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^{1}H- AND ^{13}C-NMR SPECTRAL STUDIES OF SOME 2,4-DIMETHOXYQUINOLINES. INCONSISTENCIES WITH MONTRUTANINE, AN ALKALOID FROM *RUTA MONTANA*

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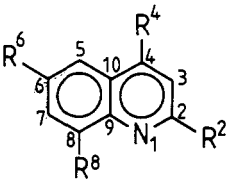
ABSTRACT.—Unambiguous ^{1}H- and ^{13}C-nmr spectral assignments are reported for 2,4-dimethoxyquinoline [**1**], verified by a parallel study of the 6-methyl derivative. From the results it would appear that the structure of the alkaloid montrutanine is unlikely to be **1**. Some comments regarding possible alternative structures are given.

Ulubelen (1) has recently reported the isolation of a new alkaloid, montanine, subsequently renamed (2) montrutanine, from *Ruta montana* L. (Rutaceae). Its structure was proposed as 2,4-dimethoxyquinoline [**1**] by ^{1}H- and ^{13}C-nmr spectroscopy and by comparison with an authentic sample obtained from 2,4-dihydroxyquinoline (4-hydroxy-2-quinolone) [**8**].



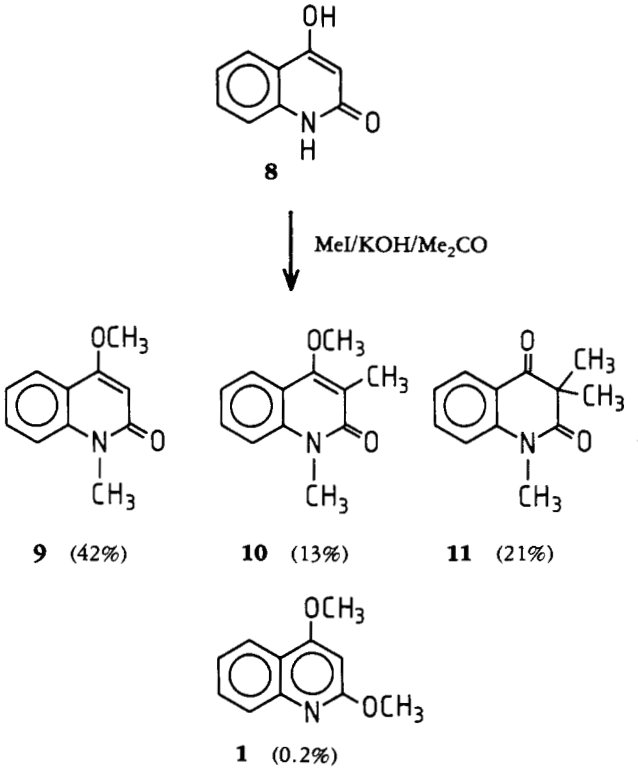
1 $R^2=R^4=OMe$, $R^6=R^8=H$
2 $R^2=R^4=OMe$, $R^6=Me$, $R^8=H$
3 $R^2=R^4=Cl$, $R^6=R^8=H$
4 $R^2=R^4=Cl$, $R^6=Me$, $R^8=H$
5 $R^2=R^4=R^6=R^8=OMe$
6 $R^2=R^4=OEt$, $R^6=R^8=H$
7 $R^2=OMe$, $R^4=R^6=R^8=H$

In continuation of our nmr spectral studies of 2,4-disubstituted quinolines (3,4), we now report that the spectral data of synthetic **1** prepared from 2,4-dichloroquinoline [**3**] are considerably different from those of the isolated alkaloid; these data suggest that the structure of montrutanine is unlikely to be 2,4-dimethoxyquinoline.

Previously Ulubelen (1) obtained a sample of synthetic **1** by methylation of **8**. However, a thorough study made by Reische and Mester (5) indicated that this simple reaction is actually a complex process leading to four products (Scheme 1), with **1** being classified only as a by-product.

It should perhaps be noted that the major methylation product **9** has the same molecular formula, $C_{11}H_{11}NO_2$, as montrutanine.

Accordingly, a doubt is cast about the authenticity of the synthetic sample of **1** obtained by Ulubelen (1); this sample, incidentally, was not examined by nmr spectroscopy. In the present work, compounds **1** and **2** were instead synthesized from **3** and **4**, respectively, with NaOMe and MeOH solution (6). The required dichloroquinolines were obtained from the appropriate aniline, malonic acid, and $POCl_3$ by the general procedure of Ziegler and Gelfert (7). This preferred alternative pathway has also been

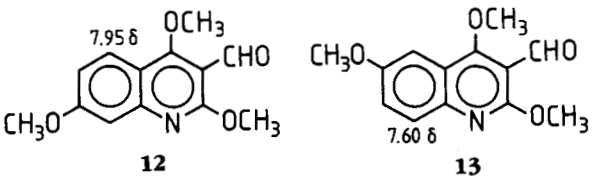


SCHEME 1. Methylation of 4-hydroxy-2-quinolone (isolated yields in parentheses) as presented by Reische and Mester (5).

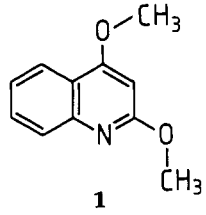
employed (8) for the synthesis of the quinolone alkaloid, halfordamine, by demethylation of the tetramethoxyquinoline **5**.

Apart from the work of Ulubelen (1), as far as the present authors are aware there are no specific chemical shift assignments for **1** yet available. Accordingly, the precise magnitude of the appropriate peri-deshielding effects of the nitrogen lone electron pair and of the 4-MeO group remain unquantified. Narasimhan and Mali (9) have studied some isomeric quinoline 3-carboxaldehydes **12** and **13** from which it may be anticipated that H-5 should resonate downfield of H-8 in **1**. In these formyl compounds assignment of the AMX patterns is unambiguous, and the substituent effects at the respective meta positions considered are minimal.

The 270 MHz ^{1}H nmr of **1** in $CDCl_3$ comprised a well separated 4H ABCD system, a 1H singlet for H-3, and two 3H methoxy singlets. The two lowest field aromatic signals were each gross doublets, indicating one ortho neighbor only; hence these may be assigned to H-5/H-8. At higher precision (digital resolution = 0.04 Hz) these signals were each ddd with the upfield signal (δ 7.780) more clearly defined, which suggested



that this may be ascribed as H-8 in accordance with the work of Attimonelli and Sciacovelli (10) which indicated that ${}^{6}J_{3,8} < {}^{5}J_{3,5}$. The initial assignments were thus in accordance with the earlier predictions made from the 3-formyl derivatives. A spin decoupling experiment at H-5 then located H-6 (collapse of ortho coupling) and H-7 (collapse of meta coupling). An nOe difference spectrum (11) was then examined. Irradiation of the OMe signal of **1** at δ 3.984 gave a strong enhancement at H-3 but only a weak enhancement at H-5 at δ 8.045. A similar result was obtained when the 4-OCH_2 signal of **6** was irradiated. In contrast, irradiation of the OMe signal of **1** at δ 4.056 produced a minimal enhancement at H-3 only. These results supported the location of H-5, provided initial assignments for the MeO signals, and suggested that the preferred conformation of the molecule is likely to be as shown in Figure 1.



1

FIGURE 1. Suggested preferred conformation of **1**.

The initial aromatic assignments were then verified by a study of **2**, for which the AMX pattern analysis is unambiguous. For this compound the signals for H-5 and H-8 were much closer together ($\Delta = 0.146$ ppm), since H-5 was now subject to an upfield Me substituent effect while H-8 was little affected. Had the original assignments for H-5 and H-8 in **1** been in the reverse order, then a wider chemical shift separation in **2** should have resulted. The ^{1}H-nmr spectral assignments were subsequently confirmed by 2D HETCOR and COLOC experiments (12).

A comparison of the ^{1}H-nmr spectral results for synthetic **1** and those reported for montrutanine (1) is shown in Table 1; there is a considerable discrepancy, particularly in relation to the order and position of the aromatic signals.

TABLE 1. ^{1}H-nmr Spectral Parameters for **1** and Montrutanine ($CDCl_3$, δ values, coupling constants in Hz).[a]

Synthetic **1**				Montrutanine[b]			
3.984	s		(4-OMe)	3.70	s		(OMe)
4.056	s		(2-OMe)	3.95	s		(OMe)
6.218	s		(H-3)	6.05	s		(H-3)
7.327	ddd	$J_{5,6}$ 8.2 $J_{6,7}$ 6.9 $J_{6,8}$ 1.2	(H-6)	7.24	dt	J 8 J 2	(H-7)[c]
7.592	ddd	$J_{7,8}$ 8.4 $J_{6,7}$ 6.9 $J_{5,7}$ 1.6	(H-7)	7.35	br d	J 8	(H-8)
7.780	ddd	$J_{7,8}$ 8.4 $J_{6,8}$ 1.2 $J_{5,8}$ 0.6	(H-8)	7.59	dt	J 8 J 2	(H-6)[c]
8.045	br ddd	$J_{5,6}$ 8.2 $J_{5,7}$ 1.6	(H-5)	7.97	dd	J 8 J 2	(H-5)

[a]Assignments in parentheses.
[b]Data for this compound are from Ulubelen (1).
[c]Assignments interchangeable.

The ^{13}C-nmr spectrum of **1** has been previously reported by Reische and Mester (5). Since these workers only isolated a very low yield of **1** from the methylation of **8** (Scheme 1) they were apparently unable to detect the quaternary ipso-methoxy carbons C-2 and C-4. In the present work, initial spectral assignments for **1** were made by comparison with the estimated ^{13}C chemical shifts calculated by addition of the reported (13) substituent chemical shifts (S.C.S.) for a 4-MeO group to the reported (14) ^{13}C chemical shifts of **7** (Table 2). A fair correlation was obtained, which suggested that the earlier assignments (5) for C-5 to C-8 were in error. These initial spectral assignments were then substantiated by comparison of the experimental spectrum of **2** with that calculated by addition of 6-Me S.C.S. values (15) to the re-assigned **1**; an excellent correlation was found (Table 2, maximum error 0.40 ppm).

TABLE 2. Observed and Calculated ^{13}C Chemical Shifts (δ) for **1** and **2**.

Carbon	7	4-MeO S.C.S.	1 Calcd[a]	1 Found[b]	6-Me S.C.S.	2 Calcd[c]	2 Found
C-2	162.2	+1.3	163.5	163.77	−0.8	162.97	163.29
C-3	112.9	−20.9	92.0	90.62	0.0	90.62	90.58
C-4	138.4	+26.3	164.7	163.81	−0.7	163.11	163.48
C-5	129.2	−5.8	123.4	121.80	−1.2	120.60	120.97
C-6	123.8	−1.0	122.8	123.21	+9.8	133.01	132.86
C-7	127.2	+0.6	127.8	129.86	+2.3	132.16	131.79
C-8	127.0	−0.6	126.4	126.86	−0.3	126.56	126.61
C-9	146.3	+0.8	147.1	147.04	−1.4	145.64	145.24
C-10	124.9	−6.8	118.1	119.23	0.0	119.23	118.99
2-OMe	53.2		53.2	53.31		53.31	53.30
4-OMe		56.3	56.3	55.56		55.56	55.61
6-Me					21.5	21.5	21.40

[a]From **7** Schleinitz *et al.* (14) + S.C.S. 4-MeO, Zuika *et al.* (13).
[b]See also Table 4.
[c]**1** (this work) + S.C.S. 6-Me from Su *et al.* (15)

The ^{13}C-nmr assignments were further supported by a thorough examination of the proton-coupled spectra (Table 3). The quaternary C-6 carbon was readily identified in the spectrum of **2**, as was C-8 which appeared only as a simple doublet. The methine carbons, C-5 and C-7, could be specifically located by application of the rule (16) that $^3J_{CH}$ meta couplings that involve β carbons are generally stronger than those at α carbons; thus, the fine splittings at these carbons appeared as a quintet and doublet of quartets, respectively. The couplings at C-10 comprised a $J_{10,3}$ "cross" ring coupling via a substituted pathway and a typically smaller $J_{10,8}$ "through" ring interaction (17).

In the present work the signals for C-2 and C-4 were almost coincident in **1** but better separated in **2**; C-2 appeared as a quintet, while C-4 was a sextet. Each carbon exhibited a typical ^3J splitting (18) to the MeO protons (J = 3.6/3.7 Hz). Although a $^2J_{4,3}$ interaction has not been observed in the parent quinoline (19), such an enhanced coupling is characteristic for an ipso-carbon in a meta-dioxygen substituted system (18); the observed value of $J_{2,3}$ is also consistent with this substitution pattern. The additional $J_{4,5}$ coupling at C-4 gave the sextet splitting. The coupled spectrum of **1** was generally similar, with C-5 to C-8 each doublets of doublets with $J_{6,8}$ and $J_{7,5}$ (β carbon splittings) > $J_{5,7}$ and $J_{8,6}$ (α-carbon splittings) (16) and an additional $J_{10,6}$ "cross" ring coupling through an unsubstituted pathway (17).

Inspection of Table 4 indicates that the ^{13}C chemical shifts for the sample of **1** isolated by Reische and Mester (5) as a by-product from the methylation of **8** and those found for synthetic **1** obtained from **3** in the present work are consistent. However,

TABLE 3. ^{13}C-^{1}H Coupling Constants (Hz) for **1** and **2**.

				Short range		
	$J_{3,3}$	$J_{5,5}$	$J_{6,6}$	$J_{7,7}$	$J_{8,8}$	J_{OMe}[a]
1	163.6	162.4	161.2	162.4	162.3	145.3
2	163.6	159.9	—	158.7	162.3	145.3
				Long range		
	$J_{2,3}$	$J_{2,OMe}$	$J_{4,3}$	$J_{4,5}$	$J_{4,OMe}$	$J_{5,7}$
1	3.7	3.7	3.7	3.7	3.7	7.3
2	3.6	3.6	3.6	3.6	3.6	6.1
	$J_{6,8}$	$J_{7,5}$	$J_{8,6}$	$J_{9,5}$	$J_{9,7}$	$J_{10,3}$
1	8.6	8.5	7.3	7.3	7.3	4.9
2	6.1[b]	7.3	—	7.3	7.3	4.9
	$J_{10,6}$	$J_{10,8}$	$J_{5,Me}$	$J_{6,Me}$	$J_{7,Me}$	
1	8.5	4.9	—	—	—	
2	—	4.9	6.1	6.1	4.9	

[a]$J_{2\text{-OMe}}$ and $J_{4\text{-OMe}}$ were both 145.3 Hz.
[b]Coupling possibly unreliable due to overlap.

there is a considerable discrepancy between these results and the chemical shifts reported by Ulubelen (1) for montrutanine.

A 2D HETCOR spectrum (12) of **1** was also determined; it included the expected connectivities between δ 8.045 (H-5) and δ 121.80 (C-5) and between δ 7.780 (H-8) and δ 126.86 (C-8). Connectivities were also obtained between δ 53.31 and δ 4.056 and between δ 55.56 and δ 3.984, which verified the MeO signal allocations made following the nOe difference experiments. A 2D COLOC spectrum was finally measured to provide definitive assignments for the very closely separated C-2 and C-4 ipso-methoxy carbons. This was achieved through the appropriate $^{3}J_{C,OMe}$ interactions. The spectrum required zerofilling to provide adequate separation in the ^{13}C dimension.

The question then remains as to the correct structure of the alkaloid montrutanine. From the spectral evidence originally provided (1), the compound appeared to be consistent with a dimethoxyquinoline with an unsubstituted carbocyclic ring. Accord-

TABLE 4. A Comparison of ^{13}C Chemical Shifts for Synthetic **1** and Montrutanine ($CDCl_3$, δ values).

1[a]	**1**, this work	Montrutanine[b]
53.18 (2-OMe)	53.31 (2-OMe)	55.0 (4-OMe)
55.46 (4-OMe)	55.56 (4-OMe)	55.3 (2-OMe)
90.52 (C-3)	90.62 (C-3)	105.0 (C-3)
119.18 (C-10)	119.23 (C-10)	125.6 (C-6)
121.71 (C-6)	121.80 (C-5)[c]	126.9 (C-5)
123.11 (C-7)	123.21 (C-6)[c]	127.2 (C-10)
126.81 (C-5)	126.86 (C-8)[c]	129.6 (C-7)
129.77 (C-8)	129.86 (C-7)[c]	129.6 (C-8)
147.03 (C-9)	147.04 (C-9)	143.8 (C-9)
	163.77 (C-2)	157.3 (C-4)
	163.81 (C-4)	165.3 (C-2)

[a]Data are from Reische and Mester (5).
[b]Data are from Ulubelen (1).
[c]Assignments revised as indicated.

ingly, estimated ^{13}C chemical shifts, calculated from the parent heterocycles by addition of appropriate positional MeO S.C.S. values for pyridine (20,21), have been obtained for the residual heterocyclic methine carbons in all of the possible dimethoxyquinoline and isoquinoline isomers; the results are shown in Table 5. Although these estimations are not expected to be completely accurate (compare C-3 of **1** with result in Table 2), it appears that none of the ^{13}C chemical shifts for these compounds corresponds with the δ 105 resonance reported for montrutanine (1). Since natural montrutanine was reported to be identical with a synthetic product obtained by Ulubelen (1) by methylation of **8** (Scheme 1), the alkaloid could be one of the other methylation products. At present we can only conclude that montrutanine is not 2,4-dimethoxyquinoline [**1**].

TABLE 5. Estimated ^{13}C Chemical Shifts (δ) for Heterocyclic Methine Carbons in Some Dimethoxyquinolines.

Compound[a]	Residual heterocyclic methine	Estimated ^{13}C chemical shift[b]
2,3-DMQ	C-4	123.1
2,4-DMQ [**1**]	C-3	88.9[d]
3,4-DMQ	C-2	139.5
1,3-DMIQ	C-4	95.2
1,4-DMIQ	C-3	128.3[d]
3,4-DMIQ	C-1	141.9

[a]DMQ = dimethoxyquinoline, DMIQ = dimethoxyisoquinoline.

[b]For examples of calculations see footnotes c and d, Py = pyridine.

[c]From quinoline Su *et al.* (15), + S.C.S. 2-MeO (ex 2-MeOPy) Denisov *et al.* (20), + S.C.S. 4-MeO (ex 4-MeOPy) Denisov *et al.* (21).

[d]From isoquinoline Su *et al.* (15), + S.C.S. 1-MeO (ex 2-MeOPy; 1-MeO = C-2, 4-MeO = C-5) Denisov *et al.* (20), + S.C.S. 4-MeO (ex 3-MeOPy; 1-MeO = C-6, 4-MeO = C-3) Denisov *et al.* (20).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—^1H- and ^{13}C-nmr spectra were measured at 270.17 and 67.94 MHz, respectively, on a Jeol EX270 FT spectrometer. The 2D COSY and COLOC spectra were measured at the University of Warwick on a Bruker WH400 instrument, courtesy of the S.E.R.C.-supported service.

2,4-DICHLOROQUINOLINE [**3**].—A mixture of aniline (4.65 g), malonic acid (4.0 g), and $POCl_3$ (30 ml) was boiled under gentle reflux for 3 h, cooled, poured into H_2O (500 ml), and allowed to stand overnight. After neutralization with NaOH and filtration there was obtained 6.3 g (63%) of **3**, mp 65–66° (EtOH/H_2O) [lit. (22) 66–67°].

2,4-DICHLORO-6-METHYLQUINOLINE [**4**].—From *p*-toluidine (5.35 g), using the same method, there was obtained 8.9 g (84%) of **4**, mp 93–94° (EtOH/H_2O) [lit. (22) 94–95°].

2,4-DIMETHOXYQUINOLINE [**1**].—A mixture of **3** (5.0 g) and NaOMe solution (from 4 g Na and 60 ml MeOH) was boiled under reflux for 25 h, cooled, poured into H_2O (200 ml), and allowed to stand overnight. After filtration there was obtained 3.4 g (71%) of **1**, mp 81–82° (MeOH/H_2O) [lit. (6) 81–82°].

2,4-DIMETHOXY-6-METHYLQUINOLINE [**2**].—From **4** (5.35 g), using the same method, there was obtained 2.3 g (45%) of **2** as colorless needles: mp 55–56° (MeOH/H_2O); found C 70.80, H 6.45, N 6.89; calcd for $C_{12}H_{13}NO_2$, C 70.92, H 6.23, N 7.00%; ^1H nmr ($CDCl_3$) 2.475 (3H, s, 6-Me), 3.976 (3H, s, 4-OMe), 4.041 (3H, s, 2-OMe), 6.197 (1H, s, H-3), 7.426 (1H, dd, $J_{7,8}$ = 8.5 Hz, $J_{5,7}$ = 2.0 Hz, H-7), 7.670 (1H, d, $J_{7,8}$ = 8.5 Hz, H-8), 7.825 (1H, br, H-5). Irradiation of 6-Me collapsed δ 7.825 to clear fine d ($J_{5,7}$ = 2.0 Hz).

2,4-DIETHOXYQUINOLINE [**6**].—Compound **6** was prepared from **3** and NaOEt by the procedure of Buchmann and Hamilton (23): mp 55–56° (EtOH/H_2O) [lit. (23) 56°].

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