Alkaloids of the Annonaceae. Part 33. Annomontine and Methoxyannomontine, two new Pyrimidine-β-Carboline-type Alkaloids from *Annona montana*

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Two new alkaloids, which we have named annomontine (1) and methoxyannomontine (2), have been isolated from the trunk- and root-barks of *Annona montana* Macf. (Annonaceae). Their structures have been deduced by spectral analysis and confirmed by an *X*-ray structure determination of (2). They are the first members of the new class of 1-(2′-aminopyrimidin-4-yl)-β-carboline alkaloids.†

Annona montana Macf. (Annonaceae) is a small- or medium-sized glabrous tree; the species contains several poorly defined varieties.[1] The tree is widely distributed from the West Indies to Southern Brazil. In French Guiana it occurs only along the coastline, at the edge of the mangrove swamps; this tree is known in French as ' Corossolier batard,' its fruit pulp being edible, but an inferior quality to that of 'Corossol ' (*Annona muricata*) because it is slightly acid and hence has a somewhat acrid taste.[2] In folk medicine *A. montana* is used as a remedy for several disorders; for example, it is known as ' Boucha toukou ' by the Boni who recommend that a decoction made from its leaves be taken in the evening ' to calm the nerves and induce sleep.'

A previous investigation [3] of *Annona montana* resulted in the isolation of seven alkaloids; five were isoquinoline bases (aporphines, oxoaporphines, benzyltetrahydroisoquinolines, and phenanthrenes); the other two were not identified. We now present the structure of two new alkaloids of a new structural type, annomontine (1) and methoxyannomontine (2), which were isolated from both trunk- and root-barks of a Guianese specimen of *Annona montana* together with several isoquinoline alkaloids previously found in *A. montana*.‡

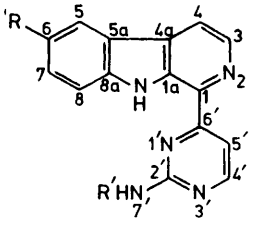
RESULTS AND DISCUSSION

The crude alkaloids from trunk barks and root barks were extracted separately, according to a classical procedure. Annomontine is the major alkaloid in trunk bark, whereas methoxyannomontine predominates in root bark. By direct crystallization, the crude trunk-bark alkaloids yielded annomontine and those from the root bark gave methoxyannomontine, both products being contaminated by the other alkaloid. Their purification was carried out by repeated recrystallization until pure products were obtained, homogeneous by t.l.c. and h.p.l.c. The respective yields were 0.5 g kg^{-1} of annomontine from trunk barks and 0.45 g kg^{-1} of methoxyannomontine from root barks.

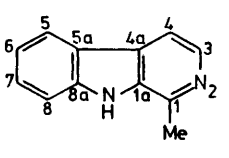
Annomontine (1) and methoxyannomontine (2), both optically inactive, were obtained as yellow to orange-yellow crystals, very slightly soluble in chlorinated solvents, ethyl acetate, and ethanol, slightly soluble in methanol or methanol–methylene dichloride mixtures, and freely soluble in dimethyl sulphoxide. Both compounds are dibasic and give a dihydrochloride.

A comparison of the formulae of compounds (1) and (2), together with a study of their u.v., mass, and ^1H n.m.r. spectra, show clearly that these two alkaloids possess the same skeleton, the only difference being the presence of a methoxy-group in (2) which is absent in (1). The highly conjugated aromatic nature of these molecules is apparent from their electron-impact mass spectra in which the base peak is the molecular ion in (1) and the $M - 15$ ion in (2). Neither spectrum showed any notably intense fragmentation peaks.

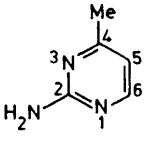
The general appearance of the ^1H n.m.r. spectra of the



(1) R = R′ = H
(2) R = OMe, R′ = H
(3) R = OMe, R′ = Ac



(4)



(5)

Crystallographic numbering scheme given for the β-carbolines

† The crystallographic numbering scheme is used throughout this paper (except where indicated).
‡ A full report of the alkaloidal content of *A. montana* will be published separately.

alkaloids led us to suspect the presence of a moiety of the harman type (4) in compound (1) and a methoxyharman type in compound (2), both linked *via* their respective C(1) atom to the other half of the molecule, which has formula $C_4H_4N_3$. The presence of a primary or secondary amine function on this second moiety was indicated by the formation of a mono-*N*-acetyl derivative, and this led us to the assumption that the other half of the molecule was an aminodiazine. Biogenetic considerations are *a priori* in favour of a pyrimidine nucleus rather than a pyridazine or a pyrazine, and this is in agreement with the ^{1}H- and ^{13}C-n.m.r. spectral data.

The ^{1}H n.m.r. spectrum[$(CD_3)_2SO$; 80 MHz] of methoxyannomontine (2), wherein the aromatic part is more easily interpreted than that of annomontine (1), is in accord with that of a methoxy-β-carboline substituted at C(1) by a 2-aminopyrimidine.[4-6] This spectrum exhibits, apart from the singlet (3 H) of the aromatic methoxy-group at δ 3.85, two 1 H-doublets (*J* 5.2 Hz) at δ 8.36 and 7.61 (3-H and 4-H), as well as three 1 H-signals at δ 7.20 (double doublet, *J* 2.5 and 9 Hz), 7.62 (doublet, *J* 9 Hz), and 7.79 (doublet, *J* 2.5 Hz) corresponding to the three aromatic protons of the methoxyindole moiety. Moreover, two 1 H-doublets (*J* 5 Hz) at δ 8.39 and 8.19 may be assigned to the 4′- and 5′-protons of the 2′-aminopyrimidine moiety; the strong deshielding of the latter signal may be explained by the influence of the β-carboline moiety. Signals for three D_2O-exchangeable protons are also observed at δ 6.91br (2 H, s, NH_2) and 11.67 br (1 H, s, indolic NH). In the ^{1}H n.m.r. spectrum of compound (3), the *N*-acetyl derivative of (2), the signal at δ 6.91 disappears, to be replaced by two singlets at δ 2.30 and 12.80, which are attributed, respectively, to the $COCH_3$ and NH protons of the NHAc function. In addition the 3-, 4-, 4′-, 5′-H signals undergo more-or-less marked shifts.

The splitting pattern in the ^{1}H n.m.r. spectrum for the three aromatic protons of the methoxyindolic part of compound (2) clearly reveals that the methoxy-group is located either at C(6) or C(7); the chemical shift values of these protons led us to favour the C(6) position.[5] The 6-position for the methoxy-group was confirmed by an analysis of the ^{13}C n.m.r. spectrum [$(CD_3)_2SO$; 15.08 MHz] of compound (2), and by comparison with the data measured and published [4] for harman and harmine (7-methoxyharman), as well as that for 2-amino-4-methylpyrimidine (5).[6,7] The absence from the spectrum of compound (2) of any methine signal upfield of δ_C 100 p.p.m., the region characteristic of C(8) in a 7-methoxyindole,[8] enables us to reject the possibility of a 7-methoxy-substituent and hence to place the methoxy-group of compound (2) at C(6). Moreover, the chemical shift values noted for all the carbons of annomontine and methoxyannomontine (Table 1) are in good agreement with the proposed structures (1) and (2).

TABLE 1

^{13}C N.m.r. data [a] for compounds (1), (2), (4), and (5)

	Compound			
Carbon	(4) [b]	(5) [c]	(1)	(2)
1	142.0		141.2	136.4
1a	140.5		136.6	135.8
3	137.3		138.3	137.3
4	112.2		117.1	118.6 [d]
4a	121.1		120.6	120.7
5	121.2		120.1 [d]	103.7
5a	127.0		130.6	130.2
6	119.0		122.2 [d]	153.8
7	127.5		129.0	116.8 [d]
8	111.5		112.6	113.0
8a	134.6		134.7	135.0
2′		163.2	164.8	163.5
4′		157.5	159.4	159.0
5′		109.4	105.9	105.7
6′		166.9	164.8	164.7

[a] δ (p.p.m.) downfield from internal $SiMe_4$, for solutions in $(CD_3)_2SO$. [b] Ref. 4. [c] Refs. 6 and 7. [d] Signals within a vertical column may be interchanged.

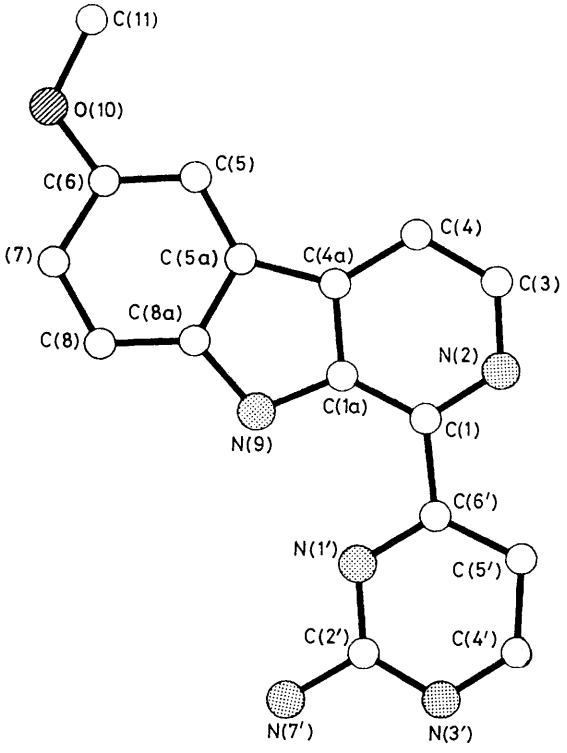


FIGURE *X*-ray crystal structure of methoxyannomontine, with crystallographic numbering scheme

The collective spectroscopic data strongly suggest, therefore, that methoxyannomontine (2) contains both a 6-methoxyharman moiety and a 2-aminopyrimidine, the bond between these two moieties being from C(1) of the former and C(4) of the latter. Since the structural interpretation of compound (2) was somewhat speculative, a single-crystal *X*-ray diffraction experiment was performed.

Methoxyannomontine (2) crystallizes in the triclinic system, space group $P\bar{1}$, with two molecules in the unit cell. A view of the molecule is shown in the Figure. The molecule is approximately planar, the angle between the β-carboline and the pyrimidine mean planes being 4°. An intramolecular hydrogen bond of length 2.74 Å is

observed between N(9) and N(1′). In the crystal, a solvating molecule of ethanol bridges two molecules of methoxyannomontine. The ethanol molecule is disordered and can occupy two positions, in which the hydroxy-groups are superimposed, with hydrogen-bond lengths as follows:

N(7′)–H · · · O–H · · · N(2)			
	3.08	2.83	
and	3.06	2.94	Å

Crystallographic data are given in Tables 2 and 3.

TABLE 2

Fractional atomic co-ordinates (× 10^4) with estimated standard deviations in parentheses and equivalent isotropic temperature factors (Å²) for non-hydrogen atoms in compound (2)

	x/a	*y/b*	*z/c*	*B*
C(1)	6 571(6)	1 855(10)	4 405(9)	3.48
N(2)	6 495(5)	3 320(7)	3 832(8)	3.85
C(3)	5 603(7)	3 426(9)	2 428(10)	3.92
C(4)	4 758(6)	2 145(10)	1 516(10)	3.76
C(4a)	4 801(6)	580(9)	2 063(9)	3.48
C(5a)	4 103(6)	−1 022(9)	1 480(9)	3.12
C(5)	3 099(6)	−1 621(9)	123(9)	3.40
C(6)	2 662(6)	−3 239(11)	−60(10)	4.23
C(7)	3 186(7)	−4 306(10)	1 073(11)	4.57
C(8)	4 179(7)	−3 715(9)	2 437(10)	3.93
C(8a)	4 639(6)	−2 050(9)	3 613(9)	3.40
N(9)	5 631(5)	−1 120(8)	3 833(8)	3.61
C(1a)	5 737(6)	467(9)	3 522(9)	3.04
O(10)	1 642(5)	−4 058(7)	−1 314(7)	5.61
C(11)	1 064(8)	−3 060(12)	−2 564(12)	5.86
N(1′)	7 635(5)	303(7)	6 366(7)	3.51
C(2′)	8 520(7)	196(10)	7 777(10)	3.67
N(3′)	9 313(5)	1 437(8)	8 754(8)	3.78
C(4′)	9 211(7)	2 866(10)	8 246(10)	4.39
C(5′)	8 347(7)	3 146(9)	6 823(10)	4.06
C(6′)	7 548(6)	1 780(9)	5 916(9)	3.26
N(7′)	8 601(6)	−1 301(8)	8 215(9)	5.30
OH	7 479	−3 434	4 952	6.50
CH_2	7 779	−2 673	3 464	7.50
CH_3	9 092	−2 086	3 899	8.50
OH *	7 297	−3 304	4 910	6.50
CH_2 *	8 330	−2 960	4 520	7.50
CH_3 *	8 442	−1 537	3 206	8.50

Our *X*-ray analysis showed that methoxyannomontine definitely has structure (2), and consequently annomontine has structure (1). This new type of alkaloid is interesting from both the structural and biogenetic points of view, because annomontine and methoxyannomontine are the only two known examples of alkaloids in which a harman-type moiety is linked to a 2-aminopyrimidine. Moreover, whereas the known natural 7-substituted derivatives of harman (4) are relatively numerous, 6-substituted derivatives, such as methoxyannomontine in the present case, are much rarer;[9] *e.g.* whereas harmine occurs in many plants, 6-methoxyharman appears to have been found in only two species, *Virola cuspidata* (Myristicaceae)[10] and *Mucuna pruriens* (Leguminosae).[11]

Finally, it should be noted that the structures of annomontine and methoxyannomontine are totally unexpected for compounds isolated from an Annonaceous species, since the alkaloids of the Annonaceae, and to a greater extent those of the Magnoliales, are of the isoquinoline type (with very few exceptions). In this connection it would be very interesting to see if compounds of this new structural type are present in other species of the genus *Annona*, in other genera of the Annonaceae family or other families belonging to the Magnoliales or to closely related orders such as the Laurales, Piperales, and Aristolochiales.

TABLE 3

Interatomic distances (Å) and angles (°) for non-hydrogen atoms in compound (2); mean standard deviations: 0.01 Å and 0.8°, respectively

C(1)–N(2)	1.35	C(7)–C(8)	1.38
C(1)–C(1a)	1.41	C(8)–C(8a)	1.39
C(1)–C(6′)	1.47	C(8a)–N(9)	1.40
N(2)–C(3)	1.36	N(9)–C(1a)	1.36
C(3)–C(4)	1.36	O(10)–C(11)	1.45
C(4)–C(4a)	1.41	N(1′)–C(2′)	1.36
C(4a)–C(5a)	1.43	N(1′)–C(6′)	1.34
C(4a)–C(1a)	1.42	C(2′)–N(3′)	1.34
C(5a)–C(5)	1.39	C(2′)–N(7′)	1.36
C(5a)–C(8a)	1.40	N(3′)–C(4′)	1.32
C(5)–C(6)	1.35	C(4′)–C(5′)	1.39
C(6)–C(7)	1.42	C(5′)–C(6′)	1.39
C(6)–O(10)	1.40		

N(2)–C(1)–C(1a)	119.5	C(5a)–C(8a)–C(8)	121.4
N(2)–C(1)–C(6′)	117.8	C(5a)–C(8a)–N(9)	109.1
C(1a)–C(1)–C(6′)	122.6	C(8)–C(8a)–N(9)	129.5
C(1)–N(2)–C(3)	119.1	C(8a)–N(9)–C(1a)	109.1
N(2)–C(3)–C(4)	124.9	C(1)–C(1a)–C(4a)	121.2
C(3)–C(4)–C(4a)	118.2	C(1)–C(1a)–N(9)	130.6
C(4)–C(4a)–C(5a)	135.1	C(4a)–C(1a)–N(9)	108.2
C(4)–C(4a)–C(1a)	117.0	C(6)–O(10)–C(11)	116.2
C(5a)–C(4a)–C(1a)	107.8	C(2′)–N(1′)–C(6′)	117.1
C(4a)–C(5a)–C(5)	132.6	N(1′)–C(2′)–N(3′)	125.5
C(4a)–C(5a)–C(8a)	105.8	N(1′)–C(2′)–N(7′)	116.5
C(5)–C(5a)–C(8a)	121.6	N(3′)–C(2′)–N(7′)	118.0
C(5a)–C(5)–C(6)	117.0	C(2′)–N(3′)–C(4′)	115.6
C(5)–C(6)–C(7)	122.5	N(3′)–C(4′)–C(5′)	124.8
C(5)–C(6)–O(10)	125.0	C(4′)–C(5′)–C(6′)	115.4
C(7)–C(6)–O(10)	112.4	C(1)–C(6′)–N(1′)	115.8
C(6)–C(7)–C(8)	120.6	C(1)–C(6′)–C(5′)	122.6
C(7)–C(8)–C(8a)	116.9	N(1′)–C(6′)–C(5′)	121.6

Because of their novel pyrimidinyl-β-carboline structure, annomontine, methoxyannomontine, and various semisynthetic derivatives of the latter compound were subjected to pharmacological screening; results will be given in a separate publication.

EXPERIMENTAL

Melting points were taken with a Köfler hot-stage and microscope. I.r. spectra were recorded on a Perkin-Elmer 237 spectrometer. U.v. spectra were recorded on a Beckman 25 instrument. ^{1}H N.m.r. spectra were recorded at 80 MHz on a Bruker WP80 spectrometer, and ^{13}C n.m.r. spectra at 15.08 MHz on a Bruker WP60 instrument operating in the Fourier-transform mode. All n.m.r. measurements were run on samples in $(CD_3)_2SO$. Mass spectra were run on a VG Micromass 70 spectrometer. *X*-Ray intensity data were collected with Cu-K_α radiation on a Philips PW 1100 automatic diffractometer.

Collection of Plant Material.—Trunk- and root-barks of *Annona montana* were collected in November 1979 and June 1980, at Tonate, French Guiana. Specimens were sent to the Herbarium of the Museum National d'Histoire Naturelle de Paris (reference HJ 2258).

Isolation of Alkaloids.—(a) *Annomontine* (1) [1-(2′-

aminopyrimidin-4′-yl)-β-*carboline*].* From powdered trunk bark (10.5 kg), crude alkaloids (21 g) were extracted using a previous procedure.[12] Crystallization from methylene dichloride yielded two crops (total of 5.1 g) of crude annomontine which was purified by four recrystallizations (three times in ethanol, then once in methylene dichloride) to give pure *annomontine* (1) (0.85 g) (homogeneous by t.l.c. and h.p.l.c.), as yellow crystals, m.p. 247—248 °C (CH_2Cl_2); $[\alpha]_D = 0$; (Found: C, 68.5; H, 4.4; N, 26.6. $C_{15}H_{11}N_5$ requires C, 68.95; H, 4.24; N, 26.81%); $\nu_{max.}$ (KBr) 3 340, 1 600, and 1 570 cm^{-1}; $\lambda_{max.}$ (EtOH) 244sh (log ε 4.24), 292 (4.18), 305sh (4.05), and 392 nm (4.08); $\lambda_{max.}$ (EtOH + HCl) 292sh, 313, and 426 nm; *m/z* (rel. intensity) 261 ($M^{+\bullet}$, 100), 260 (14), 245 (14), 220 (8), 194 (8), 193 (8), 168 (11), and 117 (12); high-resolution *m/z* 261.1015 (M^+). $C_{15}H_{11}N_5$ requires *m/z* 261.1014 (*M*); δ_H 7.01br (2 H, s, NH_2), 7.69 (1 H, d, *J* 5 Hz, 4-H), 7.15—7.80 (3 H, m, 6-, 7-, and 8-H), 8.29, 8.44, and 8.51 [3 H, 3 × d, *J* 5 Hz, 3-, 4′-, and 5′-H (specific signals not assigned)], 8.35 (1 H, m, 5-H), and 11.75br (1 H, s, indole NH); δ_C data given in Table 1.

(b) *Methoxyannomontine* (2) [1-(2′-*aminopyrimidin-4′-yl*)-6-*methoxy*-β-*carboline*].* Crude alkaloids (13.7 g) from powdered root bark (4.3 kg) yielded, by direct crystallization (CH_2Cl_2–MeOH; 2 : 1 v/v), crude methoxyannomontine (2) (1.8 g); column chromatography of the mother liquor on alumina afforded a second crop of compound (2) (0.2 g). Seven recrystallizations from ethanol afforded pure *methoxyannomontine* (2) (homogeneous by t.l.c. and h.p.l.c.) as yellow crystals, m.p. 223 °C (CH_2Cl_2) or orange crystals, m.p. 229—230 °C (EtOH); $[\alpha]_D = 0$; (Found: C, 66.1; H, 4.6; N, 24.2. $C_{16}H_{13}N_5O$ requires C, 65.97; H, 4.50; N, 24.04%); $\nu_{max.}$ (KBr) 3 370, 1 640, 1 600, 1 570, and 1 490 cm^{-1}; $\lambda_{max.}$ (EtOH) 246sh (log ε 4.38), 308sh (4.29), 322 (4.30), and 401 nm (3.98); $\lambda_{max.}$ (EtOH + HCl) 304sh, 333, and 443 nm; *m/z* (rel. intensity) 291 ($M^{+\bullet}$, 91), 277 (19), 276 (100), 235 (9), 207 (15), and 145.5 (10); high-resolution *m/z* 291.1115 (M^+). $C_{16}H_{13}N_5O$ requires *m/z* 291.1120 (*M*); δ_H 3.85 (3 H, s, OCH_3), 6.91br (2 H, s, NH_2), 7.20 (1 H, dd, *J* 9 and 2.5 Hz, 7-H), 7.61 (1 H, d, *J* 5.2 Hz, 4-H), 7.62 (1 H, d, *J* 9 Hz, 8-H), 7.79 (1 H, d, *J* 2.5 Hz, 5-H), 8.19 (1 H, d, *J* 5 Hz, 5′-H), 8.36 (1 H, d, *J* 5.2 Hz, 3-H), 8.39 (1 H, d, *J* 5 Hz, 4′-H), and 11.67br (1 H, s, indole NH); δ_C data given in Table 1.

Crystal Data and Structure Determination of Methoxyannomontine (2).—$C_{16}H_{35}N_5O{\cdot}C_2H_6O$. Triclinic, a = 13.207(2), b = 8.831(1), c = 8.200(2) Å, α = 83.0(1), β = 110.0(1), γ = 110.0(1)°, Z = 2. Space group $P\bar{1}$. Cu-K_α radiation (graphite monochromator), λ = 1.5418 Å. Intensity data were collected on a Philips PW 1100 diffractometer using the ω–2θ scan technique. Of the 3 073 reflections measured, 1 513 having $I > 3\sigma(I)$ were considered as observed. The structure was solved by direct methods and refined by full-matrix least-squares with the programme ORION.[13] Peaks located on a difference-Fourier map were interpreted as a disordered molecule of ethanol. This molecule can occupy two different positions in which the oxygen atoms are superimposed. The solvent molecules were treated as rigid groups of equal weight 0.5 with fixed β-values. Hydrogen atoms were introduced into the structure factor calculations in theoretical positions (*d* C–H = 1.0 Å, β of H = β of C or N). The final *R*-factor was 0.108. Final atomic co-ordinates are listed in Table 2, and bond lengths and angles in Table 3.†

N(7′)-*Acetyl Derivative* (3) *of Methoxyannomontine* [1-(2′-*Acetamidopyrimidin-4′-yl*)-6-*methoxy*-β-*carboline*].*—Acetylation of methoxyannomontine (2) was carried out with acetic anhydride and pyridine, overnight, at room temperature; work-up gave the crystalline *monoacetyl derivative* (3), m.p. 291—292 °C (EtOH); $\nu_{max.}$ (KBr) 1 720, 1 605, 1 550, 1 490, and 1 245 cm^{-1}; $\lambda_{max.}$ (EtOH) 240sh (log ε 4.35), 322 (4.25), and 407 nm (3.86); $\lambda_{max.}$ (EtOH + HCl) 330sh, 345, and 450 nm; δ_H 2.30 (3 H, s, $COCH_3$), 3.86 (3 H, s, OCH_3), 7.23 (1 H, dd, *J* 9 and 2.5 Hz, 7-H), 7.58 (1 H, d, *J* 9 Hz, 8-H), 7.83 (1 H, d, *J* 2.5 Hz, 5-H), 8.09, 8.27, 8.47, and 8.78 (4 H, 4 × d, *J* 5 Hz, 3-, 4-, 4′-, and 5′-H (specific signals not assigned)], 11.10br (1 H, s, indole NH), and 12.80br (1 H, s, N*H*Ac).

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* Systematic numbering scheme.

† Structure factors are available as Supplementary Publication No. SUP 23259 (9 pp.). For details, see Notice to Authors No. 7 in *J. Chem. Soc., Perkin Trans. 1*, Index issue, 1981.

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