A Facile Synthesis of Colchiceine Analogues [4-(1-Acetamido-3-arylpropyl)tropolones][1,2]

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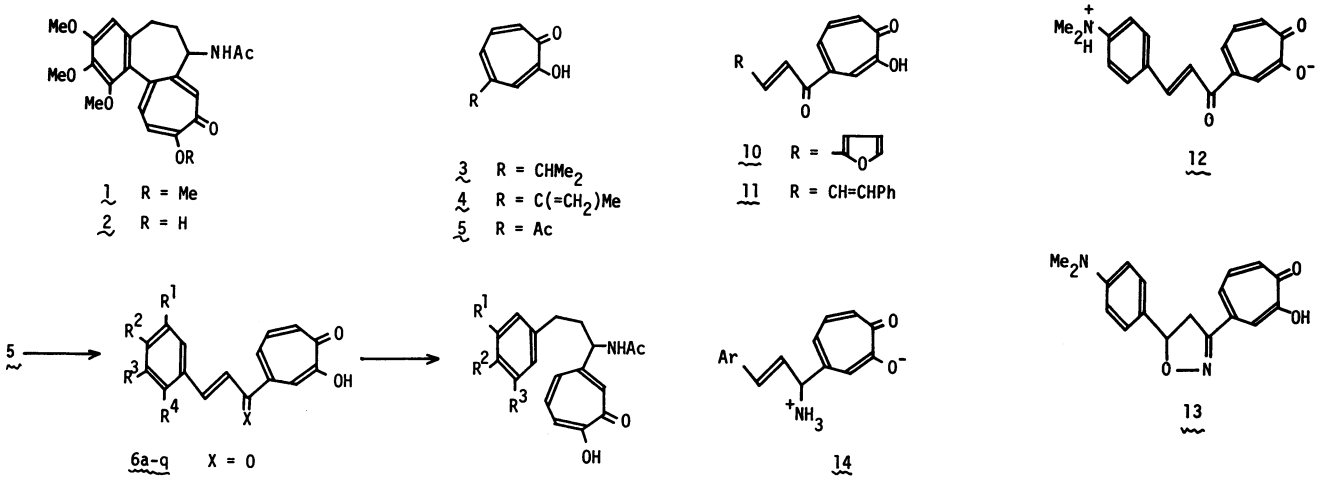
The condensation of 4-acetyltropolone with various arenecarbaldehydes gave a wide variety of 4-cinnamoyltropolone derivatives in good yield. The same reaction with 2-furaldehyde and cinnamaldehyde also afforded the corresponding 4-substituted tropolones. These products were converted to their oximes (with hydroxylamine hydrochloride), which in turn were hydrogenated over 5% Pd/C in acetic acid and then acetylated with acetic anhydride, to yield 4-(1-acetamido-3-aryl-2-propenyl)tropolones. The catalytic hydrogenation of these olefinic products over 10—30% Pd/C in aqueous KOH gave various 4-(1-acetamido-3-arylpropyl)tropolones, which possess a B-ring-open structure of colchiceine. The structures of these products are discussed on the basis of UV, IR, and ^{1}H-NMR spectra.



6 - 9, 15	R^1	R^2	R^3	R^4
a	OMe	OMe	OMe	H
b	OMe	OMe	H	H
c	O—CH_2—O		H	H
d	H	H	H	H
e	H	Me	H	H
f	OMe	OCH_2Ph	H	H
g	OCH_2Ph	OMe	H	H
h	H	Cl	H	H
i	H	Cl	H	Cl
j	H	OMe	H	H
k	H	Br	H	H
l	NO_2	OMe	H	H
m	NO_2	H	H	H
n	H	NO_2	H	H
o	OH	OMe	H	H
p	H	H	H	OH
q	H	NMe_2	H	H

Colchicine (**1**), one of the major alkaloid constituents of the autumn crocus (*Colchicum automnale L.*), is well known to block cell division during mitosis, and has been valued for its use in the treatment of gout.[3] This compound has also drawn the attention of synthetic organic chemists for almost three decades, and the total synthesis has been accomplished by several groups.[4] These synthetic routes, however, are apparently unsuitable not only for the practical synthesis of colchicine but also for the preparation of various kinds of colchicine analogues having potential utility of their biological activity.

A considerable interest in the physiological activity of colchicine, particularly concerning the binding sites of the microtubrins in the muscle and nerve cells,[3] led us to complete our longstanding, convenient synthetic scheme involving variously substituted 4-cinnamoyltropolones as intermediates.[1,2] As the intial part of our reinvestigation, we have recently reported[5] a convenient synthesis of 4-acetyltropolone (**5**) from hinokitiol (**3**), because of the limited supply of naturally occurring β-dolabrin[6] (**4**) which had previously been used[1,2] as the starting material for the preparation of **5**. We now wish to describe a convenient synthesis of analogues of colchiceine (**2**) starting from 4-acetyltropolone (**5**).

The condensation of compound **5** with various

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Table 1. Analysis and spectra of thf 4-substituted tropolones

Compd	Formula	Calcd Found (%) C	H	N	IR Spectra[a] (KBr) $\tilde{\nu}$/cm^{-1}	UV Spectra[b] λ_{max}/nm	log ε	S[c]
4-Cinnamoyltropolones and related compounds								
6a	$C_{19}H_{18}O_6$	66.66	5.30	—	3226, 1664,	255, 342	4.41, 4.31	0
		67.06	5.09	—	1597	260, 347, 441	4.20, 4.41, 3.73	—
6b	$C_{18}H_{16}O_5$	69.22	5.16	—	3268, 1653,	252, 368	4.45, 4.30	0
		69.21	5.21	—	1610	263, 350, 430	4.34, 4.47, 3.86	—
6c	$C_{17}H_{12}O_5$	68.91	4.08	—	3279, 1642,	255, 335	4.33, 4.30	0
		69.31	3.91	—	1610	270, 350, 430	4.27, 4.39, 3.79	—
6d	$C_{16}H_{12}O_3$	76.18	4.80	—	3155, 1664,	252, 318, 380	4.43, 4.37, 3.82	0
		76.25	5.01	—	1623, 1602	265, 318, 444	4.23, 4.36, 3.80	—
6e	$C_{17}H_{14}O_3$	76.67	5.30	—	3185, 1661,	253, 328, 384	4.33, 4.27, 3.87	0
		76.46	5.37	—	1592	266, 326, 440	4.14, 4.27, 3.57	—
6f	$C_{24}H_{20}O_5$	74.21	5.19	—	3205, 1626,	254, 332, 375	4.44, 4.19, 4.32	0
		73.95	5.01	—	1613, 1600	262, 353, 440	4.31, 4.44, 3.80	—
6g	$C_{24}H_{20}O_5$	74.21	5.19	—	3155, 1656,	253, 332, 376	4.48, 4.15, 4.44	0
		74.40	5.30	—	1608	263, 351, 440	4.33, 4.44, 3.80	—
6h	$C_{16}H_{11}O_3Cl$	66.95	3.86	—	3135, 1667,	254, 322, 380	4.42, 4.39, 3.86	0
		66.99	3.89	—	1623, 1600	284, 316, 440	4.28, 4.31, 3.66	—
6i	$C_{16}H_{10}O_3Cl_2$	59.86	3.16	—	3205, 1669,	254, 320, 380	4.43, 4.34, 3.82	0
		59.54	3.13	—	1621, 1597	240, 283, 445	4.25, 4.29, 3.63	—
6j	$C_{17}H_{14}O_4$	72.33	5.00	—	3185, 1634,	250, 348	4.45, 4.38	0
		72.16	5.34	—	1616, 1605	267, 347, 440	4.23, 4.52, 3.79	—
6k	$C_{16}H_{11}O_3Br$	58.05	3.35	—	3226, 1664,	252, 322, 385	4.39, 4.39, 3.77	0
		58.33	3.59	—	1621, 1600	324, 440	4.35, 3.73	—
6l	$C_{17}H_{13}O_6N$	62.38	4.00	4.28	3125, 1658,	252, 326, 390	4.26, 4.30, 3.70	0
		62.64	4.06	4.10	1592	278, 330, 440	4.28, 4.44, 3.74	—
6m	$C_{16}H_{11}O_5N$	64.64	3.73	4.71	3226, 1664,	259, 300, 386	4.40, 4.25, 3.68	0
		64.48	3.98	4.37	1605	270, 345, 444	4.26, 3.90, 3.49	—
6n	$C_{16}H_{11}O_5N$	64.64	3.73	4.71	3240, 1672,	255, 318, 400	4.35, 4.51, 3.73	0
		64.61	3.93	4.89	1610	271, 319, 448	4.27, 4.43, 4.68	—
6o	$C_{17}H_{14}O_5$	68.45	4.73	—	3236, 1653,	258, 350	4.35, 4.41	0
		68.15	4.94	—	1592	268, 345, 426	4.39, 4.43, 4.28	— —
6p	$C_{16}H_{12}O_4$	71.63	4.51	—	3145, 1637,	250, 320, 370	4.40, 4.16, 4.20	0
		71.67	4.25	—	1613	259, 335, 444	4.34, 4.21, 4.17	—
6q	$C_{18}H_{17}O_3N$	73.20	5.80	4.74	3236, 1642,	252, 312, 393	4.48, 4.37, 3.94	+
		72.94	5.54	5.07	1613	255, 325, 432	4.39, 4.13, 4.47	±
						273, 345, 430	4.35, 4.18, 4.57	—
10	$C_{14}H_{10}O_4$	69.42	4.16	—	3326, 1664,	250, 347	4.41, 4.33,	0
		69.41	4.02	—	1605	264, 345, 445	4.19, 4.50, 3.77	—
11	$C_{18}H_{14}O_3$	77.68	5.07	—	3226, 1653,	258, 345	4.28, 4.57,	0
		77.43	5.30	—	1603	280, 342, 450	4.25, 4.63, 3.78	—
4-Cinnamoyltropolone oximes								
7a	$C_{19}H_{19}O_6N$	63.86	5.36	3.92	3333, 1608	238, 315, 375	4.58, 4.48, 3.82	0
		63.72	5.55	3.95		395	3.68	
7b	$C_{18}H_{17}O_5N$	66.05	5.24	4.28	3367, 3145,			
		65.76	5.03	4.63[d]	1605[d]	243, 328, 390	4.49, 4.46, 3.84[d]	0
		66.41	4.97	4.57[e]		245, 328, 395	4.51, 4.48, 3.90[e]	0
7c	$C_{17}H_{13}O_5N$	65.59	4.21	4.50	3311, 1608[d]			
		65.59	3.99	4.54[d]		245, 333, 402	4.53, 4.50, 3.96[d]	0
		65.50	4.43	4.61[e]		243, 330, 402	4.53, 4.47, 3.90[e]	0
7d	$C_{16}H_{13}O_3N$	71.96	4.90	5.24	3205, 3096			
		71.68	4.85	5.35[d]	1603[d]	246, 290, 372	4.43, 4.44, 3.79[d]	0
		71.77	4.95	5.37[e]		245, 288, 372	4.45, 4.51, 3.78[e]	0
7e	$C_{17}H_{15}O_3N$	72.58	5.37	4.98	3333, 1608	231, 302, 370	4.43, 4.45, 3.70	0
		72.75	5.40	5.27		230, 301, 402	4.21, 4.28, 3.51	—
7f	$C_{24}H_{21}O_5N$	71.45	5.25	3.47	3378, 1613	240, 325, 375	4.51, 4.47, 3.92	0
		71.20	5.23	3.42		239, 326, 402	4.39, 4.33, 3.69	—

Table 1. (Continued)

Compd	Formula	Calcd Found (%) C	H	N	IR Spectra[a] (KBr) $\tilde{\nu}$/cm^{-1}	UV Spectra[b] λ_{max}/nm	log ε	S[c]
7g	$C_{24}H_{21}O_5N$	71.45	5.25	3.47	3195, 1603	241, 325, 380	4.50, 4.42, 3.77	0
		71.27	5.32	3.49		240, 325, 402	4.38. 4.31, 3.69	—
7h	$C_{16}H_{12}O_3NCl$	63.63	4.01	4.64	3205, 1608	245, 293, 380	4.38, 4.48, 3.74	0
		63.90	4.35	4.46				
7i	$C_{16}H_{11}O_3NCl_2$	55.70	3.21	4.06	3333, 3125,	238, 293, 363	4.49, 4.47, 3.83	0
		55.98	3.35	4.04	1613	248, 331, 406	4.48, 4.45, 4.13	—
7j	$C_{17}H_{15}O_4N$	68.67	5.08	4.77	3226, 3155,	233, 317, 378	4.44, 4.50, 3.83	0
		68.53	5.12	4.83	1600			
7k	$C_{16}H_{12}O_3NBr$	55.54	3.50	4.05				
		55.93	3.74	3.85				
7l	$C_{17}H_{14}O_6N_2$	59.65	4.12	8.18				
		58.97	4.36	7.93				
7m	$C_{16}H_{12}O_5N_2$	61.54	3.87	8.97	3268, 3096,	249, 272, 377	4.52, 4.55, 3.79	0
		60.94	3.78	8.42	1610	227, 273, 403	4.13, 4.26, 3.55	—
13	$C_{18}H_{18}O_3N_2$	69.66	5.85	9.03	3257, 1613	266, 380, 400	4.49, 3.83, 3.78	0
		69.93	5.88	8.85				
4-(1-Amino-3-aryl-2-propenyl)tropolones								
8a	$C_{19}H_{21}O_5N$	66.46	6.16	4.08	3534, 3414,	245, 335, 395	4.44, 3.96, 3.52	±
		64.78[f]	6.15	4.26	1590			
8b	$C_{18}H_{19}O_4N$	68.99	6.11	4.47		228, 317, 350	4.52, 4.20, 3.85	+
		68.21[f]	6.07	4.49	1587	245, 307, 393	4.47, 4.13, 3.70	±
8c	$C_{17}H_{15}O_4N$	68.67	5.08	4.71		237, 317, 355	4.46, 4.17, 3.82	+
		68.04[f]	5.02	4.55	1590	245, 317, 395	4.41, 4.12, 3.72	±
8d	$C_{16}H_{15}O_2N$	76.96	5.70	5.28		245, 335, 395	4.49, 3.96, 3.57	±
		[f]			1590			
8e	$C_{17}H_{17}O_2N$	76.38	6.41	5.24		247, 335, 394	4.45, 3.99, 3.77	±
		75.29[f]	6.31	4.92	1590			
8f	$C_{24}H_{23}O_4N$	74.02	5.95	3.60	3425, 1590	246, 309, 393	4.47, 4.16, 3.72	±
		73.27[f]	5.73	3.46				
8g	$C_{24}O_{23}O_4N$	74.02	5.95	3.60				
		[f]			1587			
8h	$C_{16}H_{14}O_2NCl$	66.79	4.90	4.86		248, 335, 373,	4.44, 3.90, 3.83,	±
		64.45[f]	4.98	4.28	1587	400	3.50	
8i	$C_{16}H_{13}O_2NCl_2$	59.68	4.07	4.35		260, 335, 373,	4.45, 3.99, 3.74,	±
		59.14	4.10	4.52	1590	394	3.77	
8j	$C_{17}O_{17}O_3N$	72.06	6.05	4.49		247, 334, 372,	4.44, 4.02, 3.74,	±
		69.61[f]	6.10	4.83	1608, 1592	394	3.76	
4-(1-Acetamido-3-aryl-2-propenyl)tropolones								
9a	$C_{21}H_{23}O_6N$	65.44	6.02	3.63	3268, 3165,	242, 335, 370	4.52, 3.96, 3.79	0
		65.17	6.31	3.96	1639, 1610			
9b	$C_{20}H_{21}O_5N$	67.59	5.96	3.94	3311, 3125,	243, 313, 350	4.52, 4.17, 3.81	+
		67.19	5.81	3.86	1637, 1608	245, 307, 370	4.53, 4.15, 3.97	0
						248, 337, 395	4.52, 4.12, 4.14	—
9c	$C_{19}H_{17}O_5N$	67.25	5.05	4.13	3322, 3195,	246, 315, 372	4.49, 4.19, 3.75	0
		67.22	4.97	4.08	1637, 1613			
9d	$C_{18}H_{17}O_3N$	73.20	5.80	4.74	3311, 3125,	243, 328, 370	4.56, 3.96, 3.76	0
		72.15[f]	5.85	4.57	1639, 1610			
9e	$C_{19}H_{19}O_3N$	73.76	6.19	4.53	3322, 3125,	245, 333, 370	4.56, 3.96, 3.75	0
		73.46	6.18	4.35	1642, 1610			
9f	$C_{26}H_{25}O_5N$	72.37	5.84	3.25	3250, 3210,	247, 309, 371	4.49, 4.17, 3.73	0
		72.58	5.77	3.14	1644, 1611	251, 339, 402	4.48, 4.11, 4.09	—
9g	$C_{26}H_{25}O_5N$	72.37	5.84	3.25	3247, 1642,	250, 305, 370	4.40, 4.10, 3.60	0
		72.09	6.07	3.14	1610	265, 340, 401	4.26, 3.93, 3.75	—
9h	$C_{18}H_{16}O_3NCl$	65.51	4.89	4.24	3322, 3135,	246, 335, 370,	4.56, 3.96, 3.75,	0
		65.41	4.66	4.19	1645, 1613	394	3.65	
9i	$C_{18}H_{15}O_3NCl_2$	59.39	4.15	3.85	3322, 3175,	248, 309, 335,	4.51, 3.85, 3.97,	0
		59.70	4.07	3.83	1645, 1613	371, 397	3.77, 3.67	

Table 1. (Continued)

Compd	Formula	Calcd Found (%) C	H	N	IR Spectra[a] (KBr) $\tilde{\nu}$/cm^{-1}	UV Spectra[b] λ_{max}/nm	log ε	S[c]
9j	$C_{19}H_{19}O_4N$	70.14	5.89	4.31	3310, 1643,	244, 305, 352,	4.45, 3.99, 3.78,	0
		69.85	5.78	4.17	1608	368	3.74	
4-(1-Acetamido-3-arylpropyl)tropolones								
15a	$C_{21}H_{25}O_6N$	65.10	6.50	3.62	3333, 3226,	238, 325, 370,	4.49, 4.09, 3.87,	0
		65.01	6.57	3.54	1647, 1610	386	3.84	
15b	$C_{20}H_{23}O_5N$	67.21	6.49	3.92	3333, 3155,	233, 325, 370	4.45, 3.80, 3.67	0
		67.49	6.50	3.76	1642, 1610	235, 338, 399	4.32, 3.90, 3.85	—
15c	$C_{19}H_{19}O_5N$	66.85	5.61	4.10	3300, 3226,	240, 330, 369	4.46, 3.89, 3.71	0
		67.18	5.51	3.99	1642, 1608,			
15d	$C_{18}H_{19}O_3N$	72.70	6.44	4.71	3300, 1640,	244, 327, 359	4.45, 3.91, 3.76	0
		72.49	6.16	4.96	1611			
15e	$C_{19}H_{21}O_3N$	73.29	6.80	4.50	3333, 3155,	245, 327, 368	4.43, 3.87, 3.70	0
		73.12	6.67	4.41	1642, 1610	251, 337, 400	4.43, 4.05, 4.09	—

a) Characteristic absorptions due to NH, OH, and C=O groups. b) Inflections in underlines. c) Species: Monocation (+) in 0.1 M (1 M=1 mol dm^{-3}) HCl/MeOH; neutral species (0) and Zwitterion (±) in MeOH; monoanion (−) and dianion (− −) in 0.1 M NaOH/MeOH. d) For oximes of the lower melting point. e) For oximes of the higher melting point. f) No satisfactory analytical figures available even by repeating the analysis.

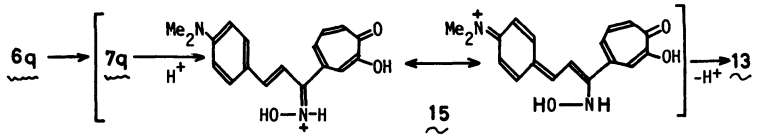
substituted benzaldehydes in methanolic potassium hydroxide at 0 °C readily afforded 17 4-cinnamoyltropolones (**6a**—**q**) in most cases in excellent yields. Similarly, the reaction of **5** with 2-furaldehyde and cinnamaldehyde gave 4-[3-(2-furyl)propenoyl]- (**10**) and 4-(5-phenyl-2,4-pentadienoyl)tropolone (**11**), respectively. However, the condensation with isovanilline and salicylaldehyde afforded the products (**6o** and **6p**, respectively) in moderate or poor yields, whereas that with vanilline failed to give any condensation products. These results, together with the elemental analysis and spectral data, are summarized in Table 1.

The presence of a conjugated carbonyl group was supported by the IR (≃1660 cm^{-1}) and ^{1}H-NMR spectra: The *E*-configuration of the olefinic group of these products was established from the large magnitude (14—16 Hz) of the coupling constants of the olefinic proton signals in the NMR spectra. The neutral species of these compounds exhibited the longest wavelength absorption maxima at 340—390 nm in the UV spectra, whereas the anionic species (troponate anions) showed a significant bathochromic shift (50—100 nm) in these absorption maxima; the acidic pK_a values of these compounds are considered to be *ca.* 6, as exemplified by the value (6.08)[5] of **6a**. The red-colored *p*-dimethylamino derivative (**6q**) apparently exists mostly as the Zwitterion form (**12**) on the evidence of the UV spectrum in methanol; the spectra of the neutral and anionic species of **6q** closely resembled those of anionic species of other cinnamoyltropolones, whereas the spectrum of the monocation of **6q** corresponded to those of the neutral species of the other derivatives (**6**) (see Table 1).

The treatment of compounds **6** with hydroxylamine hydrochloride in refluxing ethanol gave the corresponding oximes (**7a**—**m**); in some cases two isomers (*syn* and *anti*) were separated by fractional recrystallization. The structures of these oximes were supported by the elemental analysis and the IR spectra (namely, the disappearance of the strong absorptions at ≃1660 cm^{-1} due to the conjugated carbonyl group; see Table 1).

The isoxazoline structure (**13**) was assigned for the product derived from the *p*-dimethylamino compound (**6q**) on the basis of the ^{1}H-NMR spectrum, which showed three aliphatic proton signals of an ABX type at δ 3.32, 3.67, and 5.71 in addition to the signals due to the dimethylamino group (δ 2.94) and the aromatic ring-protons [δ 6.68 (2H), 7.1—7.4 (5H), and 7.77 (1H)]. Moreover, the UV spectrum of **13** closely resembled that of the 4-acetyltropolone oxide,[6] supporting the isoxazoline structure for this product. The exclusive formation of **13** (instead of an oxime derivative **7q**) from **6q** could be explained by the presence of the strongly electron-donating *p*-dimethylamino group, which should facilitate protonation at the intermediately formed oxime nitrogen even under the weakly acidic conditions compared to other oximes **7a**—**m**; the resonance-stabilized monocation (**15**) thus formed would in turn easily result in the isoxazoline ring closure to give **13** (Scheme 1).

The catalytic hydrogenation of the oximes (**7**) in the presence of 5% Pd/C in acetic acid containing a small amount of hydrochloric acid smoothly afforded the corresponding 4-(1-amino-3-aryl-2-propenyl)tropolones (**8a**—**j**) in good yields (see Table 1 for the summarized results). These yellow-colored amino compounds were considered to exist mostly as the Zwitterion form (**14**)



Scheme 1. A reaction pathway for the formation of **13** from **6q**.

on the evidence of the UV spectra; in this case, the longest wavelength absorptions of the neutral species of **8** resembled those of the troponate anions and, on acidification, an appreciable hypsochromic shift (≃40 nm) was observed in these absorptions (see Table 1). This ionic form **14** would be in conformity with the generally observed pK_a values of usual primary amines (9—10)[7] and tropolones (6.7—7.1).[5,8]

These amino compounds were acetylated with acetic anhydride to afford the stable acetamido derivatives (**9a—j**) (see Table 1). The presence of an acetamido group and two olefinic protons of *E*-configuration in **9** were confirmed by the IR and ^{1}H-NMR spectra. Because of the disappearance of the basic amino group, compounds **9** exist in the normal tropolone form, as shown by the UV spectra of their neutral species, which became similar to those of the cationic species of the amino compounds **8**.

After intensive studies, we found that the reduction of the olefinic group in compounds **9** was best accomplished by catalytic hydrogenation over 10—30% Pd/C in aqueous potassium hydroxide at room temperature (*ca.* 50 h). The 4-(1-acetamido-3-arylpropyl)tropolones (**15a—e**) were thus obtained in good yields. The structures of these reduced products were readily established by elemental analysis and spectroscopy (NMR, IR, and UV, see Table 1 and Experimental part).[9]

Among these products, compound **15a**, which was readily available from **5** in four steps in an overall yield of *ca.* 40—45% as shown above, possesses a structure analogous to that of colchiceine (**2**), in which the C_{1a}–C_{12a} bond is disconnected, having the B-ring-open form.

These findings so far described are believed to be of considerable value not only for the exploration of a convenient and efficient route to prepare various kinds of colchicine analogues but also for the development of the fundamental chemistry of troponoid compounds,[10] which are currently under investigation.

Experimental

All melting points are uncorrected. The microanalyses were carried out at Tohoku University and the results are summarized in Table 1. The ^{1}H-NMR spectra were recorded in $CDCl_3$ with a Hitachi R-22 (90 MHz). 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 each proton signal to confirm the coupling constants. IR and UV spectra were obtained on Hitachi 215 and 340 spectrometers, respectively, and the characteristic absorption maxima are recorded in Table 1. All reactions were monitored by paper chromatography (on phosphoric acid-treated Toyo paper developed in benzene) or TLC [conducted on plates precoated with silica gel (0.25 mm, Merck)]. The yields referred to in this section are in most cases those of crude, but chromatographically pure, products; specimens for analysis can be purified by recrystallization from the appropriate solvents.

General Procedure for the Reaction of 4-Acetyltropolone (5) with Arenecarbaldehydes. A 50% aqueous potassium hydroxide solution (5 ml) was added dropwise, at 0 °C, to a stirred suspension of **5** (4.0 g) and 1.2 mol equiv of an arenecarbaldehyde in methanol (60 ml) over a period of 20 min. The mixture was stirred for 4—10 h, allowed to stand overnight at 0 °C, and then diluted with cold water (100 ml). On acidification with 6 M HCl, the corresponding 4-cinnamoyltropolone (**6**) [or compounds **10** and **11**] precipitated. The product was filtered off and recrystallized.

*4-(3,4,5-Trimethoxycinnamoyl)tropolone (**6a**)*: Yellow needles (≃100% yield), mp 185—186 °C (from MeOH–$CHCl_3$); ^{1}H-NMR 3.92 (9H, s, 3MeO), 6.87 (2H, s, H-2′,6′), 7,21 (1H, d, J=14 Hz, H-9), 7.5 (3H, m, H-5,6,7), 7.6 (1H, m, HO-2, exchangeable with D_2O), 7.67 (1H, d, J=14 Hz, H-10), and 7.80 (1H, s, H-3).

*4-(3,4-Dimethoxycinnamoyl)tropolone (**6b**)*: Yellow crystals (≃100% yield), mp 154—155 °C (from MeOH–$CHCl_3$).

*4-(3,4-Methylenedioxycinnamoyl)tropolone (**6c**)*: Orange-yellow scales (≃100% yield), 162—163 °C (from AcOH).

*4-Cinnamoyltropolone (**6d**)*: Yellow crystals (≃100% yield), mp 132—133 °C (from AcOH).

*4-(4-Methylcinnamoyl)tropolone (**6e**)*: Yellow plates (≃100% yield), mp 175—176 °C (from EtOAc).

*4-(4-Benzyloxy-3-methoxycinnamoyl)tropolone (**6f**)*: Yellow plates (≃100% yield), mp 146—147 °C (from MeOH).

*4-(3-Benzyloxy-4-methoxycinnamoyl)tropolone (**6g**)*: Yellow crystals (95% yield), mp 143—144 °C (from EtOH).

*4-(4-Chlorocinnamoyl)tropolone (**6h**)*: Yellow prisms (≃100%) mp 208—209 °C (from $CHCl_3$).

*4-(2,4-Dichlorocinnamoyl)tropolone (**6i**)*: Yellow scales (≃100 % yield), mp 162—163 °C (from EtOAc).

*4-(4-Methoxycinnamoyl)tropolone (**6j**)*: Yellow needles (≃100 % yield), mp 163—164 °C (from $CHCl_3$).

*4-(4-Bromocinnamoyl)tropolone (**6k**)*: Yellow crystals (94% yield), mp 213—214 °C (from $CHCl_3$).

*4-(4-Methoxy-3-nitrocinnamoyl)tropolone (**6l**)*: Yellow crystals (≃100% yield), mp 272—273 °C (from dioxane).

*4-(3-Nitrocinnamoyl)tropolone (**6m**)*: Yellow crystals (≃100% yield), mp 185—186 °C (from EtOH–dioxane).

*4-(4-Nitrocinnamoyl)tropolone (**6n**)*: Orange needles (77% yield), mp 216—217 °C (from AcOH).

*4-(3-Hydroxy-4-methoxycinnamoyl)tropolone (**6o**)*: Yellow crystals (49% yield), mp 174—175 °C (from AcOH).

*4-(2-Hydroxycinnamoyl)tropolone (**6p**)*: Pale yellow crystals (22% yield), mp 172—173 °C (from EtOAc).

*4-[4-Dimethylamino)cinnamoyl]tropolone (**6q**)*: Red needles (79% yield), mp 160—161 °C (from AcOH).

*4-[3-(2-Furyl)propenoyl]tropolone (**10**)*: Yellow needles (91% yield), mp 160—161 °C (from EtOAc).

*4-(5-Phenyl-2,4-pentadienoyl)tropolone (**11**)*: Yellow crystals (83% yield), mp 134—135 °C (from AcOH).

*General Procedure for the Preparation of Oximes (**7a—m**) and Isoxazoline (**13**).* A solution of 4-cinnamoyltropolone **6** (1 g) and 6.6 mol equiv of hydroxylamine hydrochloride in ethanol (10 ml) was refluxed for 4—13 h, and then, after cooling, diluted with water (30 ml), affording **7** (or **13**) as precipitates.

*4-(3,4,5-Trimethoxycinnamoyl)tropolone Oxime (**7a**)*: Pale yellow crystals (75% yield), mp 230 °C (decomp) (from AcOH).

*4-(3,4-Dimethoxycinnamoyl)tropolone Oximes (**7b**)*: Two isomers both as pale yellow crystals (75% combined yield), mp 216—217 and 219—220 °C after fractional recrystallization from dioxane.

*4-(3,4-Methylenedioxycinnamoyl)tropolone Oximes (**7c**)*: Two isomers both as pale yellow crystals (76% combined yield), mp 176—178 and 208—209 °C (decomp) after fractional recrystallization from dioxane.

*4-Cinnamoyltropolone Oximes (**7d**)*: Two isomers of colorless needles, mp 171—172 °C, and colorless prisms, mp 190—191 °C (43% combined yield) after fractional recrystallization

from EtOH.

4-(4-Methylcinnamoyl)tropolone Oxime (7e): Pale amber crystals (85% yield), mp 177—178 °C (from benzene).

4-(4-Benzyloxy-3-methoxycinnamoyl)tropolone Oxime (7f): Pale yellow crystals (92% yield), mp 180—181 °C (from benzene).

4-(3-Benzyloxy-4-methoxycinnamoyl)tropolone Oxime (7g): Pale yellow crystals (59% yield), mp 174—175 °C (from benzene).

4-(4-Chlorocinnamoyl)tropolone Oxime (7h): Pale yellow crystals (90% yield), mp 153—154 °C (from benzene).

4-(2,4-Dichlorocinnamoyl)tropolone Oxime (7i): Colorless crystals (59% yield), mp 219—220 °C (from EtOAc–dioxane).

4-(4-Methoxycinnamoyl)tropolone Oxime (7j): Pale amber crystals (45% yield), mp 178—179 °C (from dioxane).

4-(4-Bromocinnamoyl)tropolone Oxime (7k): Colorless crystals (81% yield), mp 163—164 °C (from benzene).

4-(4-Methoxy-3-nitrocinnamoyl)tropolone Oxime (7l): Yellow crystals (73% yield), mp 167—168 °C (decomp) (from benzene–EtOAc).

4-(3-Nitrocinnamoyl)tropolone Oxime (7m): Pale amber crystals (86% yield), mp 196—197 °C (from acetone).

4-[5-[4-(Dimethylamino)phenyl]-4, 5-dihydro-3-isoxazolyl]tropolone (13): Yellow crystals (91% yield), mp 172—173 °C (from benzene–$CHCl_3$); ^{1}H-NMR 2.94 (6H, s, Me_2N), 3.32, 3.67 (1H each, dd, J=16, 10 Hz, 2H-9), 5.71 (1H, t, J=10 Hz, H-10), 6.68 (2H, d, J=8.8 Hz, H′-3,5), 7.1—7.4 (5H, m, H-4,5,6 and H′-2,6), and 7.77 (1H, s, H-3).

General Procedure for the Hydrogenation of Oximes (7). A solution of the oxime (3.8 g) in acetic acid (47 ml) containing conc hydrochloric acid (5 ml) was hydrogenated in the presence 5% Pd/C at room temperature, until 2 mol equiv of hydrogen was absorbed. The catalyst was removed by filtration, the filtrate diluted with water (150 ml) and then washed with chloroform. The aq layer was neutralized with 59% aq KOH, depositing the corresponding amino compounds (**8**).

4-[1-Amino-3-(3,4,5-trimethoxyphenyl)-2-propenyl]tropolone(8a): Yellow crystals (82% yield), mp 153—154 °C (decomp) (from aq MeOH).

4-[1-Amino-3-(3,4-dimethoxyphenyl)-2-propenyl]tropolone (8b): Yellow crystals (85% yield), mp 154—155 °C (decomp) (from EtOH).

4-[1-Amino-3-(3, 4-methylenedioxyphenyl)-2-propenyl]tropolone (8c): Yellow crystals (77% yield), mp 187—188 °C (decomp) (from EtOH).

4-(1-Amino-3-phenyl-2-propenyl)tropolone (8d): Yellow crystals (98% yield), mp 191—192 °C (decomp) (from dioxane).

*4-(1-Amino-3-*p*-tolyl-2-propenyl)tropolone (8e)*: Yellow crystals (97% yield), mp 185—186 °C (decomp) (from dioxane).

4-[1-Amino-3-(4-benzyloxy-3-methoxyphenyl)-2-propenyl]tropolone (8f): Yellow crystals (80% yield), mp 146—147 °C (decomp) (from EtOH).

4-[1-Amino-3-(3-benzyloxy-4-methoxyphenyl)-2-propenyl]tropolone (8g): Yellow crystals (88% yield), mp 155—156 °C (decomp) (from EtOH).

4-[1-Amino-3-(4-chlorophenyl)-2-propenyl]tropolone (8h): Yellow crystals (93% yield), mp 198—199 °C (decomp) (from MeOH).

4-[1-Amino-3-(2,4-dichlorophenyl)-2-propenyl]tropolone (8i): Yellow crystals (93% yield), mp 185—186 °C (decomp) (from MeOH).

4-[1-Amino-3-(4-methoxyphenyl)-2-propenyl]tropolone (8j): Yellow crystals (90% yield), mp 182—183 °C (decomp) (from EtOH).

General Procedure for the Acetylation of the Amino Compounds (8). A mixture of **8** (2 g) and acetic anhydride (8 ml) was heated until it became a solution and then, after cooling, diluted with water (50 ml), depositing the acetamido compounds (**9**).

4-[1-Acetamido-3-(3,4,5-trimethoxyphenyl)-2-propenyl]tropolone (9a): Colorless leaflets (85% yield), mp 192—193 °C (from EtOH); ^{1}H-NMR 2.06 (3H, s, AcN), 3.84 (9H, s, 3MeO),5.2 (2H, m, OH. NH, exchangeable with D_2O), 5.60 (1H, m, H-8), 6.48 (1H, dd, J=14, 5 Hz, H-9) 6.55 (2H, s, H-2′,6′), 7.05—7.35 (4H, m, H-5,6,7,10), 7.25 (1H, d, J=14 Hz, H-10), and 7.40 (1H, s, H-3).

4-[1-Acetamido-3-(3, 4-dimethoxyphenyl)-2-propenyl]tropolone (9b): Colorless needles (93% yield), mp 183—184 °C (from MeOH).

4-[1-Acetamido-3-(3,4-methylenedioxyphenyl)-2-propenyl]tropolone (9c): Colorless needles (86% yield), mp 177—178 °C (from MeOH).

4-(1-Acetamido-3-phenyl-2-propenyl)tropolone (9d): Colorless needles (79% yield), mp 162—163 °C (from MeOH).

*4-(1-Acetamido-3-*p*-tolyl-2-propenyl)tropolone (9e)*: Colorless needles (92% yield), mp 182—183 °C (from EtOAc).

4-[1-Acetamido-3-(4-benzyloxy-3-methoxyphenyl)-2-propenyl]tropolone (9f): Colorless crystals (62% yield), mp 148—149 °C (from EtOAc).

4-[1-Acetamido-3-(3-benzyloxy-4-methoxyphenyl)-2-propenyl]tropolone (9g): Colorless crystals (89% yield), mp 154—155 °C (from EtOAc).

4-[1-Acetamido-3-(4-chlorophenyl)-2-propenyl]tropolone (9h): Colorless crystals (95% yield), mp 154—155 °C (from EtOAc).

4-[1-Acetamido-3-(2,4-dichlorophenyl)-2-propenyl]tropolone (9i): Colorless needles (54% yield), mp 121—122 °C (from EtOAc).

4-[1-Acetamido-3-(4-methoxyphenyl)-2-propenyl]tropolone (9j): Colorless crystals (90% yield), mp 122—123 °C (from EtOH).

General Procedure for the Preparation of Compounds **15.** A solution of the olefin **9** (3 g) in 0.25—1.0 M aq KOH (30 ml) was reduced with hydrogen in the presence of 10—30% Pd/C at room temperature until the starting material disappeared (*ca.* 50 h). After filtration of the catalyst, the filtrate was acidified with 6 M HCl, depositing the product **15**; when necessary, the product was extracted with chloroform.

4-[1-Acetamido-3-(3,4,5-trimethoxyphenyl)propyl]tropolone (15a): Colorless needles (98% yield), mp 129—130 °C (from EtOAc); ^{1}H-NMR 1.97 (3H, s, AcN), 2.0 (2H, m, 2H-9), 2.55 (2H, m, 2H-10), 3.92 (9H, s, 3MeO), 4.3 (1H, m, NH), 4.90 (1H, q, J=7 Hz), 6.36 (2H, s, H-2′,6′), and 7.1—7.4 (4H, m, H-3,4,6,-7).

4-[1-Acetamido-3-(3,4-dimethoxyphenyl)propyl]tropolone (15b): Colorless crystals (93% yield), mp 143—144 °C (from EtOAc–MeOH).

4-[1-Acetamido-3-(3, 4-methylenedioxyphenyl)propyl]tropolone (15c): Colorless crystals (67% yield), mp 168—169 °C (from EtOAc).

4-(1-Acetamido-3-phenylpropyl)tropolone (15d): Colorless needles (88% yield), mp 148—149 °C (EtOH).

*4-(1-Acetamido-3-*p*-tolypropyl)tropolone (15e)*: Colorless needles (90% yield), mp 149—150 °C ($CHCl_3$).

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References

1) An initial part of the results have been presented: a) T. Nozoe, 16th IUPAC Congress, Paris, July, 1957, *Experientia, Suppl. VII*, 306 (1957); b) T. Nozoe, K. Takase, Y. Kitahara, and K. Doi, 132nd National Meeting of the American Chemical Society, New York, Sept. 1957; c) T. Nozoe, K. Takase, and

H. Matsumura, "Comprehesive Organic Chemistry (Dai Yuki Kagaku)," ed by M. Kotake, Asakura, Tokyo (1960), Vol. 13, pp. 340—374; T. Nozoe, *Prog. Org. Chem.*, **5**, 132 (1961).

2) A part of the results in the Experimental section have been taken from M. Sc. Thesis of N. Kawabe, Tohoku Univ. (1965); publication of the present work has been delayed for a long period for various reasons.

3) M. H. Zweig and C. F. Chignell, *Biochem. Pharmacol.*, **22**, 2141 (1973); J. B. Olmstead and G. G. Borisy, *Annu. Rev. Biochem.*, **42**, 507 (1973).

4) J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threefall, and A. Eschenmoser, *Helv. Chim. Acta*, **44**, 540 (1961); E. E. van Tamelen, T. R. Spencer, Jr., D. B. Allen, and R. L. Orvis, *Tetrahedron*, **14**, 8 (1961); T. Nakamura, Y. Murase, R. Hayashi, and Y. Endo, *Chem. Pharm. Bull.*, **10**, 281 (1962), G. Sunagawa, T. Nakamura, and J. Nakazawa, *ibid.*, **10**, 291 (1962), T. Nakamura, *ibid.*, **10**, 299 (1962); A. I. Scott, F. McCapra, R. L. Buchanan, A. C. Day, and D. W. Young, *Tetrahedron*, **21**, 3605 (1965); R. B. Woodward, "The Harvey Lecture," Ser. 59, 31, Academic Press, New York, N. Y. (1965); J. Martel, E. Toromonoff, and C. Huyuh, *J. Org. Chem.*, **30**, 1752 (1965); S. Kaneko and M. Matsui, *Agric. Biol. Chem.*, **32**, 995 (1968); K. Kato, F. Kido, M. D. Wu, and A. Yoshikoshi, *Bull. Chem. Soc. Jpn.*, **47**, 1516 (1974); E. Kotani, F. Miyazaki, and S. Tobinaga, *J. Chem. Soc., Chem. Commun.*, **1974**, 300; D. A. Evans, S. P. Tanis, and D. J. Hart, *J. Am. Chem. Soc.*, **103**, 5813 (1981).

5) H. Yamamoto, A. Hara, A. Noguchi, H. Kawamoto, S. Inokawa, and T. Nozoe, *Bull. Chem. Soc. Jpn.*, **55**, 1594 (1982).

6) T. Nozoe, *Fortschr. Chem. Org. Naturst.*, **13**, 232 (1956); T. Nozoe, K. Takase, and M. Ogata, *Chem. Ind.*, **1957**, 1070.

7) See, *e.g.* A. Albert and E. P. Sergent, "The Determination of Ionization Constants of Acids and Bases," Chapman and Hall, London (1972); D. D. Perrin, B. Dempsey, and E. P. Sergent, "pK_a Prediction for Organic Acids and Bases," Chapman and Hall, London (1981).

8) J. W. Cook, A. R. Gibb, R. A. Raphael, and A. R. Sommerville, *Chem. Ind.*, **1950**, 427, *J. Chem. Soc.*, **1951**, 503; W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, **72**, 2305 (1950); **73**, 828 (1951).

9) Employing our method,[1,2] M. Oda and H. Ogawa have prepared a dichloro compound (**15**; $R^1=R^2=Cl$, $R^3=H$) from **5**: Japan Kokai Koho 61156-61158 (1979); *Chem. Abstr.*, 193025 (1980).

10) Ref. 1c, pp. 1—691; D. Lloyd, "Carbocyclic Non-benzenoid Aromatic Compounds," Elsevier, Amsterdam (1966), pp. 134—144; F. Pietra, *Chem. Rev.*, **73**, 293 (1973).