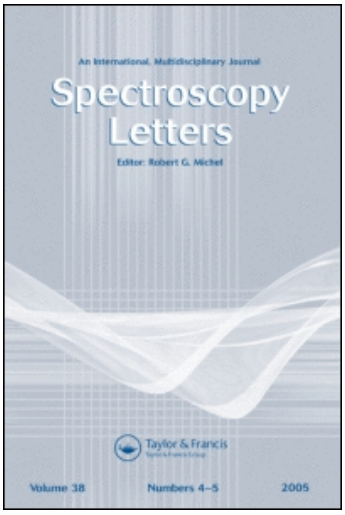

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Carbon-13 Nuclear Magnetic Resonance Spectrum of Colchicine

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CARBON-13 NUCLEAR MAGNETIC RESONANCE SPECTRUM OF COLCHICINE

KEY WORDS: Carbon-13 NMR, single frequency off-resonance decoupled (SFORD), chemical shift, assignments, tropolone, tropolone methyl ether and colchicine.

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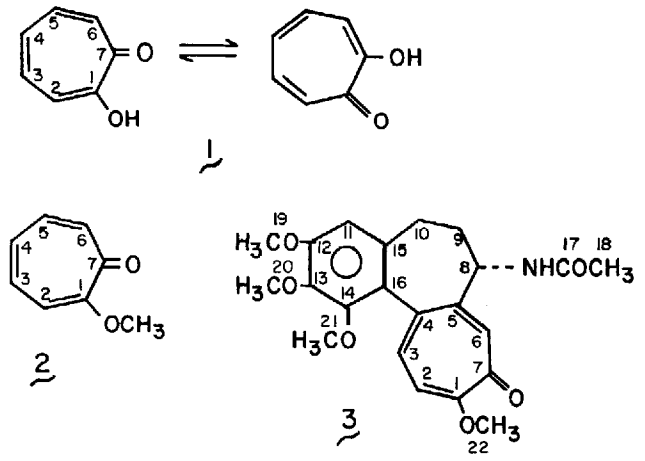
ABSTRACT: ^{13}C NMR chemical shifts of tropolone, tropolone methyl ether and colchicine are reported. The various carbon resonances have been assigned on the basis of substituent effects on benzene shifts, intensities, multiplicities generated in SFORD spectra and the comparison with structurally related compounds like tropolone and tropolone methyl ether.

INTRODUCTION

Colchicine 3 is an alkaloid of Colchicum autumnale. Von Störck in 1763 introduced colchicura in the treatment of acute gout. Colchicine is a selective anti-inflammatory agent in the treatment of acute gouty arthritis. The structure and stereochemistry of colchicine are well characterized[1,2], but there are no reports in the

literature about the assignments of the carbon resonances of colchicine. As a part of our continuing efforts to assign the ^{13}C NMR spectra of therapeutic agents[3-5], both synthetic and natural, we now wish to report the complete assignments of the various carbon resonances of colchicine. In the present investigation we have also assigned ^{13}C NMR spectra of tropolone 1 and tropolone methyl ether 2 as model compounds in support of the assignments of ^{13}C NMR spectrum of colchicine.

The ^{13}C NMR spectra of 1, 2 and 3 were obtained in $CDCl_3$ as an internal lock and solvent and tetramethylsilane as a reference. In each case a proton noise decoupled and single frequency off-resonance decoupled (SFORD) spectra were recorded. The signals obtained from ^{13}C NMR spectra were assigned on the basis of ^{13}C NMR chemical shift theory, the multiplicities generated in the SFORD spectra, the intensities of the signals and the comparison with structurally related compounds.



Results and Discussion

Tropolone 1

The ^{13}C NMR chemical shifts of tropolone are recorded in Table 1 and illustrated in Figure I. As is evident from Figure I, there are four signals which account for all the seven carbon resonances of 1. The singlet which occur at the farthest downfield (171.8 ppm) is assigned to C-1 and C-7 on the basis of the chemical shift theory for the carbon of carbonyl group[6]. The signal exhibited by C-1 and C-7 are at the same place due to the keto-enol tautomerism. The three

Table I

Carbon-13 NMR Chemical Shifts of Tropolone[a]

Assignments[b]	Multiplicity[c]	Chemical Shift
C_1, C-7	s	171.8
C-3, C-5	d	137.5
C-4	d	128.2
C-2, C-6	d	123.9

[a]Chemical shifts are expressed in ppm relative to tetramethylsilane.

[b]Numbering of carbons is shown in the structure 1.

[c]Signal multiplicity obtained from SFORD; s = singlet, d = doublet.

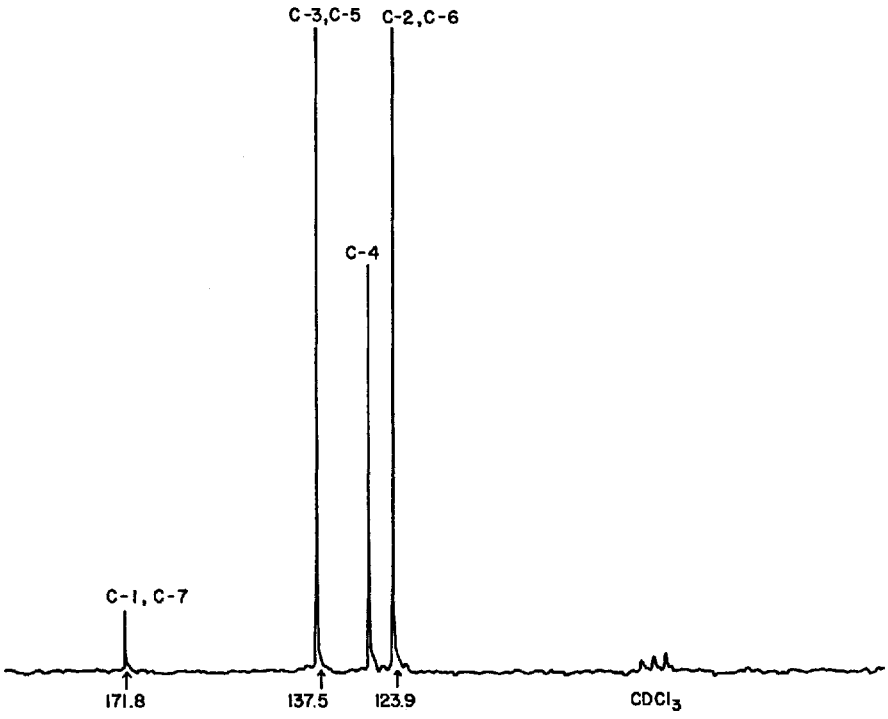


Figure 1. The proton noise decoupled ^{13}C NMR spectrum of tropolone.

doublets centered at 137.5, 128.2 and 123.9 ppm have been assigned to the carbon resonances of C-2, C-3, C-4, C-5 and C-6. Since a directly bonded-OH group to the benzene nucleus produces an upfield shift[6] in the order of ortho > para > meta > ipso, the signal at 137.5 ppm is assigned to C-3 and C-5, signal at 128.2 ppm to C-4 and signal at 123.9 to C-2 and C-6.

Tropolone methyl ether 2

The ^{13}C NMR chemical shifts of 2 obtained from its ^{13}C NMR spectrum (Figure 2) are recorded in Table 2. The six separate signals in

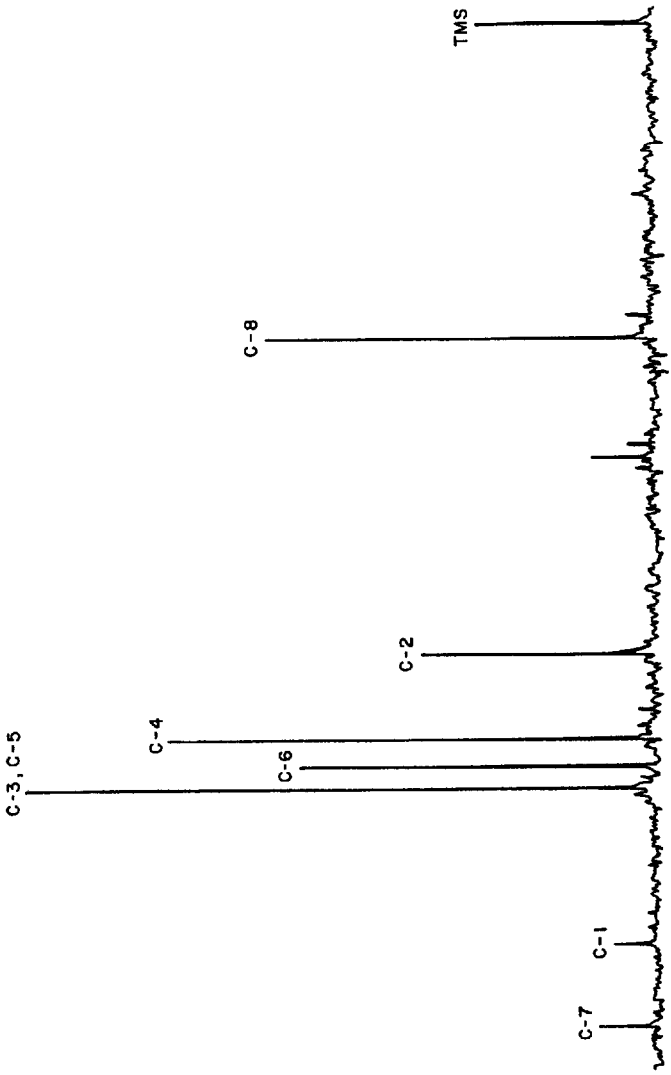


Figure 2. The proton noise decoupled ^{13}C NMR spectrum of tropolone methyl ether.

Table 2

Carbon-13 NMR Chemical Shifts of Tropolone Methyl Ether[a]

Assignments[b]	Multiplicity[c]	Chemical Shift
C-7	s	180.3
C-1	s	165.4
C-3, C-5	d	136.7
C-6	d	132.9
C-4	d	127.8
C-2	d	112.6
C-8	q	56.2

[a,c]See footnote in Table I.

[b]Numbering of carbons is shown in the structure 2.

the region of 112 to 181 ppm, relative to tetramethylsilane, represented the seven carbon resonances of tropolone ring. The signal at 56.2 ppm which is a quartet in SFORD spectrum is due to the C-8 carbon resonance of the methoxy group. The two singlets at 180.3 and 165.4 ppm are assigned to C-7 and C-1 on the basis of chemical shift theory[6]. By comparing the effect of the methoxy group on the tropolone ring with its influence on the benzene nucleus the doublets centered at

112.6, 127.8 and 132.9 ppm are assigned to C-2, C-4 and C-6, respectively. The signal at 136.7 ppm represents two near equivalent carbons at C-3 and C-5.

Colchicine 3

The chemical shifts of various carbon resonances of 3 are recorded in Table 3. The ^{13}C NMR spectrum of 3 is illustrated in Figure 3. There are fourteen separate signals at lower field which account for the aromatic carbons and the carbons of the carbonyl groups. The remaining eight carbon resonances are represented by seven signals which have been observed at higher fields (Table 3).

The two singlets farthest downfield, 179.6 and 170.3 ppm, are readily assigned to C-7 and C-17, respectively, by comparing the chemical shifts of the carbonyl carbons of 2 and 4[6]. The methoxy group attached to a benzene nucleus causes lower field shifts of 31.4 and 1.0 ppm at the ipso and meta carbons, respectively, relative to the benzene ^{13}C signal and upfield shifts of 14.4 and 7.7 ppm for the ortho and para carbons, respectively.[6] Since C-11 has ortho, meta and para methoxy groups, the doublet centered at 107.5 ppm may be best assigned to it. The other three doublets centered at 135.8, 130.5 and 113.2 ppm are attributed to the carbon resonances of C-3, C-6 and C-2, respectively, by comparing the chemical shifts of 2. The singlets at 164.1 and 137.2 ppm have been assigned to C-1 and C-5, respectively, by comparing the chemical shifts of corresponding carbons of 2. The chemical shift observed for C-5 is at slightly lowerfield compared to C-3 due to the β effect of nitrogen.[6] By considering the influence of the methoxy group on the chemical shifts of benzene[6], the singlets at 153.6, 152.9 and

Table 3

Carbon-13 NMR Chemical Shifts of Colchicine[a]

Assignments[b]	Multiplicity[c]	Chemical Shift
C-7	s	179.6
C-17	s	170.3
C-1	s	164.1
C-12	s	153.6
C-14	s	152.9
C-15	s	151.1
C-4	s	141.6
C-5	s	137.2
C-3	d	135.8
C-13	s	134.5
C-6	d	130.5
C-16	s	125.7
C-2	d	113.2
C-11	d	107.5
C-20	q	61.3
C-19, C-21	q	56.4
C-22	q	56.1
C-8	d	52.9
C-10	t	36.2
C-9	t	30.0
C-18	q	22.6

[a,c] See footnote in Table I.

[b] Numbering of carbons is shown in the structure 3.

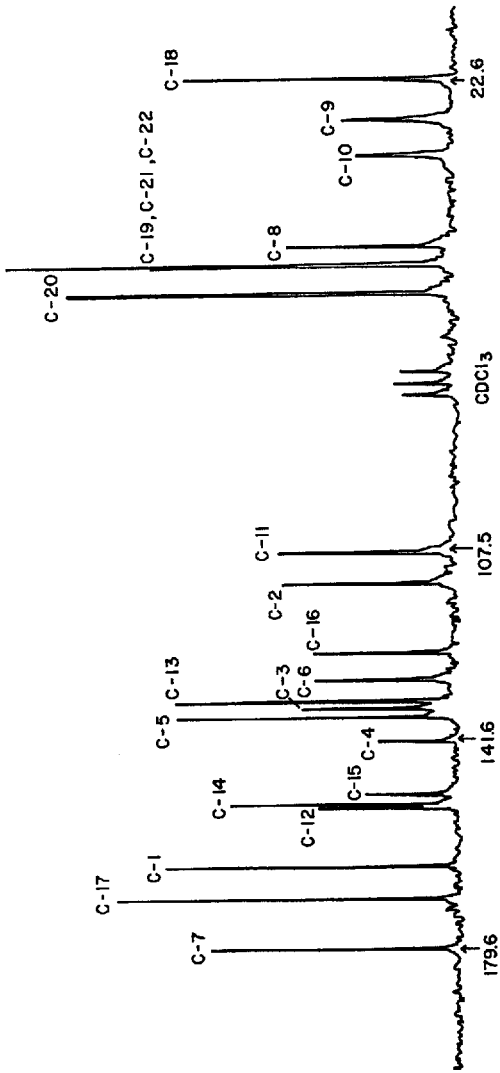
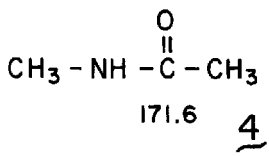


Figure 3. The proton noise decoupled ^{13}C NMR spectrum of colchicine.

134.5 ppm are best assigned to C-12, C-14 and C-13, respectively, though the assignments of C-12 and C-14 may be reversed.

The linkage between C-4 of tropolone ring and C-16 of benzene ring are analogous to that of the biphenyl. Considering the ortho, meta and para effects of methoxy groups on C-16 and comparing the chemical shifts of corresponding carbons of 4-iodo biphenyl 5[7], the singlets at 125.7 and 141.6 ppm are assigned to C-16 and C-4, respectively. The C-15 carbon is under influence of the methoxy groups as well as the α, β and γ carbons where α and β carbons produce a large downfield shift in comparison to γ carbon which induces a slight upfield shift. On this basis, the remaining singlet at 151.1 ppm is attributed to the carbon resonance of C-15.



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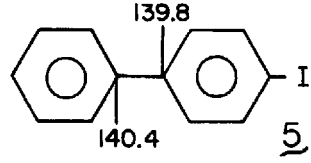

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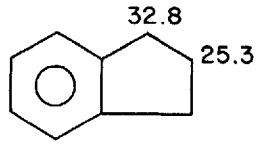
As is evident from Table 3, the four quartets in the ^{13}C NMR spectrum of 3 are due to the four methoxy groups and the C-18 methyl group. The quartet that is farthest upfield, 22.6 ppm, is assigned to C-18 and comparable with acetanilide.[7] The quartet at 56.1 ppm is assigned to C-22 by comparing with 2. The resonance of C-20 will be observed at lowerfield as compared to the C-19 and C-21 resonances.[6] Thus the quartet centered at 61.3 ppm is assigned to C-20 while C-19 and C-21 resonances are represented at 56.4 ppm. The C-8 is directly attached to nitrogen which produces a large downfield shift,[6] thus the doublet centered at 52.9 ppm is assigned to C-8. By comparing the

chemical shifts of indane 6,[7] the triplet centered at 36.2 and 30.0 ppm have been assigned to C-10 and C-9, respectively.



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Experimental

The ^{13}C NMR spectra of troplone, troplone methyl ether and colchicine were obtained on a JEOL FX 60 spectrometer operating at 15.03 KHz. The samples were run in 10 mm tubes using $CDCl_3$ (concentration 30% w/v) as solvent and internal lock and tetramethylsilane as reference. The spectrometer setting during experiment was as following: spectra width $4KH_Z$, pulse width 18 μ sec (90°), repetition rate 2.5 sec. and data points 4K.

Tropolone and colchicine were purchased from Aldrich chemical Co. Milwaukee, Wisconsin. The tropolone methyl ether was prepared in our laboratory[8] by mixing etherial solution of tropolone with freshly prepared diazomethane[9] in dry ether. Removal of ether under reduced pressure yielded 2. NMR (CCl_4) δ 6.5 to 7.3 (m, 5H, ring protons) and 3.8 (5, 3H, $O\underline{CH_3}$).

Acknowledgment

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