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TWO TRIOXYGENATED PHENETHYLISOQUINOLINE ALKALOIDS FROM *COLCHICUM SZOVITSII*

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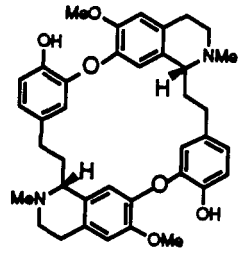
ABSTRACT.—The bulbs of *Colchicum szovitsii* of Turkish origin produce the phenethylisoquinolines (+)-colchiethanamine [**2**] and (+)-colchiethine [**3**].

The well-characterized hexaoxygenated bisphenethylisoquinoline alkaloid (−)-melanthioidine [**1**], present in *Androcymbium melanthioides* (Liliaceae) (1), is possibly formed in nature by phenolic oxidative coupling of two identically substituted trioxygenated phenethylisoquinolines. The monomer in question should be dioxygenated in ring A and monooxygenated in ring C. At the initiation of the present work, four monomeric phenethylisoquinolines were known, namely (−)-autumnaline (2), (−)-isoautumnaline (2), (+)-dysoxyline (3), and (+)-homolaudanosine (3). Interestingly, all four are either dioxygenated or trioxygenated in ring C, and thus bear no direct relationship to the putative precursor for (−)-melanthioidine [**1**].

We now describe two new phenethylisoquinolines which are, indeed, dioxygenated in ring A and monooxygenated in C.

The bulbs of *Colchicum szovitsii* Fish. et Mey. (Liliaceae) are known to produce a variety of colchicine and homomorphinandienone alkaloids (4). We have found that the bulbs of *C. szovitsii* of Turkish origin also produce the phenethylisoquinolines (+)-colchiethanamine [**2**] and (+)-colchiethine [**3**].



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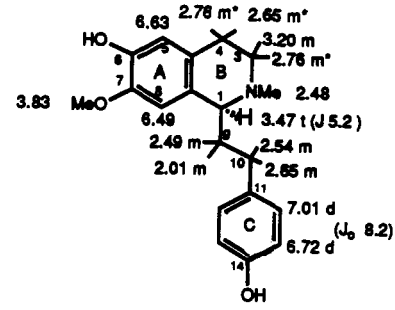

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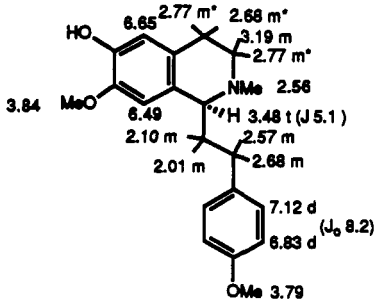

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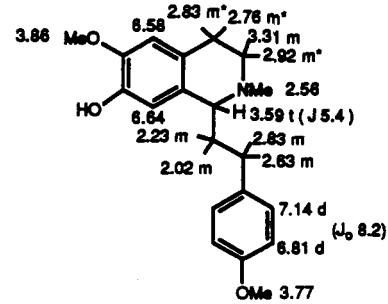

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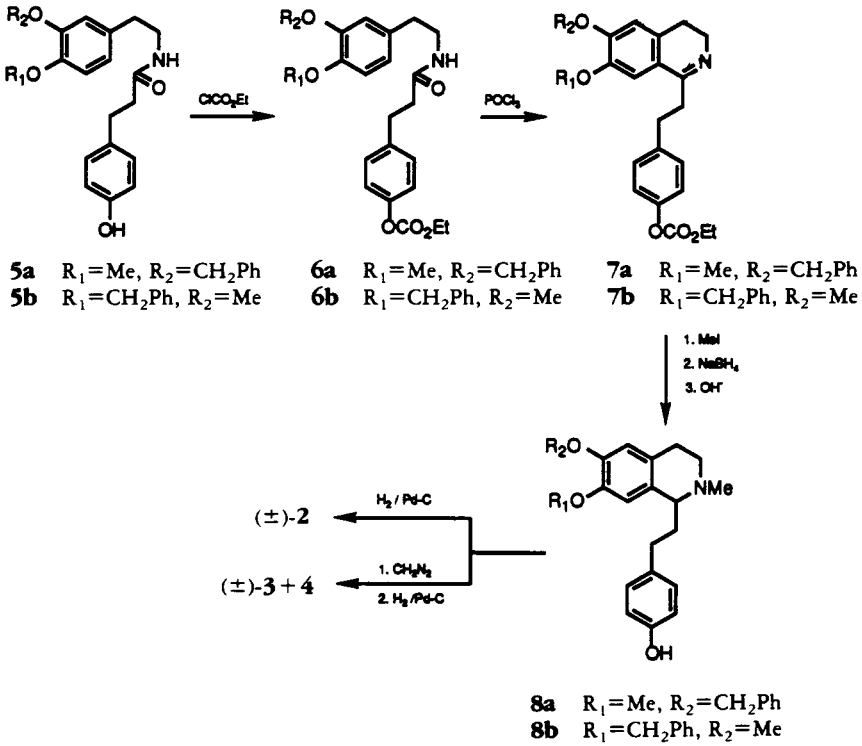
The ir spectrum of (+)-colchiethanamine [**2**], $C_{19}H_{23}NO_3$, showed a broad hydroxyl absorption, while the uv spectrum underwent a bathochromic shift in base, denoting the presence of at least one phenolic function.

The mass spectrum displayed a small molecular ion *m/z* 313 and base peak *m/z* 192, representing rings A and B of the alkaloid.

The ^{1}H-nmr spectrum in $CDCl_3$ at 360 MHz is summarized around structure **2**. Chemical shift assignments were confirmed through appropriate spin decoupling and nOe experiments (see Experimental).

In order to confirm the assigned structure, the total synthesis of (±)-colchiethanamine was carried out via a classical route as shown in Scheme 1, i.e., through the sequence **5a**→**6a**→**7a**→**8a**→**2**. The spectral data for the synthetic (±)-colchiethanamine were identical with those of the natural product **2**.



5a R_1=Me, R_2=CH_2Ph **6a** R_1=Me, R_2=CH_2Ph **7a** R_1=Me, R_2=CH_2Ph
5b R_1=CH_2Ph, R_2=Me **6b** R_1=CH_2Ph, R_2=Me **7b** R_1=CH_2Ph, R_2=Me

8a R_1=Me, R_2=CH_2Ph
8b R_1=CH_2Ph, R_2=Me

SCHEME 1.

The uv, ir, and ms spectra of (+)-colchiethine [**3**], $C_{20}H_{25}NO_3$, our second new alkaloid, were very close to those of (+)-colchiethanamine [**2**]. The mass spectrum again showed base peak *m/z* 192 and a very small molecular ion *m/z* 327, suggesting the presence of a second methoxyl group in place of a hydroxyl. This was confirmed by the nmr spectrum, which showed two methoxyl singlets, one at δ 3.79 and the other at 3.84. In order to elucidate the complete structure of (+)-colchiethine, and in particular the positions of the two methoxyl groups and the hydroxyl function, the total syntheses of the two isomers (±)-[**3**] and (±)-[**4**] were carried out as shown in Scheme 1, following the sequences **8a**→**3** and **5b**→**6b**→**7b**→**8b**→**4**. The chemical shifts for **3** and **4** are given around the respective structures. The spectral data for our second alkaloid, (+)-colchiethine, corresponded to those for synthetic isomer **3**.

The absolute configurations for both (+)-colchiethanamine [**2**] and (+)-col-

chiethine [**3**] were indicated by their positive specific rotations, which derive from their *S* configurations (5).

While (+)-colchiethanamine [**2**] and (+)-colchiethine [**3**] are the first phenethylisoquinolines dioxygenated in ring A and only monooxygenated in ring C, it is doubtful that they bear a direct relationship to the presumed biogenetic precursor for (−)-melanthioidine [**1**]. In the first place, a phenethylisoquinoline of the *R* configuration is required as the building block of **1**, whereas (+)-**2** and (+)-**3** have the *S* configuration. Secondly, the (−)-melanthioidine precursor demands a phenol at C-7 and a methoxyl at C-6, while (+)-**2** and (+)-**3** have the opposite arrangement, with the phenol at C-6 and the methoxyl at C-7.

EXPERIMENTAL

PLANT COLLECTION, EXTRACTION, AND ALKALOID ISOLATION.—The bulbs of *C. szovitsii* (14.2 kg) were collected in February 1986 at Burdur, in Bagsaray township, Turkey. A voucher specimen was deposited in the Herbarium of the Department of Pharmacognosy, Faculty of Pharmacy, Ege University. The plant was dried, powdered, and extracted with cold EtOH. The concentrated extract was treated with 5% HCl and filtered. The acid solution was basified with NH_4OH and extracted with $CHCl_3$. Solvent evaporation afforded a dark residue (5 g) that was chromatographed over Si gel using a $CHCl_3$/MeOH gradient for elution. Final purification was by tlc on Si gel glass plates using $CHCl_3$-MeOH (10:1) as solvent system. Nmr spectra were obtained at 360 MHz in $CDCl_3$ solution.

(+)-COLCHIETHANAMINE [**2**].—Weight 4 mg; $[\alpha]_D$ +10° (c = 0.2, MeOH); uv λ max (MeOH) 223, 282 nm (log ε 3.98, 3.49); λ max (MeOH-OH^-) 243, 296 nm (log ε 4.10, 3.71); ir ν max ($CHCl_3$) 3510, 2980, 1610, 1590, 1500 cm^{-1}; eims *m/z* $[M]^+$ 313 (0.2), 193 (12), 192 (100), 177 (17); hreims *m/z* found 313.1695, calcd 313.1674. Significant ^{1}H-nmr nOe's are H-10 (δ 2.65) to H-12, 8%, H-10′ (δ 2.54) to H-12, 9%; H-9 (δ 2.01) to H-8, 5%; H-9′ (δ 2.49) to H-8, 3%; H-9 (δ 2.01) to H-1, 6%; H-9′ (δ 2.49) to H-1, 10%; H-8 to 7-OMe, 18%; 7-OMe to H-8, 17%; H-4 (δ 2.76) to H-5, 9%; H-1 to NMe, 6%; NMe to H-1, 10%.

(+)-COLCHIETHINE [**3**].—Weight 2 mg; $[\alpha]_D$ +8° (c = 0.2, MeOH); uv λ max (MeOH) 224, 284 nm (log ε 4.08, 3.65); λ max (MeOH-OH^-) 245, 285 nm (log ε 3.76, 3.59); ir ν max ($CHCl_3$) 3500, 3000, 1609, 1500 cm^{-1}; eims *m/z* $[M]^+$ 327 (<0.1), 193 (13), 192 (100), 177 (17); hreims found *m/z* 327.1823, calcd 327.1834. Significant ^{1}H-nmr nOe's are 7-OMe to H-8, 16%; H-13 to 14-OMe, 16%; 14-OMe to H-13, 34%.

N-(3′-BENZYLOXY-4′-METHOXYPHENETHYL)-4-HYDROXYPHENYLPROPIONAMIDE [**5a**].—A mixture of 3-benxyloxy-4-methoxyphenethylamine (3 g, 11.67 mmol) and 4-hydroxyphenylpropionic acid (1.94 g, 11.67 mmol) was heated at 180° for 1.3 h. The product was cooled and chromatographed on a Si gel column to give 3.78 g (80%) **5a**, $C_{25}H_{27}NO_4$, as a syrup: uv λ max (MeOH) 225, 279 nm (log ε 4.33, 3.76); λ max (MeOH-OH^-) 231, 280 nm (log ε 4.29, 3.72); ir ν max ($CHCl_3$) 1658 cm^{-1}; relevant ^{1}H nmr δ 5.10 (s, 2H, OCH_2Ph), 3.86 (s, 3H, OMe); eims *m/z* $[M]^+$ 405 (3), 240 (51), 91 (100).

N-(4′-BENZYLOXY-3′-METHOXYPHENETHYL)-4-HYDROXYPHENYLPROPIONAMIDE [**5b**].—A mixture of 4-benzyloxy-3-methoxyphenethylamine (1.8 g, 7.0 mmol) and 4-hydroxyphenylpropionic acid (1.16 g, 7.0 mmol) was heated at 180° for 1.3 h. The product was cooled and chromatographed on a Si gel column to give 2.04 g of **5b** (85%), $C_{25}H_{27}NO_4$, as white needles: mp 144–145° (MeOH); uv λ max (MeOH) 225, 278 nm (log ε 4.30, 3.75); λ max (MeOH-OH^-) 230, 280 nm (log ε 4.30, 3.70); ir ν max ($CHCl_3$) 1675 cm^{-1}; relevant ^{1}H nmr δ 5.13 (s, 2H, OCH_2Ph), 3.87 (s, 3H, OMe); eims *m/z* $[M]^+$ 405 (3), 240 (48), 91 (100).

N-(3′-BENZYLOXY-4′-METHOXYPHENETHYL)-4-ETHOXYCARBONYLOXYPHENYLPROPIONAMIDE [**6a**].—To a stirred solution of amide **5a** (3 g, 7.40 mmol) and triethylamine (6 ml) in $CHCl_3$ (100 ml) was added dropwise with cooling a solution of ethyl chlorocarbonate (0.8 g, 7.40 mmol) in $CHCl_3$ (5 ml). The mixture was stirred for 2 h at room temperature, washed with H_2O (25 ml), 10% HCl (2 × 25 ml), and H_2O again (2 × 25 ml), and dried (Na_2SO_4). Evaporation of the solvent left amide **6a** (3.35 gr, 95%), $C_{28}H_{31}NO_6$, as white prisms: mp 118–119° (MeOH); uv λ max (MeOH) 227, 279 nm (log ε 4.10, 3.60); ir ν max ($CHCl_3$) 1660, 1756 cm^{-1}; ^{1}H nmr δ 5.13 (s, 2H, OCH_2O), 4.32 (q, 2H, OCH_2Me), 3.88 (s, 3H, OMe), 1.39 (t, 3H, OCH_2CH_3); eims *m/z* $[M]^+$ 477 (2), 240 (54), 91 (100).

N-(4′-BENZYLOXY-3′-METHOXYPHENETHYL)-4-ETHOXYCARBONYLOXYPHENYLPROPIONAMIDE [**6b**].—The same procedure as above was followed to afford **6b** (90%), $C_{28}H_{31}NO_6$, as white needles: mp

124–125° (MeOH); uv λ max (MeOH) 226, 276 nm (log ε 4.41, 4.09); ir ν max ($CHCl_3$) 1660, 1709 cm^{-1}; relevant ^1H nmr δ 5.13 (s, 2H, OCH_2Ph), 4.28 (q, 2H, OCH_2Me), 3.86 (s, 3H, OMe), 1.38 (t, 3H, OCH_2CH_3); eims *m/z* $[M]^+$ 477 (3), 240 (63), 91 (100).

6-BENZYLOXY-1-(4′-ETHOXYCARBONYLOXYPHENETHYL)-3,4-DIHYDRO-7-METHOXYISOQUINOLINE [**7a**].—A mixture of amide **6a** (3 g, 6.28 mmol), phosphorus oxychloride (3.85 g, 25 mmol), and dry C_6H_6 (40 ml) was heated under reflux for 1 h. After evaporation of C_6H_6, a solution of the residue in $CHCl_3$ was washed with NaOH (2 N) and H_2O until neutral. Evaporation of the dried solution left 2.22 g (77%) of **7a**, $C_{28}H_{29}NO_5$, as a yellow syrup: uv λ max (MeOH) 240, 307, 354 nm (log ε 4.86, 4.77, 4.76); λ max (MeOH-OH^-) 238, 273, 307 nm (log ε 4.85, 4.74, 4.68); ir ν max ($CHCl_3$) 1645, 1756 cm^{-1}; ^1H nmr δ 5.18 (s, 2H, OCH_2Ph), 4.31 (q, 2H, OCH_2Me), 3.88 (s, 3H, OMe), 1.39 (t, 3H, OCH_2CH_3); eims *m/z* $[M]^+$ 459 (49), 368 (30), 91 (100).

7-BENZYLOXY-1-(4′-ETHOXYCARBONYLOXYPHENETHYL)-3,4-DIHYDRO-6-METHOXYISOQUINOLINE [**7b**].—The same procedure as above was followed to afford **7b** (80%), $C_{28}H_{29}NO_5$, as a yellow syrup: uv λ max (MeOH) 228, 272, 307, 361 nm (log ε 4.66, 4.16, 4.17, 3.63); λ max (MeOH-OH^-) 229, 272, 306 nm (log ε 4.72, 4.24, 4.13); iv ν max ($CHCl_3$) 1642, 1756 cm^{-1}; relevant ^1H nmr δ 5.16 (s, 2H, OCH_2Ph), 4.32 (q, 2H, OCH_2Me), 3.94 (s, 3H, OMe), 1.39 (t, 3H, OCH_2CH_3); eims *m/z* $[M]^+$ 459 (5), 368 (100), 91 (52).

6-BENZYLOXY-1,2,3,4-TETRAHYDRO-1-(4′-HYDROXYPHENETHYL)-7-METHOXY-2-METHYLISOQUINOLINE [**8a**].—A mixture of the 3,4-dihydroisoquinoline **7a** (2 g, 4.35 mmol) and MeI (20 ml) was set aside at room temperature for 10 h. Evaporation of the excess reagent left a yellow powder which was dissolved in MeOH (70 ml) and H_2O (0.3 ml) and treated with an excess of $NaBH_4$ (800 mg). After 2 h of stirring at room temperature, 2 N methanolic KOH (10 ml) was added, and the mixture was heated under reflux for 30 min. Workup provided **8a** (1.22 g, 70%), $C_{26}H_{29}NO_3$, as a yellow syrup: uv λ max (MeOH) 227, 282 nm (log ε 4.55, 4.05); λ max (MeOH-OH^-) 234, 286 nm (log ε 4.49, 4.06); relevant ^1H nmr δ 5.11 (s, 2H, OCH_2Ph), 3.85 (s, 3H, OMe), 2.46 (s, 3H, NMe); eims *m/z* $[M]^+$ 403 (<0.1), 282 (100), 191 (38).

7-BENZYLOXY-1,2,3,4-TETRAHYDRO-1-(4′-HYDROXYPHENETHYL)-6-METHOXY-2-METHYLISOQUINOLINE [**8b**].—The same procedure as above was followed to afford **8b** (80%), $C_{26}H_{29}NO_3$, as a yellow syrup: uv λ max (MeOH) 225, 282 nm (log ε 4.32, 3.85); λ max (MeOH-OH^-) 235, 285 nm (log ε 4.23, 4.84); eims *m/z* $[M]^+$ 403 (<1), 282 (100), 191 (38).

(±)-COLCHIETHANAMINE [(±)-**2**].—A solution of **8a** (1 g, 2.48 mmol) in EtOAc (50 ml) was hydrogenated using 125 mg of 10% Pd/C. Workup afforded 686 mg (88%) (±)-colchiethanamine [(±)-**2**]. This material was spectrally (nmr, uv, ir, ms) identical with the natural compound (+)-colchiethanamine.

(±)-COLCHIETHINE [(±)-**3**].—A solution of **8b** (0.2 g, 0.5 mmol) in MeOH (25 ml) was treated with excess ethereal CH_2N_2 for 12 h. Evaporation and workup provided the corresponding *O*-methyl ether, which was hydrogenated as described above to give (±)-**3** (80%). The nmr, uv, ir, and ms spectra were identical with those of the natural compound (±)-colchiethine.

1,2,3,4-TETRAHYDRO-7-HYDROXY-1-(4′-METHOXYPHENETHYL)-6-METHOXY-2-METHYLISOQUINOLINE [**4**].—The same procedure as above was followed to give **4** (72%), $C_{20}H_{25}NO_3$: uv λ max (MeOH) 225, 284 nm (log ε 4.35, 3.90); λ max (MeOH-OH^-) 244, 285, 296 nm (log ε 3.94, 3.85, 3.80); eims *m/z* $[M]^+$ 327 (0.14), 193 (12), 192 (100), 177 (10). ^1H-nmr nOe's 14-OMe to H-13, 24%; H-13 to 14-OMe, 26%; H-8 to H-1, 4%; H-1 to H-8, 6%; H-1 to NMe, 3%; NMe to H-1, 7%; H-5 to 6-OMe, 16%; 6-OMe to H-5, 13%; H-4 (δ 2.83) to H-5, 9%; H-5 to H-4 (δ 2.83), 3%.

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