99. Simple Conversion of Colchicine into Demecolcine

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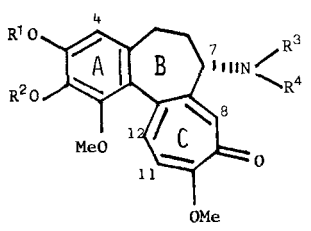
Summary

N-Deacetylcolchiceine (**7**), readily available from colchicine (**1**), was converted into *N*-trifluoroacetyl-deacetylcolchiceine (**8**). Methylation of **8** with methyl iodide in the presence of potassium carbonate afforded a mixture of *N*-trifluoroacetyl-demecolcine (**10**) and its isomer **11**. The mixture of **10** and **11** was detrifluoroacetylated and separated by chromatography to afford demecolcine (**2**) and isodemecolcine (**12**). A more practical route to **2** started with **8**, and gave *N*-trifluoroacetyl-deacetylcolchicine (**13**) and its isomer **14** after *O*-methylation with diazomethane. *N*-Methylation of **13** and **14** with methyl iodide and potassium carbonate afforded **10** and **11**. The overall yield in the conversion of colchicine (**1**) into demecolcine (**2**) *via* **7**, **8** and **13** was 55%.

Demecolcine (**2**) [1] [2], identical with *N*-methyl-*N*-deacetylcolchicine [3] [4], is an antitumor alkaloid, and present besides colchicine (**1**) in *Colchicum autumnale* L. Demecolcine (**2**) is a direct chemical precursor of other Colchicum alkaloids, such as *N*-methyldemecolcine (**3**) [5], speciosine (**4**) [6] [7], and closely related to its phenolic congeners 2-*O*-demethyldemecolcine (**5**) [5] and 3-*O*-demethyldemecolcine (**6**) [5]. Demecolcine (**2**) is in addition a convenient intermediate for the preparation of other *N*-substituted derivatives. Supplies of demecolcine were so far derived from natural sources, and studies of it and its analogs with regard to tubulin binding [8], *in vivo* antitumor activity, and animal toxicity, were incomplete owing to inacessability of the alkaloids.

Scheme 1



	R^1	R^2	R^3	R^4
1	Me	Me	H	Ac
2	Me	Me	Me	H
3	Me	Me	Me	Me
4	Me	Me	Me	$-CH_2$  HO
5	Me	H	H	Me
6	H	Me	H	Me

[1]) Presented at the 177th ACS-meeting in Honolulu, Hawaii, April 1979.

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We now report a simple and practical conversion of colchicine (**1**), the major alkaloid in *Colchicum autumnale* L., into demecolcine (**2**). The crucial intermediate in this degradation is the crystalline *N*-trifluoroacetyl-deacetylcolchiceine (**8**), shown in its colchicine structure[2]) [9].

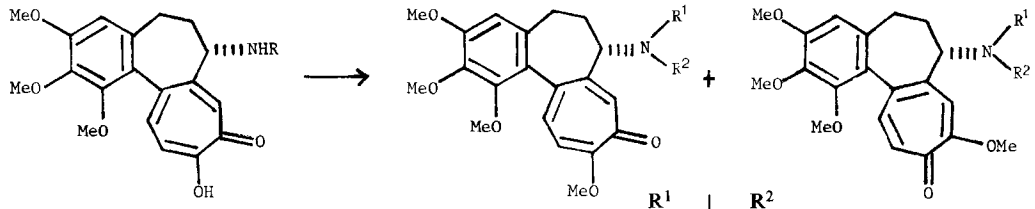
The *N*-trifluoroacetamide **8** is readily available from *N*-deacetylcolchiceine (**7**) by trifluoroacetylation, and contains, in accord with earlier findings [10], a much more acidic amide hydrogen atom, succeptible to *N*-alkylation. The conversion of **8** into demecolcine (**2**) could be accomplished by 2 routes (A and B, *Scheme 2*).

Route A. Methylation of trifluoroacetamide **8** with methyl iodide in acetone in the presence of potassium carbonate, and monitored by TLC., indicates that *O*-methylation of the enol function in the tropolonic moiety precedes *N*-methylation. The ultimate *O*,*N*-methylated mixture contained, according to NMR. and HPLC. analysis, about 65% of *N*-trifluoroacetyldemecolcine (**10**) and about 35% of its isomer **11**.

Detrifluoroacetylation of the above mixture afforded demecolcine (**2**) and isodemecolcine (**12**), separated by careful chromatography over silica gel. Demecolcine (**2**) was identical with an authentic sample[3]). Demecolceine (**9**), already prepared by *Reichstein et al.* [11], was obtained by acid hydrolysis of the mixture of **10** and **11**. *O*-Methylation of **9** with ethereal diazomethane again afforded a mixture of demecolcine (**2**) and its isoderivative (**12**).

Route B. *O*-Methylation of the *N*-trifluoroacetamide **8** with ethereal diazomethane in methanol afforded *N*-trifluoroacetyl-deacetylcolchicine (**13**) and its isoderivative **14**. Both compounds were isolated after chromatography in about equal amounts and their structures assigned by ^{1}H-NMR. analysis (see exper. part). *N*-Methylation of both ethers with methyl iodide in acetone, in the presence of potassium carbonate, afforded the *N*-trifluoroacetylated derivatives of demecolcine (**10**)

Scheme 2



7 R = H
8 R = $COCF_3$
9 R = Me

	R^1	R^2	
10	Me	$COCF_3$	**11**
2	Me	H	**12**
13	H	$COCF_3$	**14**
15	H	H	

Route A: **8** → **10** + **11**
Route B: **8** → **13** + **14**

[2]) Compounds **7**, **8** and **9** are shown with the arrangements of the oxygen functions in the tropolonic moiety as in colchicine. This is not secured by available data and only presented for reasons of simplicity.

[3]) We thank Prof. *T. Reichstein*, University of Basle, for a supply of natural demecolcine for comparison.

and isodemecolcine (**11**), already obtained by *route A*. Since the chromatographic separation of **13** and **14** is easier than the tedious separation of demecolcine (**2**) and isodemecolcine (**12**), *route B* presents a more practical route for the conversion of colchicine (**1**) into demecolcine (**2**) than *route A*. *N*-Trifluoroacetyl-deacetylcolchicine (**13**) is a key intermediate in the synthesis of a wide variety of colchicine and demecolcine analogs, such as *N*-methyldemecolcine (**3**) [11] [12], speciosine (**4**) [6] [7] and *N*-deacetylcolchicine (**15**) [13]. The preparation of **3**, **4** and **5** was repeated for their biological evaluation[4]).

Structure assignment. – The correct structure assignment of the individual compounds, especially the arrangement of the keto and enol ether function in the tropolonic ring, was possible by ^{1}H-NMR. spectroscopy and by chemical correlation. The ^{1}H-NMR. characteristics of the new compounds are similar to those already reported for colchicine, isocolchicine and derivatives (see [9] [14] and ref. therein). The aromatic proton H–C(4) appears for all the compounds as a singlet at 6.55 ± 0.05 ppm and is largely unaffected by different substituents on C(7), or changes in the tropolonic ring C. On the other hand, the chemical shifts of the H–C(8) singlet, and the H–C(11) and H–C(12) *AB*-quartet, are influenced by changes at C(7) and in the C-ring. The iso-series is characterized by a shift to slightly higher field and smaller differences in the chemical shifts in the *AB*-system (~ 0.25 ppm) in comparison to compounds with colchicine structures (~ 0.5 ppm). These differences in the ^{1}H-NMR. spectra can be used for assigning the colchicine (normal) or the iso-structure. It is generally assumed that the higher field proton of the *AB*-System in the normal series belongs to H–C(11). Such an assignment is more difficult to make in the iso-series, where the signals for the protons of the *AB*-system are closer *(Table)*.

The observations that $[\alpha]_D$ and m.p. in the iso-series are generally higher than those found for compounds with colchicine structure is supported by our data (see exper. part).

Table. ^{1}*H-NMR. Spectral Data*[5])

Compound	H–C(4)	H–C(8)	H–C(11)	H–C(12)
1	6.57	7.67	6.93	7.40
8	6.54	7.56	7.34	7.60
13	6.52	7.48	6.88	7.36
14	6.55	7.10	7.08	7.42
10	6.51	7.02	6.74	7.27
11	6.51	6.54	7.09	7.39
9	6.54	8.03	7.28	7.54
2	6.52	7.67	6.77	7.20
12	6.55	7.85	7.13	7.37
3	6.51	8.09	6.71	7.24

[4]) The biological properties of the various colchicine and demecolcine derivatives prepared during this study will be reported elsewhere.

[5]) In the above *table*, the higher field part of the *AB*-system has been assigned for convenience to the proton at C(11) for compounds with isocolchicine and colchiceine structure.

Experimental Part

General. Melting points (m.p.) are corrected. UV. spectra: in EtOH, λ_{max} in nm, ε in parentheses. IR. spectra: in $CHCl_3$, data in cm^{-1}; abbreviations: *s* strong, *m* medium, *w* weak, br. broad; ^{1}H-NMR. spectra: 100 MHz in $CDCl_3$, internal standard TMS ($\delta = 0$ ppm), J = coupling constant in Hz; abbreviations; *s* singlet, *d* doublet, *m* multiplet, br. broad. Mass spectra (MS.) *m/z*, electron impact 70 eV, relative intensity in parentheses. TLC.: SiO_2-GF, *Analtech,* Newark, DE. The organic phase, after work up, was dried with Na_2SO_4. Analytical data of compounds in the literature, not fully characterized by IR., NMR. and MS. data, are also reported.

N-*Trifluoroacetyl-deacetylcolchiceine* (**8**). *N*-Deacetylcolchiceine (**7**) (0.028 mol, 9.6 g) and Na_2CO_3 (0.28 mol, 30 g) were suspended in 800 ml ether cooled with ice. While stirring, trifluoroacetanhydride (0.28 mol, 58.8 g, 39.5 ml) was added in one portion. The cooling bath was removed and the orange solution stirred at RT. for 3 h. The solid materials were partly filtered off, and the filtrate poured into $CHCl_3$. The organic layer was washed with cold $NaHCO_3$ solution and H_2O until neutral. The crude product was crystallized from CH_2Cl_2/ligroin to give 10.4 g (84%) **8**. M.p. 171–172°; $[\alpha]_D^{20} = -216°$ ($c = 1.15$, $CHCl_3$). - UV.: 243 (37,300), 352 (23,200). - IR.: 3440*m*, 3240*m* (br.), 1732*s*, 1615*s*, 1597*m*, 1565*m*, 1527*m*, 1488*s*, 1457*s*, 1433*m*, 1406*m*, 1374*m*, 1351*m*, 1325*s*, 1279*s*, 1169*s*, 1142*s*, 1096*s*, 1077*w*, 1045*m*, 1007*m*, 984*w*, 943*w*, 921*w*, 901*w*, 871*w*, 859*w*, 842*m*. - NMR.: 1.8–2.8 (*m*, 2 H–C(5) and 2 H–C(6)); 3.64, 3.90 and 3.94 (3*s*, 3×3 H, OCH_3); 4.70 (*m*, H–C(7)); 6.54 (*s*, H–C(4)); 7.34 and 7.60 (2*d*, $J = 11$, H–C(11) and H–C(12)); 7.56 (*s*, H–C(8)); 8.26 (*m*, HN–C(7)). - MS.: 439 (M^+, 29), 438 (100), 411 (9), 410 (39), 283 (45), 267 (24).

$C_{21}H_{20}F_3NO_6$	Calc.	C 57.41	H 4.58	F 12.96	N 3.18%
(439.34)	Found	„ 57.33	„ 4.60	„ 12.18	„ 3.20%

N-*Trifluoroacetyldemecolcine* (**10**) *and* N-*trifluoroacetylisodemecolcine* (**11**). *N*-Trifluoroacetyl-deacetylcolchiceine (**8**) (11.8 mmol, 5.18 g), CH_3I (8 ml) and dry K_2CO_3 (8.1 g) in acetone (80 ml) were stirred at RT. for 10 days[6]). The reaction mixture was then poured into $CHCl_3$ and washed with H_2O until neutral. The crude product was dried at 100° under high vacuum. Yield: 5.25 g (95%) of **10** and **11** (*ca.* 65:35 by NMR. and HPLC.).

N-*Trifluoroacetyl-deacetylcolchicine* (**13**) *and* N-*trifluoroacetyl-deacetylisocolchicine* (**14**). *N*-Trifluoroacetyl-deacetylcolchicine (**8**) (7.37 mmol, 3.24 g) was partly dissolved in MeOH (40 ml) and treated with excess ethereal CH_2N_2. After 3 h the solvent was evaporated and the oily residue (3.9 g) chromatographed on 255 g SiO_2 ($CHCl_3$/MeOH 97:3) yielding 1.56 g (45%) **13** and 1.52 g (45%) **14**.

N-*Trifluoroacetyl-deacetylcolchicine* (**13**). M.p. 203–205° (sinters at 145–150°; from CH_2Cl_2/hexane); $[\alpha]_D^{20} = -79°$ ($c = 1.43$, $CHCl_3$). - UV.: 227 (27,100), 236 (27,800), 346 (16,100). - IR.: 3440*m*, 3230*m* (br.), 1720*s*, 1616*s*, 1589*s*, 1560*s* (br.), 1485*s*, 1452*s*, 1443*s*, 1431*m*, 1401*m*, 1375*m*, 1350*m*, 1322*s*, 1287*m*, 1142*s*, 1096*s*, 1047*m*, 1015*m*, 1000*m*, 988*m*, 939*w*, 923*w*, 899*w*, 868*w*, 839*w*. - NMR.: 1.9–2.8 (*m*, 2 H–C(5) and 2 H–C(6)); 3.64, 3.90, 3.93 and 4.00 (4*s*, 4×3 H, OCH_3); 4.70 (*m*, H–C(7)); 6.52 (*s*, H–C(4)); 6.88 (*d*, $J = 11$, H–C(11)); 7.36 (*d*, $J = 11$, H–C(12)); 7.48 (*s*, H–C(8)); 9.36 (*m*, HN–C(7)). - MS.: 453 (M^+, 60), 434 (2), 425 (100), 379 (17), 312 (34), 297 (71), 281 (35).

$C_{22}H_{22}F_3NO_6$ (453.36) Calc. C 58.28 H 4.88 N 3.08% Found C 58.17 H 5.02 N 3.14%

N-*Trifluoroacetyl-deacetylisocolchicine* (**14**). M.p. 236–239° (from MeOH/ligroin); $[\alpha]_D^{20} = -294°$ ($c = 0.595$, $CHCl_3$). - UV.: 226 (26,000), 244 (30,100), 340 (18,500). - IR.: 3435*m*, 3240*m* (br.), 1731*s*, 1618*s*, 1599*s*, 1565*s*, 1520*m*, 1481*s*, 1466*s*, 1457*s*, 1408*s*, 1375*m*, 1352*s*, 1324*s*, 1306*m*, 1287*m*, 1260*s*, 1168*s*, 1150*s*, 1142*s*, 1099*s*, 1044*m*, 1010*m*, 1000*m*, 982*m*, 945*w*, 923*w*, 875*w*, 856*w*, 843*m*. - NMR.: 2.0–2.8 (*m*, 2 H–C(5) and 2 H–C(6)); 3.64, 3.90, 3.92 and 3.96 (4*s*, 4×3 H, OCH_3); 4.64 (*m*, H–C(7)); 6.55 (*s*, H–C(4)); 7.08 and 7.42 (2*d*, $J = 12$, H–C(11) and H–C(12)); 7.10 (*s*, H–C(8)); 8.50 (*m*, HN–C(7)). - MS.: 453 (M^+, 72), 434 (3), 425 (100), 379 (21), 340 (29), 312 (59), 297 (82), 281 (40).

$C_{22}H_{22}F_3NO_6$ (453.36) Calc. C 58.28 H 4.88 N 3.08% Found C 58.48 H 5.01 N 3.01%

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[6]) Reaction monitored by TLC. ($CHCl_3$/MeOH 9:1). The starting material disappears relatively quickly, and 2 spots appear on TLC. The final products **10** and **11** (one spot on TLC.) are formed only slowly under these conditions. This suggests, that the methylation of the tropolonic hydroxyl groups occurs first, and the alkylation of the amide nitrogen later.

N-*Trifluoroacetyldemecolcine* (**10**). *N*-Trifluoroacetyl-deacetylcolchicine (**13**) (3.42 mmol, 1.55 g), CH_3I (2.5 ml) and K_2CO_3 (2.36 g) in acetone (40 ml) were stirred at RT. for 3 days (TLC.-monitoring). The reaction mixture was poured into $CHCl_3$ and washed with H_2O until neutral. The oily product (1.38 g, 86%) was crystallized from EtOH/ligroin. M.p. 180–181°; $[\alpha]_D^{20} = -188°$ ($c = 0.86$, $CHCl_3$). – UV.: 235 (29,700), 242 (29,800), 350 (17,300). – IR.: 3630*w*, 3470*w* (br.), 1691*s*, 1618*s*, 1591*s*, 1570*s*, 1485*s*, 1462*s*, 1444*m*, 1431*m*, 1412*m*, 1399*m*, 1380*m*, 1353*s*, 1324*s*, 1301*m*, 1285*m*, 1150*s*, 1096*s*, 1077*s*, 1045*m*, 1012*m*, 1004*m*, 989*m*, 959*w*, 919*w*, 898*w*, 878*w*, 853*w*, 841*m*. – NMR.: 1,8–2.9 (*m*, 2 H–C(5) and 2 H–C(6)); 3.38 (*s*, H_3CN–C(7)); 3.68, 3.88, 3.92 and 3.96 (4*s*, 4×3 H, OCH_3); 4.82 (*d*×*d*, $J = 11$ and 7, H–C(7)); 6.51 (*s*, H–C(4)); 6.74 (*d*, $J = 11$, H–C(11)); 7.02 (*s*, H–C(8)); 7.27 (*d*, $J = 11$, H–C(12)). – MS.: 467 (M^+, 75), 448 (3), 452 (3), 439 (74), 424 (9), 312 (100).

$C_{23}H_{24}F_3NO_6$ (467.39) Calc. C 59.10 H 5.17 N 2.99% Found C 58.84 H 5.22 N 2.86%

N-*Trifluoroacetylisodemecolcine* (**11**). *N*-Trifluoroacetylisocolchicine (**14**) (1,1 mmol, 0.5 g), CH_3I (1 ml) and K_2CO_3 (0.76 g) were stirred at RT. until disappearance of the starting material (TLC.-monitoring). For the work-up see preparation of **10**. Yield: 503 mg (97%) of **11** as a foam. $[\alpha]_D^{20} = -290°$ ($c = 0{,}485$, $CHCl_3$). – UV.: 245 (29,200), 343 (18,200). – IR.: 3680*w*, 3450*w* (br.), 1692*s*, 1618*s*, 1596*m*, 1565*s*, 1486*m*, 1458*m*, 1404*m*, 1375*w*, 1353*m*, 1326*s*, 1313*m*, 1302*w*, 1149*s*, 1140*s*, 1092*s*, 1072*m*, 1041*w*, 1000*m*, 983*m*, 954*w*, 913*w*, 866*w*, 838*w*. – NMR.: 2.0–3.0 (*m*, 2 H–C(5) and 2 H–C(6)); 3.39 (*s*, H_3CN–C(7)); 3.68 (*s*, 3 H, OCH_3) and 3.90 (br. *s*, 9 H, OCH_3); 4.78 (*m*, H–C(7)); 6.51 and 6.54 (2*s*, 2×1 H, H–C(4) and H–C(8)); 7.09 and 7.39 (2*d*, $J = 13$, H–C(11) and H–C(12)). – MS.: 467 (M^+, 68), 452 (5), 439 (56), 424 (18), 370 (15), 340 (35), 312 (100), 297 (68), 281 (52).

$C_{23}H_{24}F_3NO_6$ (467.39) Calc. C 59.10 H 5.17 N 2.99% Found C 58.62 H 5.15 N 2,97%

Demecolceine (**9**). A mixture of **10** and **11** (11 mmol, 5.14 g) dissolved in H_2O (100 ml) and H_2SO_4 conc. (20 ml) was heated for 5 h at 95–105°. The cold solution was brought to pH ~ 6 with solid Na_2CO_3 and extracted several times with $CHCl_3$. The oily residue was dissolved in hot MeOH from which yellow crystals of **9** separated. Yield: 2.22 g (56%). Additional 0.4 g of **9** was obtained from the mother liquor (total yield 66%). M.p. 130–134°; $[\alpha]_D^{20} = -228°$ ($c = 1.24$, $CHCl_3$). – UV.: 244 (27,500), 350 (16,900). – IR.: 3645*m*, 3480*m* (br.), 1617*s*, 1601*s*, 1545*s*, 1488*s*, 1475*s*, 1453*s*, 1407*s*, 1348*s*, 1323*s*, 1309*m*, 1277*s*, 1141*s*, 1123*s*, 1094*s*, 1065*m*, 1039*m*, 1016*s*, 979*w*, 945*w*, 922*w*, 861*w*, 844*w*. – NMR.: 1.82 (1 H) and 2.0–2.6 (3 H) (2*m*, 2 H–C(5) and 2 H–C(6)); 2.25 (*s*, H_3CN–C(7)); 3.32 (*m*, H–C(7)); 3.61 (*s*, 3 H, OCH_3) and 3.92 (*s*, 6 H, OCH_3); 4.1–4.8 (br., 2 H, HN–C(7) and HO–C(10)); 6.54 (*s*, H–C(4)); 7.28 and 7.54 (2*d*, $J = 11$, H–C(11) and H–C(12)); 8.03 (*s*, H–C(8)). – MS.: 357 (M^+, 39), 342 (21), 326 (20), 207 (100).

$C_{20}H_{23}NO_5$ (357.38) Calc. C 67.21 H 6.48 N 3.91% Found C 67.57 H 6.54 N 3.49%

Demecolcine (**2**) *by hydrolysis of* N-*trifluoroacetyldemecolcine* (**10**). A mixture of K_2CO_3 (0.5 g), acetone (10 ml), H_2O (10 ml) and **10** (2.7 mmol, 1.26 g) was heated on an oil bath at 60°. After the starting material had disappeared (TLC.-monitoring), the reaction mixture was diluted with brine and extracted several times with $CHCl_3$. The crude product was filtered on SiO_2 ($CHCl_3$/MeOH 9:1) to give 0.99 g (quantitative yield) of demecolcine (**2**). M.p. 183–185° (from ethyl acetate/ether); $[\alpha]_D^{20} = -123.5°$ ($c = 0.995$, $CHCl_3$). – UV.: 243 (30,200), 350 (16,300). – IR.: 3690*w*, 3450*w* (br.), 1619*s*, 1595*s*, 1565*s*, 1489*s*, 1467*s*, 1451*m*, 1435*m*, 1400*s*, 1351*s*, 1324*s*, 1288*m*, 1143*s*, 1099*s*, 1045*w*, 1024*m*, 1010*m*, 911*m*, 925*w*, 844*m*. – NMR.: 1.38 (br., HN–C(7)); 1.60 (1 H) and 1.9–2.7 (3 H) (2*m*, 2 H–C(5) and 2 H–C(6)); 2.24 (*s*, H_3CN–C(7)); 3.26 (*m*, 4 main lines, H–C(7)); 3.62, 3.90, 3.92 and 4.00 (4*s*, 4×3 H, OCH_3); 6.52 (*s*, H–C(4)); 6.77 (*d*, $J = 11$, H–C(11)); 7.22 (*d*, $J = 11$, H–C(12)); 7.68 (*s*, H–C(8)). – MS.: 371 (M^+, 89), 356 (20), 342 (38), 340 (30), 328 (27), 314 (28), 312 (62), 299 (22), 297 (25), 282 (21), 207 (100).

$C_{21}H_{25}NO_5$ (371,41) Calc. C 67.91 H 6.77 N 3.77% Found C 67.62 H 6.74 N 3.38%

Isodemecolcine (**12**) *by hydrolysis of* N-*trifluoroacetylisodemecolcine* (**11**). Compound **11** (0.83 mmol, 387 mg) was treated in the same way as **10**. After work-up and filtration on SiO_2 282 mg (91%) of isodemecolcine (**12**) were obtained. M.p. 143–145° (from ethyl acetate/ether); $[\alpha]_D^{20} = -255°$ ($c = 1.085$, $CHCl_3$). – UV.: 247 (33,100), 344 (19,300). – IR.: 3680*w*, 3400*w* (br.), 1615*s*, 1599*m*, 1559*s*, 1488*m*, 1463*m*,

1455*m*, 1403*m*, 1345*m*, 1321*m*, 1304*w*, 1163*m*, 1139*s*, 1095*s*, 1062*w*, 1038*w*, 1002*w*, 988*m*, 919*w*, 854*w*, 841*w*. – NMR.: 1.50 (br., HN–C(7)); 1.88 (1 H) and 2.0–2.6 (3 H) (2*m*, 2 H–C(5) and 2 H–C(6)); 2.27 (*s*, H_3CN–C(7)); 3.32 (*m*, 4 main lines, H–C(7)); 3.64 (3 H), 3.92 (6 H) and 6.02 (3 H) (3*s*, OCH_3); 6.55 (*s*, H–C(4)); 7.13 and 7.37 (2*d*, $J = 12$, H–C(11) and H–C(12)); 7.85 (*s*, H–C(8)). – MS.: 371 (M^+, 100), 356 (50), 354 (39), 343 (7), 340 (36), 328 (16), 312 (36), 297 (15), 207 (36).

Demecolcine (**2**) *and isodemecolcine* (**12**) *from demecolcine* (**9**). Compound **9** (1.73 mmol, 619 mg) suspended in a mixture of MeOH and ether, was treated with an excess of an ethereal solution of diazomethane. After the starting material had disappeared (*ca.* 15 min, TLC.), the solvent was evaporated and the oily residue (quantitative yield) partly separated by 2 chromatographies on silica gel ($CHCl_3$/MeOH 97:3) to give 159 mg **12**, 246 mg **2** and a mixture of **2** and **12**.

N-*Methyldemecolcine* (**3**) was prepared following the procedure of *Ueno* [12]. M.p. 206–208° (from ethyl acetate/ether); $[\alpha]_D^{20} = -111°$ ($c = 1.78$, $CHCl_3$). – UV.: 245 (32,800), 353 (17,100). – IR.: 1615*m*, 1590*s*, 1560*s*, 1487*m*, 1464*m*, 1398*m*, 1359*w*, 1345*m*, 1326*w*, 1313*m*, 1281*m*, 1138*s*, 1093*s*, 1011*m*, 999*m*, 986*w*, 898*w*. – NMR.: 1.74 (1 H) and 1.9–2.6 (3 H) (2*m*, 2 H–C(5) and 2 H–C(6)); 2.12 (*s*, 6 H, $(H_3C)_2N$–C(7)); 2.68 (*m*, 4 main lines, H–C(7)); 3.60, 3.90, 3.93 and 3.98 (4*s*, 4×3 H, OCH_3); 6.51 (*s*, H–C(4)); 6.76 (*d*, $J = 11$, H–C(11)); 7.24 (*d*, $J = 11$, H–C(12)); 8.09 (*s*, H–C(8)). – MS.: 385 (M^+, 100), 370 (27), 357 (36), 356 (50), 354 (27), 342 (73), 326 (73), 314 (45), 313 (50), 312 (73).

$C_{22}H_{27}NO_5$ (385.43) Calc. C 68.55 H 7.05 N 3.63% Found C 68.34 H 7.05 N 3.67%

Speciosine (**4**) was prepared following the procedure of *Ramage* [7] and obtained as amorphous material. Crystallization from ethyl acetate was achieved after seeding the solution with crystals of a sample of speciosine (**4**)[7]. The analytical data are in agreement with those reported [7].

N-*Deacetylcolchicine* (**15**). *N*-Trifluoroacetyl-deacetylcolchicine (**13**) (1.38 mmol, 628 mg) was hydrolyzed in the usual way (see preparation of **2** from **10**). After work-up and filtration on SiO_2 ($CHCl_3$/MeOH 9:1), 378 mg (77%) of *N*-deacetylcolchicine (**15**) were obtained as a foam. $[\alpha]_D^{20} = -152°$ ($c = 1.17$, $CHCl_3$). – UV.: 245 (29,400), 353 (17,200). – IR.: 3400*w* (br.), 1616*s*, 1590*s*, 1561*s*, 1486*s*, 1443*s*, 1430*m*, 1398*m*, 1374*w*, 1348*s*, 1320*m*, 1282*m*, 1154*m*, 1137*s*, 1113*m*, 1092*s*, 1049*w*, 1012*m*, 996*m*, 985*m*, 915*w*, 898*w*, 862*w*, 839*m*, – NMR.: 1.0–1.9 and 1.9–2.6 (2*m*, 2 H–C(5), 2 H–C(6), H–C(7) and H_2N–C(7)); 3.64 (3 H), 3.88 (6 H) and 3.98 (3 H) (3*s*, OCH_3); 6.52 (*s*, H–C(4)); 6.77 (*d*, $J = 11$, H–C(11)); 7.17 (*d*, $J = 11$, H–C(12)); 7.72 (*s*, H–C(8)). – MS.: 357 (100), 329 (21), 328 (22), 312 (71), 298 (77).

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