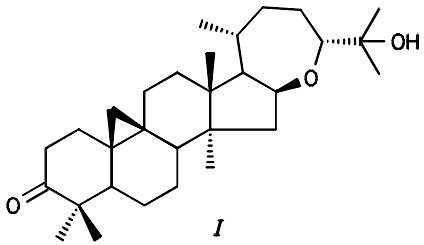
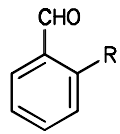


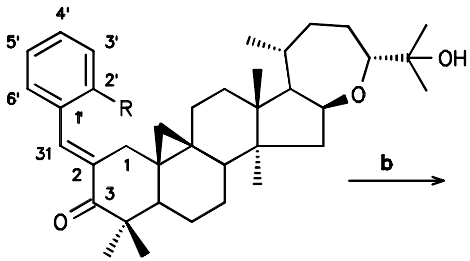
I

+

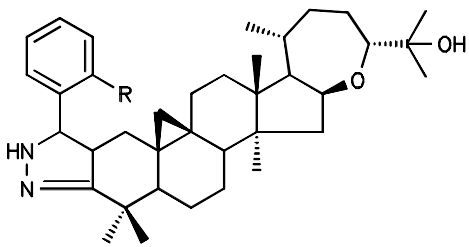


IIa – IIf

a →

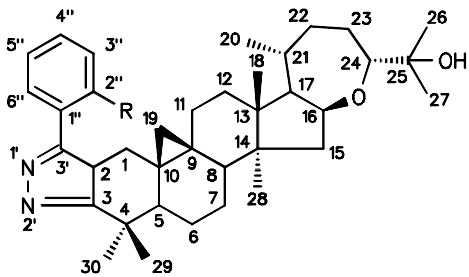


IIIa – IIIf



IVa – IVf

c →



Va – Vf

In formulae *II – V* :

	R
a	H
b	2-OCH_3
c	2-CH_3
d	2-Cl
e	2-Br
f	2-NO_2

a, KOH, EtOH; **b**, NH_2NH_2, MeOH; **c**, DDQ, dioxane

SCHEME 1

1.03 – 1.02, H-30; 1.10 – 1.11, H-26, 27; 1.25 – 1.24, H-18 and 1.30 – 1.32, H-29). Two one-proton doublets (J = 4 Hz) of the cyclopropane ring protons at C-19 are shown between δ 0.66 – 0.63 and 0.45 – 0.43; one-proton signal at δ 2.2 – 2.8 corresponds to the tertiary OH linked to C-25. The doublet at δ 3.5 – 3.6 (J = 11 Hz) for hydrogen at C-24 and the quartet (J = 7.3 Hz) at δ 4.62 – 4.60 for hydrogen at C-16 position[5]. It also displayed signals at δ 7.2 – 8.4 for vinyl and aromatic protons of the 2-arylidene moiety. The ^{13}C NMR data for *IIIa – IIIf* exhibit signals for each of the 37 carbon atoms present in the molecule and the assignment of the chemical shifts were based on APT experiments as well as for comparison with those of similar molecules. The mass spectra[6] analysis showed the molecular ion and characteristic peaks at *m/z* (M – R), (M – 59), 85 and 59 (100).

In case of *IVa – IVf* the IR data did not show as expected any carbonyl band and instead there were found low intensity bands at 3 386 – 3 309 cm^{-1} assigned to N–H of pyrazoline group and a low intensity band at 1 640 cm^{-1} for the C=N group (Table II). The mass spectra analysis showed the molecular ion and characteristic peaks at *m/z* (M – 15),

TABLE I
Yields, IR spectra and analytical data for compounds *IIIa – IIIf*

Compound	Yield, %	IR spectrum cm^{-1}	Formula M.w.	Calculated/Found	
				% C	% H
IIIa	82	1 698, 1 593	$C_{37}H_{52}O_3$	81.57	9.62
			544.8	81.60	9.60
IIIb	82	1 698, 1 597	$C_{38}H_{54}O_4$	79.40	9.47
			574.9	79.43	9.42
IIIc	81	1 698, 1 598	$C_{38}H_{54}O_3$	81.67	9.74
			558.9	81.71	9.72
IIId	94	1 679, 1 613	$C_{37}H_{51}ClO_3$	76.72	8.87
			579.3	76.68	8.85
IIIe	99	1 680, 1 610	$C_{37}H_{51}BrO_3$	71.25	8.24
			623.7	71.35	8.20
IIIf	30	1 686, 1 600	$C_{37}H_{51}NO_5$	75.35	8.72
			589.8	75.40	8.70

(M – 59), 59 (100), (M – 140), 140 and (184 + R) (c.f. ref.[6]). The NMR data for these compounds are not given due to their decomposition in solution.

The structure of pyrazole derivatives *Va – Vf* was supported by IR typical bands between 1 465 – 1 462 and 962 – 932 cm^{-1} for the pyrazole ring (Table III). The ^1H NMR spectra also displayed signals for the seven methyls[1,5] of argentatin B skeleton, one of them being secondary (δ 0.99 – 0.97, J = 8 Hz, H-20) and six being tertiary (δ 1.10 – 1.11, H-28; 1.13 – 1.12, H-30; 1.09 – 1.08, H-26, 27; 1.20 – 1.18, H-18 and 1.07 – 1.06, H-29). Two one-proton doublets (J = 4 Hz) of the cyclopropane ring protons at C-19 are shown between δ 0.42 – 0.45 and 0.65 – 0.63; one proton signal at δ 2.5 – 3.0 corresponds to the tertiary OH linked to C-25. The doublet at δ 3.6 – 3.4 (J = 11 Hz) for hydrogen at C-24 and the quartet (J = 7.3 Hz) at δ 4.60 – 4.58 for hydrogen at C-16 positions[5]. It also displayed signals at δ 7.4 – 7.2 for the aromatic protons. The ^{13}C NMR data for *Va – Vf* exhibit signals for each of the 37 carbon atoms present in the molecule and the assignment of the chemical shifts were based on APT experiments as well as

TABLE II
Yields, melting points, IR spectra and analytical data for compounds *IVa – IVf*

Compound	M.p., °C Yield, %	IR spectrum cm^{-1}	Formula M.w.	Calculated/Found	
				% C	% H
IVa	194 – 196	3 346, 1 701	$C_{37}H_{54}N_2O_2$	79.52	9.74
	52		558.9	79.60	9.43
IVb	179 – 182	3 315, 1 600	$C_{38}H_{56}N_2O_3$	77.51	9.59
	45		588.9	77.70	9.38
IVc	197 – 200	3 386, 1 654	$C_{38}H_{56}N_2O_2$	79.67	9.85
	67		572.9	79.75	9.60
IVd	208 – 210	3 331, 1 683	$C_{37}H_{53}ClN_2O_2$	74.91	9.00
	53		593.3	75.20	8.78
IVe	202 – 204	3 309, 1 690	$C_{37}H_{53}BrN_2O_2$	69.68	8.38
	77		637.8	69.91	8.18
IVf	162 – 165	3 361, 1 631	$C_{37}H_{53}N_3O_4$	73.60	8.85
	41		603.9	73.30	8.50

for comparison with those of similar molecules. The mass spectra showed *m*/*z* peaks for M^+, (M – 251), (236 + R), (M – 59) and 59 (100).

EXPERIMENTAL

Melting points were determined in Fisher–Johnes melting point apparatus and were uncorrected. Thin layer chromatography were taken on silica gel 60 aluminium sheets (Macherey–Nagel Duren Art. 818 133). IR spectra ($CHCl_3$ and Nujol) were determined on Perkin–Elmer 283-B and Nicolet FT-55X spectrometer. Mass spectra were taken on Hewlett–Packard 5985 A spectrometer. ^1H NMR and ^{13}C NMR were determined on Varian FT-80 (80 MHz for ^1H) and Varian VXR-300 (75 MHz for ^{13}C) spectrometers in deuteriochloroform with tetramethylsilane as internal standard, chemical shifts are given in ppm (δ-scale), expressed downfield from tetramethylsilane and coupling constants (*J*) in Hz.

(24*R*)-2-(2-Bromobenzylidene)-16β,24-epoxy-25-hydroxy-9,19-cyclolanostan-3-one (*IIIe*)

To a solution of argentatin B (*I*; 1.0 g, 2.2 mmol) in ethanol (15 ml) a solution of potassium hydroxide (61 mg, 1.1 mmol) and 2-bromobenzaldehyde (*IIe*; 0.41 g, 2.2 mmol) in ethanol (3 ml) was added dropwise and the reaction was stirred at room temperature for 48 h. The reaction mixture was diluted with methylene chloride (20 ml) and washed twice with water (2 × 10 ml). The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated. The oily product was purified by column chromatography on silica gel 60 and eluted with hexane–ethyl acetate to furnish 1.35 g (99%)

TABLE III
Yields, melting points, IR spectra and analytical data for compounds *Va – Vf*

Compound	M.p., °C Yield, %	IR spectrum cm^{-1}	Formula M.w.	Calculated/Found	
				% C	% H
Va	175 – 178	1 464, 962	$C_{37}H_{52}N_2O_2$	79.81	9.41
	5		556.8	80.10	9.19
Vb	172 – 175	1 465, 961	$C_{38}H_{54}N_2O_3$	77.77	9.27
	9		586.9	78.01	8.93
Vc	280 – 282	1 462, 932	$C_{38}H_{54}N_2O_2$	79.95	9.53
	13		570.9	80.20	9.28
Vd	274 – 276	1 465, 962	$C_{37}H_{51}ClN_2O_2$	75.16	8.69
	16		591.3	75.31	8.50
Ve	283 – 285	1 463, 961	$C_{37}H_{51}BrN_2O_2$	69.90	8.09
	20		635.7	70.10	7.89
Vf	262 – 264	1 465, 962	$C_{37}H_{51}N_2O_4$	73.84	8.54
	18		601.8	74.17	8.25

of oily compound *IIIe*. ^{1}H NMR spectrum: 0.45 d, 1 H, J = 4 (H-19); 0.63 d, 1 H, J = 4 (H-19′); 0.94 d, 3 H, J = 8 (3 × H-20); 0.95 s, 3 H (3 × H-28); 1.03 s, 3 H (3 × H-30); 1.10 s, 6 H (3 × H-26 and 3 × H-27); 1.25 s, 3 H (3 × H-18); 1.30 s, 3 H (3 × H-29); 2.58 s, 1 H (OH); 3.60 d, 1 H, J = 11 (H-24); 4.60 q, 1 H, J = 7.1 (H-16); 7.5 – 8.0 m, 4 H (4 × H-arom.). ^{13}C NMR spectrum: 18.9 (C-18), 19.0 (C-28), 19.6 (C-9), 19.6 (C-6), 20.8 (C-30), 21.1 (C-21), 21.8 (C-23), 23.3 (C-29), 23.9 (C-26, C-27, C-7), 25.5 (C-10), 25.9 (C-11), 28.8 (C-20), 29.9 (C-19), 32.6 (C-12), 35.3 (C-22), 44.9 (C-15), 45.3 (C-8), 45.6 (C-1), 45.7 (C-13), 45.7 (C-14), 48.0 (C-5), 48.9 (C-4), 57.3 (C-17), 73.2 (C-25), 74.7 (C-16), 82.4 (C-24), 122.6 (C-5′), 124.2 (C-4′), 129.2 (C-2′), 130.5 (C-3′), 132.5 (C-6′), 135.7 (C-31), 137.4 (C-2), 138.7 (C-1′), 207.4 (C-3).

Compounds *IIIa – IIId* and *IIIf* were obtained by the same procedure from argentatin B (*I*) and the corresponding benzaldehydes *IIa – IId* and *IIf*. For yields, IR spectra and analytical data see Table I.

(24*R*)-3′-(2-Bromophenyl)[3,2-*c*]pyrazoline-16β,24-epoxy-25-hydroxy-9,19-cyclolanostane (*IVe*)

To a solution of compound *IIIe* (1.2 g, 2.2 mmol) in methanol (10 ml) was added dropwise hydrazine monohydrate (0.90 g, 10 mmol). The mixture was stirred at room temperature for 5 h. A white solid was obtained on standing overnight at 0 °C. The solid was filtered and washed with cold methanol to give 0.92 g (77%) of pure pyrazoline derivative *IVe*.

Compounds *IVa – IVd* and *IVf* were obtained by the same procedure from *IIIa – IIId* and *IIIf*, respectively. For yields, IR spectra and analytical data see Table II.

(24*R*)-3′-(2-Bromophenyl)[3,2-*c*]pyrazole-16β,24-epoxy-25-hydroxy-9,19-cyclolanostane (*Ve*)

A mixture of *IVe* (0.50 g, 0.74 mmol), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.34 g, 1.5 mmol) in dioxane (20 ml) was refluxed for 6 h. After cooling at room temperature, the mixture was dissolved in ether (20 ml) and washed with 0.1 M NaOH (4 × 10 ml), and water (3 × 10 ml). The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The resulting oil was purified by column chromatography on silica gel 60 eluted with hexane–ethyl acetate (7 : 3) to give 0.25 g (20%) of *Ve* as a white solid. ^{1}H NMR spectrum: 0.45 d, 1 H, J = 4 (H-19); 0.63 d, 1 H, J = 4 (H-19′); 0.99 d, 3 H, J = 8, (3 × H-20); 1.06 s, 3 H (3 × H-29); 1.09 s, 6 H (3 × H-26 and 3 × H-27); 1.10 s, 3 H (3 × H-28); 1.12 s, 3 H (3 × H-30); 1.19 s, 3 H (3 × H-18); 2.58 s, 1 H (OH); 3.59 d, 1 H, J = 11 (H-24); 4.58 q, 1 H, J = 7.2 (H-16); 7.2 – 7.4 m, 4 H. ^{13}C NMR spectrum: 19.1 (C-18), 19.6 (C-10), 19.8 (C-28), 20.9 (C-21), 21.2 (C-6), 23.4 (C-23), 23.8 (C-27), 24.6 (C-26), 24.7 (C-9), 25.6 (C-30), 25.8 (C-2, C-4, C-7), 27.6 (C-29), 28.9 (C-20), 29.8 (C-19), 29.9 (C-11), 32.7 (C-12), 35.0 (C-1), 35.4 (C-22), 45.1 (C-15), 45.6 (C-14), 45.8 (C-13), 46.5 (C-8), 48.4 (C-5), 57.4 (C-17), 73.2 (C-25), 74.8 (C-16), 82.4 (C-24), 113.3 (C-3), 113.3 (C-1″), 126.5 (C-5″), 129.0 (C-4″), 129.8 (C-6″), 131.5 (C-3″), 133.1 (C-2″), 133.1 (C-3′).

Compounds *Va – Vd* and *Vf* were prepared by the same procedure from *IVa – IVd* and *IVf*, respectively. Yields, melting points, IR spectra and analytical data are given in Table III.

We are grateful to R. Patiño, R. Gavino, A. Gutierrez, J. Perez and L. Velasco for their technical assistance for the IR, NMR and MS determination. This project was supported by DGAPA, UNAM (Mexico, Grant IN-303489).

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