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AMIDES FROM *ZANTHOXYLUM RUBESCENS*

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Key Word Index—*Zanthoxylum rubescens*; Rutaceae; stem bark; root bark; rubemamin; rubemamide; dioxamin; dioxamide; zanthomamide; arnottianamide; lupeol; unsaturated aromatic amides; pungent principles; synthesis.

Abstract—The stem bark of *Zanthoxylum rubescens* has furnished two new amides identified as *N*-methyl,*N*-(3,4-dimethoxyphenylethyl)-3′,4′-dimethoxycinnamamide (rubemamide) and *N*-(3,4-dimethoxyphenylethyl)-3,4′-dimethoxycinnamamide (rubemamin). Two other novel amides, *N*-methyl,*N*-(3,4-methylenedioxyphenylethyl)-3′,4′-methylenedioxycinnamamide (dioxamide) and *N*-(3,4-methylenedioxyphenylethyl)-3′,4′-methylene dioxycinnamamide (dioxamin) were isolated from the roots. The structural assignments of these amides were confirmed by synthesis. Both the root and stem barks furnished the known aromatic amide, *N*-mathyl,*N*-(3,4-methylenedioxyphenylethyl)-cinnamamide (zanthomamide). In addition, lupeol and arnottianamide were isolated and characterized from the roots.

INTRODUCTION

Zanthoxylum rubescens (syn. *Fagara rubescens*) is reported [1] to contain rubesamide (**1**), an aromatic amide identified as *N*-(3,4-methylene-dioxyphenyl) cyclopropanecarboxamide. In a continuation of our search for novel compounds of the Rutaceae, we report here the isolation, identification and synthesis of five aromatic amides from the stem and root barks of *Z. rubescens*. These unsaturated aromatic amides have been identified as zanthomamide (**2**) and four novel structures for which the names rubemamin (**3**), rubemamide (**4**), dioxamin (**5**) and dioxamide (**6**) are proposed. Dioxamin and dioxamide were isolated from the roots along with lupeol and arnottianamide (**8**).

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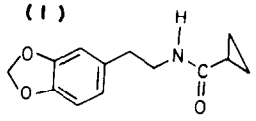

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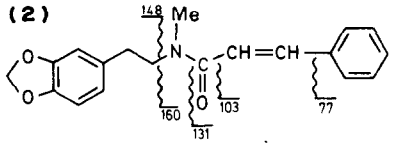

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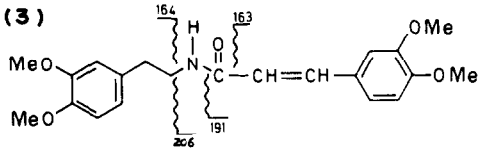

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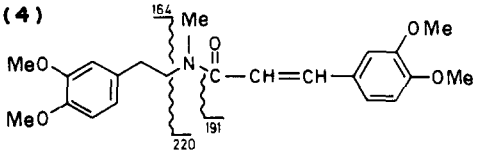

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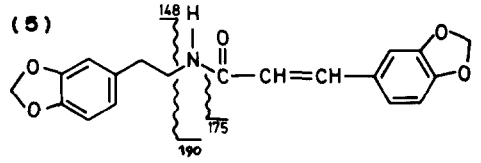

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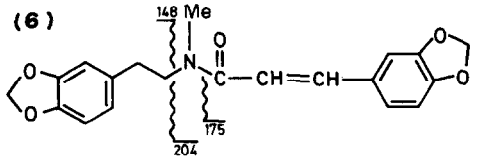

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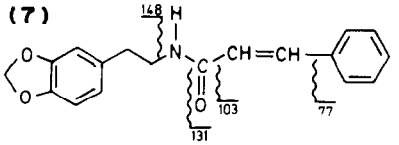

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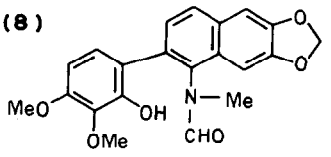

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Table 1. ^{1}H NMR data for compounds 2–7 (300

	Zanthomamide, 2	Rubemamin, 3	Rubemamide, 4
	2.81	2.84	2.84
	(2H, *t*)	(2H, *t*)	(2H, *t*)
	3.60	3.65	3.64
$-CH_2CH_2NH-$	(2H, *t*)	(2H, *q*)	(2H, *t*)
		3.85	3.85
		(3H, *s*)	(3H, *s*)
		3.86	3.86
–OMe	—	(3H, *s*)	(3H, *s*)
		3.87	3.87
		(3H, *s*)	(3H, *s*)
		3.89	3.88
		(3H, *s*)	(3H, *s*)
NH		5.80	
		(IH, *br*)	
	3.1		3.24
N–Me	(3H, *s*)		(3H, *s*)
	6.42	6.24	6.24
	(1H, *d*, $J = 15.6$ Hz)	(1H, *d*, $J = 15.5$ Hz)	(1H, *d*, $J = 15.5$ Hz)
	7.63	7.56	7.55
–CH=CH–	(1H, *d*, $J = 15.6$ Hz)	(1H, *d*, $J = 15.5$ Hz)	(1H, *d*, $J = 15.5$ Hz)
	5.91		
$-OCH_2O-$	(2H, *d*, $J = 1.7$ Hz)		
Aromatic protons	6.64–6.76 (3H, *m*) 7.28–7.49 (5H,*m*)	6.20–6.80 (2H, *m*) 6.99–7.07 (4H, *m*)	6.21–6.81 (2H, *m*) 7.00–7.07 (4H, *m*)

RESULTS AND DISCUSSION

The toluene-soluble part of the methanol extract of *Z. rubescens* stem on concentration afforded a sticky residue which after column chromatography on silica gel and elution with toluene containing increasing amounts of ethyl acetate afforded only mixed fractions. Repeated prep. TLC eventually led to the isolation of zanthomamide, mass spectrum (*m/z*, rel. int.): 131 (100), 148 (80), 309 (3). Its structure was confirmed by synthesis and by comparison of its spectra (UV, ^{1}H NMR, IR) with those of an authentic sample [2]. The synthetic product also showed identical chromatographic behaviour [EtOAc–toluene (1:1), $CHCl_3$–toluene (9:1), $CHCl_3$–EtOAc (9:1)] with the isolated material. This compound was recently reported from *Z. thomense* [2].

Rubemamin was isolated as white solid, mp 121–122° with its mass spectrum showing characteristically a weak $[M]^+$ at *m/z* 371 ($C_{21}H_{25}O_5N$). The occurrence of major ions at *m/z* 164, 191 and 206 can be explained as depicted on the structural formula. Rubemamide, the *N*-methyl derivative of (**3**) also showed a weak $[M]^+$ at *m/z* 385 ($C_{22}H_{27}O_5N$) and showed major ions at *m/z* 191, 164 and 220. It was obtained in an amorphous form. The IR spectrum of (**3**) showed a sharp band at 3320 cm^{-1} suggesting the presence of an –NH–group for a secondary amide. Similarly, the absence of bands between 3200 and 3500 cm^{-1} confirmed the tertiary nature of rubemamide. The two amides exhibited strong absorption bands at 1660 cm^{-1} (for $-HNCO$ or $>NCO$) confirming the presence of C–N bonds and carbonyl groups. The aromatic character of the two amides was further supported by their IR spectra.

The UV absorption spectra of both compounds were similar UV λ_{max}^{MeOH} 322, 284, 230, 203 nm; relative intensities of absorbance at the maxima are 25, 24, 39 and 80%, respectively. This confirmed the aromatic nature of the compounds. The UV spectra were unaltered by treatment with alkali. In the ^{1}H NMR of (**3**), characteristic signals for –CH=CH– were centred as doublets at δ 6.24 ($J = 15.5$ Hz) and 7.56 ($J. = 15.5$ Hz). An –NH– signal was observed as a deformed triplet at 5.8; this disappeared on shaking with D_2O. The four methoxy groups expected in the molecule of (**3**) were observed at δ 3.86–3.89 while a broad quartet at δ 3.65 (2H) and a triplet at δ 2.84 (2H, $J = 6.9$ Hz) were assigned to non-benzylic methylene groups. The interaction of the –NH–function with the adjacent CH_2 gives rise to the quartet for the methylene protons and the deformed triplet for NH. For rubemamide, however, two triplets (each 2H) at δ 3.64 and 2.84 ($J = 7$ Hz) were observed.

The 22.3 MHz ^{13}C NMR spectrum ($CDCl_3$, δ ppm) of rubemanin also corroborated the proposed structures. Diagnostic signals were readily assigned: δ 166.09 (amide C=O), 55.84 (2 × OMe), 55.79 (2 × OMe), 40.61 ($HN-CH_2-$) and 35.15 ($-CH_2-CH_2-$). Four of the 12 expected aromatic carbons are linked to methoxy groups and are readily assigned, viz. 147.62, 148.97, 149.04 and 150.49. Two olefinic methines at 140.7 and 121.6 were assigned to the olefinic carbons (–CH=CH–). These structural assignments of (**3**) and (**4**) were confirmed by unambiguous synthesis from the union of phenylethylamines and their cinnamic acids. The toluene-soluble part of the methanol extract of *Z. rubescens* root bark was obtained and analysed as described for the stem bark extract.

Dioxamin (**5**) was isolated as a white powder and its mass spectrum showed a weak $[M]^+$ at *m/z* 339 for $C_{19}H_{17}O_5N$. The origin of the major ions at *m/z* 148, 175 and 190 is depicted in the structural formulae. The amorphous dioxamide (**6**), the *N*-methyl derivative of (**5**)

MHz, $CDCl_3$, TMS int. standard)

Dioxamin, **5**	Dioxamide, **6**	Zanthomamin, **7**
2.79 (2H, *t*)	2.80 (2H, *t*)	2.81 (2H, *t*)
3.58 (2H, *q*)	3.60 (2H, *t*)	3.61 (2H, *q*)
—	—	—
5.79 (IH, *br*)		6.12 (1H, *br*)
	3.14 (3H, *s*)	
6.17 (1H, *d*, $J=15.5$ Hz)	6.17 (1H, *d*, $J=15.5$ Hz)	6.42 (1H, *d*, 15.6 Hz)
7.51 (1H, *d*, $J=15.5$ Hz)	7.52 (1H, *d*, $J=15.5$ Hz)	7.63 (1H, *d*, 15.6 Hz)
5.92 (2H, *s*)	5.92 (2H, *s*)	5.92 (2H, *s*)
5.97 (2H, *s*)	5.96 (2H, *s*)	
6.63–6.93 (2H, *m*)	6.62–6.92 (2H, *m*)	6.63–6.75 (3H, *m*)
6.94–6.96 (4H, *m*)	6.94–6.96 (4H, *m*)	7.28–7.48 (5H, *m*)

also showed a weak $[M]^+$ at *m/z* 353 for $C_{20}H_{19}O_5N$ and showed major ions at *m/z* 148, 175 and 204. The IR spectrum of (**5**) showed a sharp band at 3320 cm^{-1} suggesting the presence of an –NH–function, for a secondary amide. In the same way, the absence of bands between 3200 and 3500 cm^{-1} confirm the tertiary nature of dioxamide. The two amides exhibited strong absorption bands at 1655 (–HNCO or >NCO; conjugated C=O) confirming the presence of C–N bands and carbonyl groups. While bands at 1050 and 930 cm^{-1} may be assigned to the methylenedioxy groups, the bands at 1615, 872, 821 and 680 cm^{-1} may be assigned to 1,3,4-trisubstituted benzene systems.

The UV absorption spectra of both compounds were similar UV λ_{max}^{MeOH} 322, 289, 215, 202 nm; relative intensities of absorbance at the maxima were 39, 39, 36, 41 and 60%, respectively. The UV spectra were not modified by addition of alkali. The IR and UV data confirmed the aromatic nature of the compounds.

In the ^1H NMR spectrum of (**5**), characteristic signals for –CH=CH– were centred as doublets at δ 6.17 ($J=15.5$ Hz) and 7.51 ($J=15.5$ Hz) non-equivalent methines of *trans*-cinnamic acid derivative. An –NH– signal was observed at δ 5.79 exchangeable with D_2O. The four methylenedioxy protons (2 × $-OCH_2O-$) expected in the molecule of **5** were observed (2H, *s*) at δ 5.92 and (2H, *s*) at δ 5.97 while a broad quartet at δ 3.58 and triplet at δ 2.79 ($J=6.9$ Hz) were assigned to non-benzylic methylene groups. The broad quartet probably arises from the interaction of the –NH– function with the adjacent CH_2; such effects have been reported previously [1]. The –NH– function, for the same reason, appeared as a deformed triplet. The ^{13}C NMR spectrum of (**5**) supported the proposed structure. The low field region of the spectrum showed an amide carbonyl (166.0), methylenedioxy group carbons (100.8, 101.3), two allylic carbons and 12 aromatic carbons. Four of these aromatic carbons are linked to the methylenedioxy groups and are readily assigned, viz. 146.1, 147.8, 148.1, 149.0. The two expected CH_2 carbons appeared at 35.4 and 40.9 (for the CH_2 adjacent to the –NH–function).

Zanthomamide (**2**) was isolated also from the root bark and identified by comparison of its spectra (UV, mass, IR) and chromatographic behaviour with that previously isolated from the stem bark.

The identification of these novel structures adds to the variety of compounds in the Rutaceae. The structural assignments are supported by ^1H and ^{13}C NMR data, by biogenetic considerations and by synthesis. The co-occurrence of **1**–**6** in *Z. rubescens* is unique and will be of taxonomic significance if these compounds can be found in other species of *Zanthoxylum*. The roots of *Z. rubescens* like the roots of many other species of *Zanthoxylum* known in Nigeria are used as chewing sticks and pungency of these roots have been linked with the concentration of such amides as these. The amides may have some interesting biochemical properties. This is also a second report of the occurrence of arnottianamide in an African *Zanthoxylum*, the first being in *Z. gillettii* [3].

EXPERIMENTAL

Mps: uncorr. ^1H NMR spectra were recorded at 60 or 300 MHz using TMS as an int std. MS were recorded with a direct inlet system. CC and TLC were carried out using silica gel G and samples were routinely dried at 40° *in vacuo*.

Plant material. Z. rubescens (Planch ex Hook f.) Engl. was collected by SKA and Dr O. A. Olatunji from a tree growing along the Akinlalu/Famia road some 14 km from Ile-Ife, Nigeria, in November 1986, and was authenticated at source. A specimen has been deposited in the herbarium of the Botany Department, Obafemi Awolowo University.

Extraction and isolation. Powdered stem bark (1453 g) was extracted (× 3) with MeOH over 7 days. MeOH was removed under red. pres. and the residue (160 g) dissolved in toluene–MeOH–H_2O (1:1:1). The aq layer was further extracted with toluene (2 × 100 ml). The combined toluene extracts were concd to yield a sticky residue which was subjected to CC on silica gel and elution with toluene–EtOAc mixts. CC combined with repeated TLC eventually led to the isolation of the three novel amides. Powdered root bark (1720 g) was also extracted (× 3) with MeOH and processed as described for the stem bark. CC combined with repeated TLC led to the isolation of dioxamin, dioxamide, lupeol, zanthomamide and arnottianamide.

Zanthomamide (**2**). MS (*m/z*, rel. int.): 131 (100), 148 (80), 103 (32), 77 (27), 51 (12), 309 (3) for $C_{19}H_{19}O_3N$. IR ν_{max}^{KBr} cm^{-1}: 1650, 1540, 1510, 1495, 1450, 1350, 1260, 1050. UV λ_{max}^{MeOH} nm: 278, 220, 215, 203. ^1H NMR ($CDCl_3$, δ) (Table 1). Data are in close agreement with those recently published for zanthomamide isolated from *Z. thomense* [2].

Rubemamin (**3**). MS (*m/z*, rel. int.): 164 (100), 147 (88), 148 (56), 191 (20), 65 (18), 121 (13), 206 (12), 91 (10), 371 (2). (Found, C, 67.11, H 7.03, N 3.41 requires C, 67.9, H 6.7, N 3.8 for $C_{21}H_{25}O_5N$). IR ν_{max}^{KBr} cm^{-1}; 3320 (NH), 3085, 3000, 2940, 2860, 1658, 1625, 1610, 1525, 1475, 1425, 1340, 1270, 1250, 1170, 1155, 1032, 975, 850, 815; UV λ_{max}^{MeOH} nm: 316.5, 287, 230, 202 nm with intensities of *A* of 24.8, 23.5, 27 and 40.5%, respectively. ^1H NMR ($CDCl_3$, δ), see Table 1. These data are consistent with structure **3**.

Rubemamide (4). Analytical data are similar to those of (3). MS (*m/z*, rel. int.); 191 (100), 164 (82), 220 (24), 192 (20), 221 (18), 165 (17), 77 (8), 385 (3). ^{1}H NMR ($CDCl_3$, δ); N-Me group was observed at 3.24; NH signal absent. UV λ_{max}^{MeOH} nm; 322, 284, 230, 203. IR ν_{max}^{KBr} cm^{-1}; 2980–2940, 2850, 1650, 1606, 1515, 1460, 1430, 1385, 1325, 1270–1210 *br* 1170–1140, 1035, 905, 870, 860, 835.

Dioxamin (**5**). 22 mg, mp 144–146°, MS (m/z, rel. int.): 148 (100), 175 (30), 145 (20), 89 (20), 190 (16), 117 (12), 339 (2). Found: C 66.81, H 5.14, N 3.85 requires C 67.3, H 5.0, N 4.1 for $C_{19}H_{17}O_5N$). IR ν_{max}^{KBr} cm^{-1} 3320 (–NH–), 3095, 3060, 2910, 2880, 1850, 1745, 1660, 1620, 1540, 1500, 1450, 1370, 1345, 1320, 1270–1250, 1200, 1125, 1110, 1045, 985, 940, 880, 820, 790, 770, 745, 670; UV λ_{max}^{MeOH} nm: 322, 289, 233, 215, 202 with intensities of *A* of 39, 39, 36, 41 and 60%, respectively. ^{1}H NMR ($CDCl_3$, δ), see Table 1. These data are consistent with the structure (**5**).

Dioxamide (**6**). Spectroscopic data are similar to those of (**5**). MS (*m/z*, rel. int.): 175 (100), 148 (60), 145 (40), 89 (30), 117 (19), 204 (18), 176 (11), 63 (10), 51 (10), 353 (3) for $C_{20}H_{19}O_5N$. UV λ_{max}^{MeOH} nm; 322, 289, 232, 215, 203. IR ν_{max}^{KBr} cm^{-1}: 2910, 2880, 1660, 1620, 1540, 1500, 1270–1250. ^{1}H NMR ($CDCl_3$, δ): *s* 3.14, NMe; –NH– signal absent; *t* 2.80 and 3.60, two non-equivalent adjacent methylene groups.

Synthesis of N-*methyl*, N-*cinnamyl*-(3,4-*methylenedioxyphenylethyl*)-*cinnamamide* (**2**). 3,4-Methylenedioxybenzylcyanide (5 g, 0.05 mol) and $COCl_2 \cdot 6H_2O$ (24 g, 0.1 mol) were dissolved in 99% MeOH (300 ml) and $NaBH_4$ (19 g, 0.5 mol) was added in portions with stirring at room temp. With the addition of $NaBH_4$, evolution of H_2 and the formation of a black reaction mixt. was observed. After the addition of reducing agent, stirring was continued for another 2 hr. HCl (4 N, 150 ml) was poured into the reaction mixt and stirring continued until the black ppt. disappeared. MeOH was dist. off at red. pres. and unreacted 3,4-methylenedioxyphenyl acetonitrile removed with Et_2O. The reaction mixt. was then made alkaline with conc NH_4OH and extd with $CHCl_3$ (3 × 100 ml). The combined $CHCl_3$ exts were washed, dried (Na_2SO_4) and evapd to leave a residue in 63% yield. The resulting amine was 92% pure by GC.

Cinnamic acid (2g, 13.5 mmol) and excess $SOCl_2$ (3 g, 25 mmol) were heated at 100° for 30 min. Removal of excess reagent by dist. gave the cinnamoyl chloride as a liquid (2.14 g, 95%). The prepared cinnamoyl chloride (1 g, 6 mmol) in $CHCl_3$ (20 ml) was added in portions to a vigorously stirred mixt. of the preceding amine (1 g, 6.1 mmol), satd aq. $NaHCO_3$ (50 ml) and $CHCl_3$ (30 ml) with ice cooling. After the addition, cooling was stopped and stirring continued for 2 hr. The organic phase was then recovered. The aq. phase was further extracted with $CHCl_3$ (2 × 50 ml) and added to the recovered organic phase. The combined extracts were washed with satd NaCl, dried (Na_2SO_4) and evapd to give a product (502 mg). TLC purification furnished the amide zanthomamin (**7**) mp 112–114°. MS (*m/z*, rel. int.): 148 (100), 131 (42), 77 (34), 103 (30), 147 (21), 51 (21), 191 (4), 295 (3) for $C_{18}H_{17}O_3N$. UV λ_{max}^{MeOH} 278, 220, 215, 203 nm with *A* of 97, 53, 62 and 89%, respectively. IR ν_{max}^{KBr} cm^{-1}: 3305, 3080, 2900, 2780, 1660, 1620, 1545, 1505, 1495, 1350, 1295, 1255, 1200, 1100, 1050, 985, 950, 875, 815, 770. ^{1}H NMR ($CDCl_3$, δ), see Table 1.

This amide (200 mg) in dry Me_2CO and dry K_2CO_3 (2g) was refluxed with MeI for 6 hr to give the unreacted amide and (**2**) in low yield. The product (22 mg) was obtained from hexane–toluene in a sticky form but identical in all respects (UV, IR, MS, NMR) with the natural product.

Syntheses of rubemamin (**3**) *and rubemamide* (**4**). 3,4-Dimethoxybenzylcyanide (3 g, 17 mmol) was reduced ($NaBH_4$–metal salt complex) to the corresponding amine in 65% yield in the presence of $COCl_2 \cdot 6H_2O$ (8g, 33 mmol) [4] as described for 3,4-methylenedioxybenzylcyanide. 3,4-Dimethoxycinnamoylchloride was also prepared in 90% yield from the reaction of $SOCl_2$ (2.5 g, 21 mmol) with 3,4-dimethoxycinnamic acid (2 g, 9.6 mmol) as described earlier. Condensation of the amine (1 g, 5.5 mmol) with the acid chloride (0.8 gm, 3.5 mmol) furnished rubemamin (438 mg). N-Methylation with MeI in dry Me_2CO gave rubemamide also in poor yield. Both compounds showed spectral and analytical data identical to the natural materials.

Synthesis of N-(3,4-*methylenedioxyphenylethyl*)-3′,4′-*methylenedioxycinnamamide, dioxamin* (**5**) *and dioxamide* (**6**). 3,4-(Methylenedioxy) benzylacetonitrile (2g, 12.4 mmol) was reduced with $NaBH_4$ (5 g, 132 mmol) to the corresponding amine in 67% yield in the presence of $COCl_2 \cdot 6H_2O$ (6 g, 25 mmol) as described earlier. 3,4-(Methylenedioxy)-cinnamoyl chloride was also obtained in 91% yield from the reaction of 3,4-(methylenedioxy)-cinnamic acid (2 g, 10.4 mmol) and $SOCl_2$ (2.5 g, 21 mmol). The amine, 3,4-methylenedioxyphenyl ethylamine (1 g, 6.06 mmol) was reacted with the acid chloride (0.7 g, 3.3 mmol) to furnish dioxamin, 392 mg. N-Methylation gave dioxamide (17 mg) in low yield. The amides were purified by TLC. Both compounds showed identical spectral data (IR, UV, MS, ^{1}NMR) and chromatographic behaviour to the isolated natural products.

Oxidation of chelerythrine chloride. m-Chloroperbenzoic acid (100 mg, 580 mmol) was added to chelerythrine chloride (100 mg, 290 mmol) in hexamethylphosphorictriamide (HMPA) and the mixt stirred for 3 hr at 40°. Arnottianamide was recovered from the mixt. in 67.2% yield as colourless prisms, mp 268–269°, MS (*m/z*, rel. int.): 381 (100), 322 (78), 161 (64), 307 (54), 139 (48), 353 (38), 75 (67), 382 (36), 293 (32), 306 (31), 153 (30), 278 (23), 340 (20) for $C_{21}H_{19}O_6N$. The IR and UV were identical to those recorded in ref. [5]. The prepd compound formed a monoacetate (pyridine–Ac_2O), mp 237–238°, with an $[M]^+$ at *m/z* 423 (18%) for $C_{23}H_{21}O_7N$. Its ^{1}H NMR (DMSO) were identical to those reported [5] in CF_3CO_2H.

Arnottianamide (**7**). Yield 5 mg, mp 268–269°, was identified by a comparison of its spectral (MS, IR, UV) and chromatographic data with those of an authentic sample prepared by oxidation of chelerythrine chloride [3,5].

Lupeol. Yield 23 mg, mp 218–220°, was identified by a comparison of its spectral and chromatographic data with those of an authentic sample.

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