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OXIDATION PRODUCTS OF PHENOLIC THIOCOLCHICINES: RING A QUINONES AND DIENONES

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Abstract: An improved, highly selective demethylation of thiocolchicine (**1**) to the diphenol **5** is described. Oxidation of **2** to para-quinone **6** and of **4** and **5** to ortho-quinones **8** and **10** is first reported. Also, 2-demethylthiocolchicine (**3**) was oxidized to the quinone methide **7**.

Colchicine, a natural alkaloid isolated from *Colchicum autumnale*, is one of the oldest drugs still in use. However, its medical use is limited due to severe toxicity. Extensive structural modification has been directed toward improving the therapeutic index, and the phenolic congeners of colchicine were found to be less toxic than colchicine.[1] Selective ether-cleavage of colchicine[2] and of thiocolchicine[3] has been reported; however, an improved procedure that affords 2,3-didemethylthiocolchicine (**5**) in 46.8% yield is reported here.

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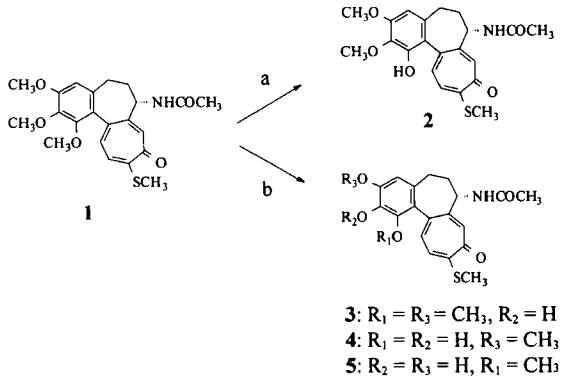
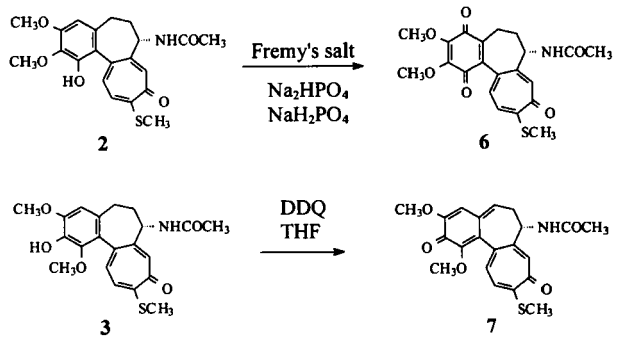
Thiocolchicine (**1**) was demethylated to **3-5** with 2 equivalents of boron tribromide at room temperature (Scheme 1). 2,3-Didemethylthiocolchicine (**5**) was the major product and was obtained in a 46.8% yield as compared with the 21% yield reported from a different procedure.[3] The two minor products were 1,2-didemethylthiocolchicine (**4**) and 2-demethylthiocolchicine (**3**). The amount of boron tribromide directly influences the selectivity. Excess boron tribromide resulted in complete demethylation, giving primarily the very polar tridemethyl derivative.



a: $SnCl_4/Ac_2O/K_2CO_3$; b: 2 eq BBr_3/CH_2Cl_2

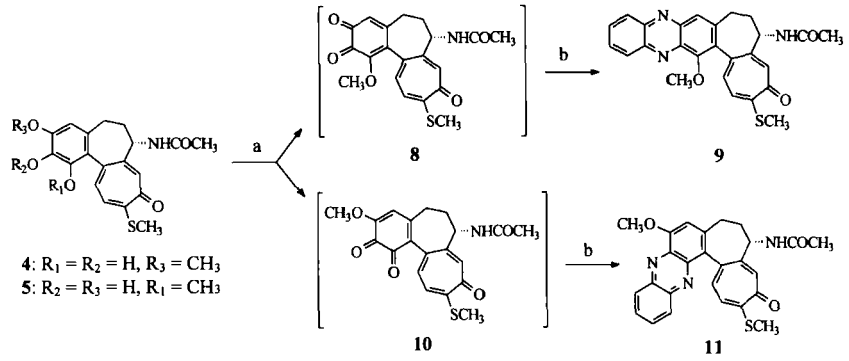
Scheme 1

Treatment of **1** with stannous tetrachloride in acetic anhydride followed by hydrolysis of the O-acetate gave 1-demethylthiocolchicine (**2**).[4] Oxidation of **2** with Fremy's salt in buffered solution (pH = 6) afforded the para-quinone **6**,[5] which showed the characteristic red color of a quinone (Scheme 2). DDQ was used to oxidize **3** to the quinone methide **7** (Scheme 2).



Scheme 2

Compounds **4** and **5** were reacted with silver carbonate giving a red color, which was attributed to quinones **8** and **10,** respectively. These unstable intermediates decomposed on silica gel and, therefore, were isolated as their phenazine derivatives **9** and **11** by *in situ* trapping with commercially available 1,2-phenylenediamine[6] (Scheme 3). The spectral data of **8** and **10** (obtained on the crude compounds) fully support their structure. The ^{1}H NMR spectra showed only one singlet (3H) located between 3.5 - 4 ppm, which was assigned to the methoxy group at the 1- or 3- position, respectively. The electron impact mass spectra of both ortho-quinones showed molecular ions at m/z 384 (base peak). Their UV patterns also were very similar showing two peaks at 260 nm and 380 nm. The para-quinone **6** had a large negative optical rotation (-359.33). Interestingly, the quinone methide **7** and phenazine **9** showed large positive optical rotations, while phenazine **11** had a negative value. These dramatic shifts may result from conformational changes.



a: Ag_2CO_3/celite; b: 1,2-phenylenediamine

Scheme 3

The oxidation products **6** and **7** showed no noteworthy inhibition of tubulin polymerization, and the phenazines **9** and **11** were considerably less active in this assay than the parent phenols **4** and **5** (unpublished data), respectively.

EXPERIMENTAL SECTION

Chemistry. Melting points were measured on a Fisher-Johns melting point apparatus without correction. Optical rotations were determined with a DIP-1000 polarimeter; ^{1}H NMR spectra were measured on a Bruker AC-300 spectrometer with Me_4Si(TMS) as internal reference. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. MS data were determined by NIH. Thin-layer chromatography (TLC) silica gel plates were purchased from Analtech, Inc. Silica gel (230-400 mesh), from Aldrich, Inc., was used for column chromatography. MCI gel was purchased from Supelco.

Phenolic thiocolchicines 3-5. To a solution of thiocolchicine (0.1 mmol) in anhydrous CH_2Cl_2 (10 ml) was added dropwise a 1M solution of boron tribromide in CH_2Cl_2 (0.3 mmol) under ice cooling. The reaction mixture was maintained at 0°C for 1h and then stirred at room temperature for 6h. The reaction mixture was

cooled in an ice bath, and methanol (5ml) was added dropwise. The solution was refluxed for 1h, then evaporated under reduced pressure. The residue was purified by MCI Gel CHP-20P column chromatography using water and then methanol as eluents. The resulting components in order of elution were 2,3-didemethylthiocolchicine **5**, 1,2-didemethylthiocolchicine **4**, and 2-demethylthiocolchicine **3**.

2-Demethylthiocolchicine (3). Yield: 4%; mp 179-180°C (lit[3] 189°C); ^{1}H NMR (CD_3OD) δ 1.99 (s, 3H, $COCH_3$), 2.15-2.38 (m, 4H, H-5,6), 2.48 (s, 3H, SCH_3-10), 3.54 (s, 3H, OCH_3-1), 3.91 (s, 3H, OCH_3-3), 4.51 (m,1H, H-7), 6.68 (s, 1H, H-4), 7.19 (s, 1H, H-8), 7.36 (d, J = 10.5Hz, 1H, H-11), 7.41 (d, J = 10.5Hz, 1H, H-12).

1,2-Didemethylthiocolchicine (4). Yield: 14%; mp 225-227°C (lit[3] 233°C); ^{1}H NMR (CD_3OD) δ 2.0 (s, 3H, $COCH_3$), 2.16-2.38 (m, 4H, H-5,6), 2.47 (s, 3H, SCH_3-10), 3.89 (s, 3H, OCH_3-3), 4.53 (m,1H, H-7), 6.47 (s, 1H, H-4), 7.19 (s, 1H, H-8), 7.36 (d, J = 10.5Hz, 1H, H-11), 7.51 (d, J = 10.4Hz, 1H, H-12).

2,3-Didemethylthiocolchicine (5). Yield: 47%; mp 180-181°C (lit[3] 185°C); ^{1}H NMR (CD_3OD) δ 1.98 (s, 3H, $COCH_3$), 2.15-2.29 (m, 4H, H-5,6), 2.46 (s, 3H, SCH_3-10), 3.50 (s, 3H, OCH_3-1), 4.52 (m,1H, H-7), 6.48 (s, 1H, H-4), 7.18 (s, 1H, H-8), 7.34 (d, J = 10.6Hz, 1H, H-11), 7.41 (d, J = 10.4Hz, 1H, H-12).

1-Demethoxythiocolchicine-1,4-quinone (6). To a suspension of thiocolchicine (1.06g, 2.64 mmol) in methanol (100 ml), was added a Na_2HPO_4/NaH_2PO_4 buffered solution (pH=6) of Fremy's salt (5.67g, 8 mol excess) with stirring at 0°C. The mixture was stirred for 5 min and the pH dropped to 4. A few drops of 1N KOH were added to raise the pH to 6.5-7.0. After the mixture was stirred for 14h, concentrated HCl and H_2O were added to terminate the reaction, and the mixture was extracted with $CHCl_3$ (3 x 150 ml). The organic phase was washed with H_2O and dried over Na_2SO_4. After the removal of solvent under reduced pressure, the residue was chromatographed ($CHCl_3$: MeOH = 50: 1) to give 385.5 mg (35% yield) of **6**: red needle crystals; mp 128-131°C (CH_2Cl_2/Et_2O); [α] -359.33° (c = 0.12 in CH_3OH); IR (KBr) 3280 (NH), 2935, and 2840 (aliphatic CH), 1655 (CO, C-1,4), 1630 (CO amide), and 1600 (CO, tropolone), and 1525 cm^{-1}; Cl-MS: 416 (M+1); ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H, $COCH_3$), 2.08-2.32 (m, 4H, H-5,6), 2.45 (s, 3H, SCH_3-10), 4.01 (s, 6H, OCH_3-2,3) 4.77 (m,1H, H-7), 7.15 (d, J = 10.5Hz, 1H, H-11), 7.19 (s, 1H, H-8), 7.22 (d, J = 10.5Hz, 1H, H-12), 7.49 (d, J = 7.7Hz, 1H, NH-7); Anal. Calcd: for $C_{21}H_{21}NSO_6 \cdot 1H_2O$: C, 58.19; H, 5.35; N, 3.23. Found C, 58.32; H, 5.33; N, 3.24.

2-Demethyl-4a,H-thiocolchicine-2-one (7). 2-Demethylthiocolchicine **3** (15.5 mg, 0.038 mmol) was dissolved in THF (2 ml), and DDQ (8.8 mg, 0.038 mmol)

added to the solution. The reaction mixture immediately turned deep green. TLC analysis indicated the consumption of starting material after 7h. The solvent was removed by vacuum evaporation and the residue was purified by preparative TLC (CH_3OH:CH_3COCH_3:EtOAc: CH_2Cl_2 = 1:1:1:5) to give 4.3 mg (27.7% yield) of **7**: amorphous; [α] + 270.75° (c = 0.16 in CH_3COCH_3); IR (KBr) 3400 (NH), 2920 and 2840 (aliphatic CH), 1730 (CO, C-2), 1640 (CO, amide), 1600 (CO, tropolone) and 1580 cm^{-1}; EI-MS: 399 (M^+); ^1H NMR (CD_3OD) δ 2.09 (s, 3H, $COCH_3$), 2.50 (s, 3H, SCH_3-10), 2.15-2.56 (m, 2H, H-6), 3.71, 3.73 (both s, 3H each, OCH_3-1,3), 5.05 (m, 1H, H-7), 5.29 (s, 1H, H-5), 6.30 (s, 1H, H-4), 6.96 (s, 1H, H-8), 7.35 (d, *J* = 10.8Hz, 1H, H-11), 8.65 (d, *J* = 10.8Hz, 1H, H-12). Anal. Calcd. for $C_{21}H_{21}NSO_5 \cdot 0.5CH_3OH$: C, 62.54; H, 5.73. Found C, 62.98; H, 6.21.

2,3-Thiocolchicinephenazine (9). Commercially available 1,2-phenylenediamine (7.8 mg, 0.072 mmol) and 2,3-didemethylthiocolchicine **5** (12.2 mg, 0.0315 mmol) were dissolved in dry ethanol (2 ml). To this solution was added freshly prepared Ag_2CO_3/Celite reagent (92.6 mg, 0.33 mmol). The reaction mixture was stirred for 1h at room temperature then filtered, and the filtrate was evaporated under reduced pressure. The desired compound was purified on a preparative TLC plate ($CHCl_3$:CH_3OH = 25:1) to give 12 mg (83.3 % yield) of **10**: amorphous; [α] + 116.33° (c = 0.035 in $CHCl_3$): IR (KBr) 3250 (NH), 2920 and 2850 (aliphatic CH), 1625 (CO, amide), 1600 (CO, tropolone), 1525 cm^{-1}; CI-MS: 458 (M+1); ^1H NMR (CD_3OD) δ 1.99 (s, 3H, $COCH_3$-7), 2.0-2.4 (m, 4H, H-5,6), 2.46 (s, 3H, SCH_3-10), 3.97 (s, 3H, OCH_3-1), 4.64 (m, 1H, H-7), 7.23 (s, 1H, H-4), 7.42 (d, *J* = 10.4Hz, 1H, H-11), 7.55 (d, *J* = 10.4Hz, 1H, H-12), 7.86 (s, 1H, H-8), 7.97 (m, 2H, H-2',3'), 8.21 (m, 1H, H-1'), 8.33 (m, 1H, H-4'). Anal. Calcd. for $C_{26}H_{23}N_3SO_3 \cdot 0.5CH_3CO_2C_2H_5$: C, 67.05; H, 5.43; N 8.38. Found C, 67.18; H, 5.72; N, 8.42.

1,2-Thiocolchicinephenazine (11). Prepared from 1,2-didemethylthiocolchicine **4** in the same manner as **10**, yield 55%. **11**:Amorphous; [α] -61.65° (c = 0.18 in $CHCl_3$); IR (KBr) 3260 (NH), 2920 and 2830 (aliphatic CH), 1650 (CO, amide), 1600 (CO, tropolone), and 1540 cm^{-1}; CI-MS: 458 (M+1); ^1H NMR (CD_3OD) δ 1.96 (s, 3H, $COCH_3$-7), 2.51 (s, 3H, SCH_3-10), 2.4-2.9 (m, 4H, H-5,6), 4.22 (s, 3H, OCH_3-3), 4.57 (m, 1H, H-7), 7.29 (s, 2H, H-4,8), 7.46 (d, *J* = 10.6Hz, 1H, H-11), 7.60 (d, *J* = 10.6Hz, 1H, H-12), 7.89 (m, 2h, H-2',3'), 8.16 (m, 1H, H-1'), 8.30 (m. 1H, H-4'). Anal. Calcd. for $C_{26}H_{23}N_3SO_3 \cdot 1.75\ CH_3CO_2C_2H_5$: C, 64.79; H, 6.10. Found C, 64.82; H, 6.09.

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