Synthesis and the Spectral Analysis of 4- and 6-[1-Acetamido-3-(3,4,5-trimethoxyphenyl)propyl]-2-methoxytropones (B-Ring-open Analogues of Colchicine)[1)]

Hiroshi YAMAMOTO,* Atsushi HARA, Saburo INOKAWA, and Tetsuo NOZOE†
Department of Chemistry, Faculty of Science, Okayama University, Tsushima, Okayama 700
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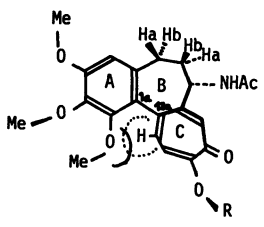
The treatment of 4-[1-acetamido-3-(3,4,5-trimethoxyphenyl)propyl]tropolone with ethereal diazomethane gave the 6- and 4-substituted title compounds in 51 and 38% yields, respectively. The 270-MHz ^{1}H-NMR spectral analysis performed on these compounds, colchicine, and two methyl ethers of hinokitiol permits unequivocal assignment of the position of the *C*-substituent on these 2-methoxytropone rings. Attempts were made to effect the direct B-ring closure of these intermediates and 4-[1-acetamido-3-(3,4,5-trimethoxyphenyl)propyl]-5-aminotropolone using various oxidizing reagents.

In our effort to explore a convenient and efficient route for the preparation of colchicine (**1**) and its analogues, and also as a part of our study of troponoid chemistry, we have previously reported[2,3)] a facile synthesis of 4-(1-acetamido-3-arypropyl)tropolones (*e.g.* **4**) from 4-acetyltropolone (**3**). We wish to describe herein the preparation of B-ring-open colchicine analogues and an effective use of ^{1}H-NMR spectroscopy in the structural assignment of the related 2-methoxytropone derivatives.

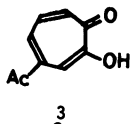
As a representative example of the derivatization to colchicine analogues, 4-[1-acetamido-3-(3,4,5-trimethoxyphenyl)propyl]tropolone (**4**) prepared[3)] from **3** in five steps with an overall yield of *ca.* 35—40% was treated with ethereal diazomethane at 0 °C to furnish colorless needles of **5** (mp 119—121 °C) and **6** (180—182 °C) after chromatographic separation. The high-resolution EI mass spectra of both compounds clearly gave the molecular ions at *m/e* 401 ($C_{22}H_{27}O_6N$) corresponding to the methyl ethers of **4**. The structural assignments of these two isomers were effectively made by the analysis of the 270 MHz ^{1}H-NMR spectral signals at δ 6.7—7.3 due to their tropolone ring moiety (see Fig. 1). Namely, the doublet at δ 6.70 in the spectrum of **5** was readily assigned to H-3 on the evidence of a long-range spin coupling (J=0.3 Hz) with the methoxyl group on C-2, as had been observed for methyl ether derivatives of salicylaldehyde[4)] and 5-aminotropolones.[5)] The other ring-proton signals were then automatically assignable by decoupling experiments, leading to structure **5**, 6-[1-acetamido-3-(3,4,5-trimethoxyphenyl)propyl]-2-methoxytropone (the colchicine molecule being cleaved at the C_{1a}–C_{12a} bond), for the product available from the faster-eluting fraction; see Table 1 for parameters of the NMR spectrum of **5**.

Similarly, the spectrum of the other product can be rationalized in terms of the isomeric structure, 4-substituted 2-methoxytropone (**6**) (an analogue of isocolchicine); the parameters of the spectrum and the assignments of the signals are also summarized in Table 1.

The remarkable difference in the splitting patterns of the H-3 signals between these two isomers **5** (doublet) and **6** (slightly broadened singlet) readily permits the assignment of the position of the *C*-substituent on the 2-methoxytropone nucleus. This evidence is of value for distinguishing between the 4- and 6-positional isomers of the methyl ethers derived from many kinds of naturally occurring 4-substituted troponoids,[6,7)] such as colchiceine (**2**), hinokitiol (**7**), and β-dolabrin (**8**). The two methyl ethers **9** and **10**, which had been reported as an inseparable mixture upon treatment of **7** with diazomethane,[8,9)] have now been separated into pure components by silica-gel column chromatography. Their structures can easily be established by their ^{1}H-NMR spectral analysis even at 60 MHz; see the assignments for each compound recorded in Table 1.[10)] The distinction between these two isomers **9** and **10** had



1 R = Me
2 R = H



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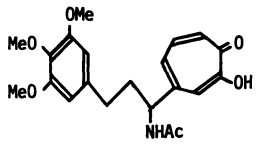

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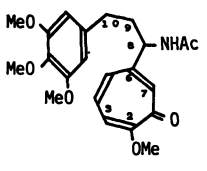

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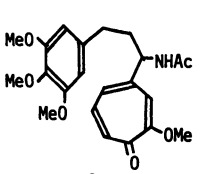

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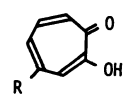
† 811, 2-5-1, Kamiyoga, Setagaya-ku, Tokyo 158.

Table 1. ^{1}H-NMR (270 MHz) Parameters for colchicine and its analogues in $CDCl_3$

Compound	Chemical shifts, δ									
	MeO-2	H-3	H-4	H-5	H-6	H-7	H-8 NH-8 AcN-8	H_a-9 H_b-9	H_a-10 H_b-10	MeO-4′ MeO-3′,5′ H-2′,6′
1[a]	4.02	6.92	7.38	—	—	7.65	4.62 8.38 1.97	2.00[b] 2.36[b]	2.40[b] 2.53[b]	3.91 3.67, 3.95 6.55
2[c]	6.7[d]	7.30	7.69	—	—	7.58	4.72 4.7 1.99	2.0 2.2	2.40 2.48	3.93 3.65, 3.93 6.57
4[c]	6.4[d]	7.3	7.3	7.1	—	7.3	4.90 4.3 1.97	2.0 2.0	2.5 2.5	3.82 3.83, 3.83 6.36
5	3.92	6.70	7.07	6.88	—	7.27	4.80 6.79 1.99	2.02 2.02	2.61 2.68	3.82 3.83, 3.83 6.37
6	3.89	6.73	—	6.88	7.19	7.12	4.86 6.49 2.03	2.07 2.11	2.60 2.65	3.82 3.83, 3.83 6.36
9[c]	3.93	6.65	7.0[e]	6.9[e]	—	7.20	2.80	1.21[f]		
10[c]	3.98	6.70	—	6.82	7.2[e]	7.1[e]	2.86	1.27[f]		
11[c]	7.1	7.33	8.10	2.45[g] 7.35[h] 7.72[h]	—	7.51	6.15 6.60	2.1 2.1	2.5 2.6	3.80 3.75, 3.75 6.30
12	7.15	7.1	7.35	5.2[i]	—	7.43	5.1 5.2 2.02	2.1	2.6	3.83 3.83, 3.83 6.40

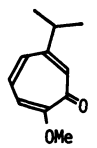
	Coupling constants/Hz[j]												
	$J_{3,4}$	$J_{3,5}$	$J_{3,OMe}$	$J_{4,5}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$	$J_{8,9a}$	$J_{8,9b}$	$J_{8,NH}$	$J_{9,9}$	$J_{9,10}$	$J_{10,10}$
1	10.8	—	0.3	—	—	—	—	11.2	5.2	6.2	15	[b]	15
2	11.0	—	—	—	—	—	—						
4			—		—		—	7.0	7.0	7.0			
5	10.0	0.5	0.3	10.7	—	1.3	—	7.0	7.0	7.0	—	7.5[k]	14
6	—	0.5	0.3	—	8.2	1.2	12.2	7.0	6.5	8.5	14	7.5[k]	14
9	8.0	1.5	0.5[e]	10[e]	—	1.3	—	7.0[l]					
10	—	0.5[e]	0.5[e]	—	8[e]	1[e]	12[e]	7.0[l]					
11	12.0	—	—	—	—	—	—	7.0	7.0	7.0			

a) The numbering of compounds **1**, **2**, **4**, **11**, and **12** corresponds to that of **5** for the purpose of comparison. b) The AMNX spin system was used for the calculation of the approximate J values (*cf.* Ref. 10): $J_{9a,10a}$ 11, $J_{9a,10b}$ 0, $J_{9b,10a}$ 4, and $J_{9b,10b}$ 6 2 Hz. c) Measured at 60 MHz. d) HO-2. e) Approximate value. f) $2H_3$-9. g) p-$C\underline{H}_3C_6H_4N_2$-5. h) $MeC_6\underline{H}_4N_2$-5 (both 2H, d, J=7.5 Hz). i) NH_2-5. j) J Values confirmed by double resonance. k) All $J_{9,10}$ values are almost identical. l) $J_{8,9}$



7 R = $CHMe_2$

8 R = $C(=CH_2)Me$



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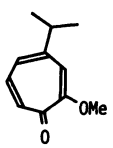

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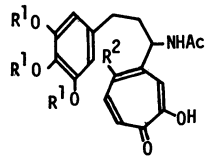

11 R^1 = Me R^2 = $N_2C_6H_4Me(p)$

12 R^1 = Me R^2 = NH_2

13 R^1 = Me R^2 = N_2^+

14 R^1 = H R^2 = H

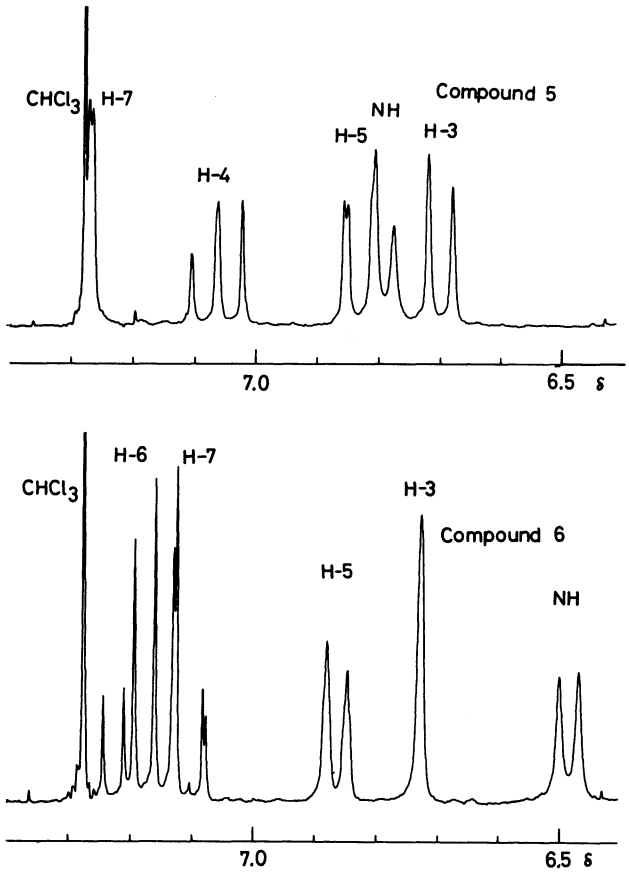

Fig. 1. Aromatic regions of the ^{1}H-NMR (270 MHz) spectra of **5** and **6**.

previously been made either by chemical conversion to the known tropolone derivatives[11] or by examining the out-of-plane bending bands in their IR spectra.[12] Although the latter method is useful for relatively simple tropolone derivatives, the distinction by the NMR spectroscopy is obviously more reliable and has a wider applicability.

The ^{1}H-NMR spectrum of colchicine (**1**) taken at 270 MHz is in accord with the characteristic features discussed above. The assignment of all signals, which can reasonably be made by considering (with the aid of the CPK and Dreiding models) the dihedral angles between the A and C rings, are recorded in Table 1. It is noted that, when **1** is hydrolyzed to colchiceine (**2**) either with hot, dilute hydrochloric acid[13] or with cold alkali, an appreciable downfield shift (0.3—0.4 ppm) of the H-3 and H-4 signals occurs. A similar shift can be seen, when the H-3 and -4 signals of the analogue **5** are compared with those of **4** (see Table 1).[14]

Various attempts were made to effect the B-ring-closure of compounds **4** and **5** to provide **2** and **1**, respectively, using the following oxidizing reagents which have been effective for the oxidative coupling of phenols:[15] i) diphenyl selenoxide,[16] ii) thallium(III) tris(trifluoroacetate),[17] and iii) manganese(III) acetylacetonate.[18] However, these procedures were found to be unsuccessful and the starting materials remained unchanged in most cases. Alternatively, in order to utilize the Pschorr reaction for the ring-closure,[19] the amino compound **12**, obtained from **4** *via* 5-*p*-tolylazo compound (**11**),[20] was first diazotized to the 5-diazonium salt (**13**) and subjected to various conditions of the Pschorr reaction,[21] but no appreciable amount of anticipated colchiceine (**2**) was detected among the reaction products. Attempts at partial or total demethylation of the methoxyl groups on the phenyl ring in **4** (to lead to *e.g.* compound **14**) using trimethylsilyl iodide[22] or conc hydrobromic acid resulted in extensive decomposition.

These findings are believed to be of value, not only from the viewpoint of modifications of the ring-closure for an efficient synthesis of various kinds of colchicine analogues having a potential biological activity, but also from that of the development of the fundamental chemistry of troponoids.[23]

Experimental

Melting points were measured with a Yanagimoto MP-3 instrument and are uncorrected. The ^{1}H-NMR spectra were recorded in $CDCl_3$ with a Hitachi R-20A (60 MHz) [or Brucker WH-270 cryospectrometer (270 MHz) for compounds **1**, **5**, and **6**]. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. Spin decoupling was performed for all proton signals to confirm the coupling constants. Mass spectra were measured with a Hitachi M-80 high-resolution instrument and are given in terms of *m/e* (relative intensity) compared with the base peak and possible assignments. IR And UV spectra were obtained on Hitachi 215 and 340 spectrometers, respectively. All reactions were monitored by TLC [conducted on plates precoated with silica gel (0.25 mm, Merck)]. Column chromatography was performed using Merck Lobar silica gel.

6-[1-Acetamido-3-(3,4,5-trimethoxyphenyl)propyl]-2-methoxytropone (5) and Its 4-Propyl Isomer (6). A solution of 257 mg of the tropolone[3] **4** in 20 ml of dry dichloromethane was treated with an excess amount of *ca.* 0.5 M (1 M=1 mol dm^{-3}) ethereal diazomethane at 0 °C for 1 h. The solvent was evaporated *in vacuo*, and the residue chromatographed on a column of silica gel with CCl_4 (which was gradually changed to $CHCl_3$) as eluent, giving **5** (136 mg, 51%) and **6** (100 mg, 38%).

5: Colorless needles, mp 119—121 °C (from CH_2Cl_2–EtOAc); R_f 0.60 (10% MeOH/$CHCl_3$, v/v); ^{1}H-NMR, see Table 1; IR (KBr) 3280, 2910, 1660, 1590, 1450, 1220, 1120, 1000, 790, and 780 cm^{-1}; EI MS *m/e* (rel intensity) 401 (29; M$^+$), 342 (35; M−$AcNH_2$), 220 (28; M−Ar*CH_2), 207 (100; M−Ar*CH=CH_2), 195 (48; Ar*CH=CH_2), 182 (43; Ar*CH_2), 181 (25), and 164 (44; M−Ar*CH=CH_2−Ac); exact mass, calcd for $C_{22}H_{27}O_6N$ 401.1837, found 401.1855.

6: Colorless needles, mp 180—182 °C (from EtOAc–hexane); R_f 0.55 (10% MeOH/$CHCl_3$); ^{1}H-NMR, see Table 1; IR (KBr) 3250, 2900, 1655, 1590—1500, 1440, 1270, 1250, 1225, 1200, 1120, 1020, 960, 820, 790, and 770 cm^{-1}; EI MS *m/e* (rel intensity) 401 (76; M$^+$), 342(18), 220(85), 207(58), 195(89), 182(51), 181(100), and 164(45); exact mass, Calcd for $C_{22}H_{27}O_6N$ 401.1837, Found 401.1841.

6- and 4-Isopropyl-2-methoxytropone (9 and 10). Hinokitiol (**7**; 200 mg) was similarly treated with cold ethereal diazomethane, and the crude products chromatographed on a column of silica gel, using benzene–ethyl acetate as eluent, thus giving **9** (47% yield) and **10** (31% yield).

Ar*: 3,4,5-Trimethoxyphenyl.

9 and **10**: Both colorless oil (*cf.* Ref. 11, oil): R_f 0.45 and 0.50, respectively, (3% EtOH–EtOAc, v/v); ^{1}H-NMR, see Table 1.

Colchiceine (2). A mixture of 49 mg of **1**, 0.5 ml of ethanol, and 0.5 ml of 1 M KOH was stirred at 20 °C for 17 h. The ethanol was removed *in vacuo*, and the residue brought to pH 4, extracted with CH_2Cl_2, dried (Na_2SO_4), and evaporated, thus giving, after recrystallization from ethyl acetate, 37 mg (78%) of **2**, mp 177—178 °C (Ref. 13, 178—179 °C).

4-[1-Acetamido-3-(3,4,5-trimethoxyphenyl)propyl]-5-(p-tolylazo)-tropolone (11). A cold solution of *p*-toluenediazonium chloride prepared from 12 mg of *p*-toluidine and 8 mg of sodium nitrite by the usual method was added to a solution of 40 mg of **4** in 0.15 ml of dry pyridine at 0 °C. After having been stirred for 3 h, the mixture was diluted with cold water (1 ml), and the precipitates were filtered off and washed with benzene, thus affording 40 mg (88% yield) of **11** as reddish orange crystals: mp 127—128 °C; ^{1}H-NMR, see Table 1; λ_{max} (MeOH) 230, 285, 430 nm (log ε 4.48, 4.06, 4.43); Found: C, 63.85; H, 6.36; N, 7.80%. Calcd for $C_{28}H_{31}O_6N_3 \cdot H_2O$: C, 64.23; H, 6.35; N, 8.03%.

4-[1-Acetamido-3-(3, 4, 5-trimethoxyphenyl)propyl]-5-aminotropolone (12). A suspension of 37 mg of **11** in 1 ml of methanol was hydrogenated over 1 mg of 10% Pd/C at 27 °C under atmospheric pressure until two equivalents of hydrogen was absorbed (20 min). The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give 28 mg (95% yield) of **12** as yellow needles: mp 122—123 °C (from EtOAc); ^{1}H-NMR, see Table 1; λ_{max} (MeOH) 232, 360, 400 nm (log ε 4.42, 4.06, 3.96); Found: C, 62.67; H, 6.76; N, 7.21%. Calcd for $C_{21}H_{26}O_6N_2$: C, 62.67; H, 6.51; N, 6.96%.

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