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SYNTHESIS OF TELITOXINE

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ABSTRACT.—The structure of telitoxine [**1**], an azafluoranthene alkaloid of *Telitoxicum peruvianum* (Menispermaceae), was confirmed by an unambiguous synthesis involving thermolysis of an isolated triazinium salt.

Telitoxine [**1**] (1) is one of the small number of indeno[1,2,3-ij]isoquinoline (azafluoranthene) alkaloids (2), and the second one to be isolated that has a phenolic function [the first being norrufescine [**2**] (3,4)]. Although structure **1** was suggested (1) as most likely for telitoxine, confirmation by unambiguous synthesis was not obtained. We now report the synthesis of **1** by the general method that was successful for preparation of norrufescine [**2**] (5) and of 5,6-dimethoxyindenol[1,2,3-ij]isoquinoline [**3**] (6) [incorrectly referred to as triclisine (7)].

RESULTS AND DISCUSSION

The synthesis of telitoxine [**1**] is outlined in Scheme 1. Oxidation of 2-nitro-5-benzyloxybenzaldehyde (8) with $NaClO_2$ (9) gave in 73% yield the known 2-nitro-5-benzyloxybenzoic acid [**4**] (10). Condensation of **4**, via the acid chloride, with 3,4-dimethoxyphenethylamine [**5**] gave a 93% yield of the amide **6**. Bischler-Napieralski cyclization of **6** with $POCl_3$/MeCN produced the dihydroisoquinoline **7** (94% yield), which underwent simultaneous debenzylation and reduction of the nitro group on hydrogenation in ethanolic HCl, affording the iminoaminophenol, isolated as the crystalline *bis* hydrochloride **8** in 72% yield. Catalytic hydrogenation of **7** in absence of acid or reduction of **7** with hydrazine and Pd/C gave the benzyloxyamine **9** as the primary product.[1]

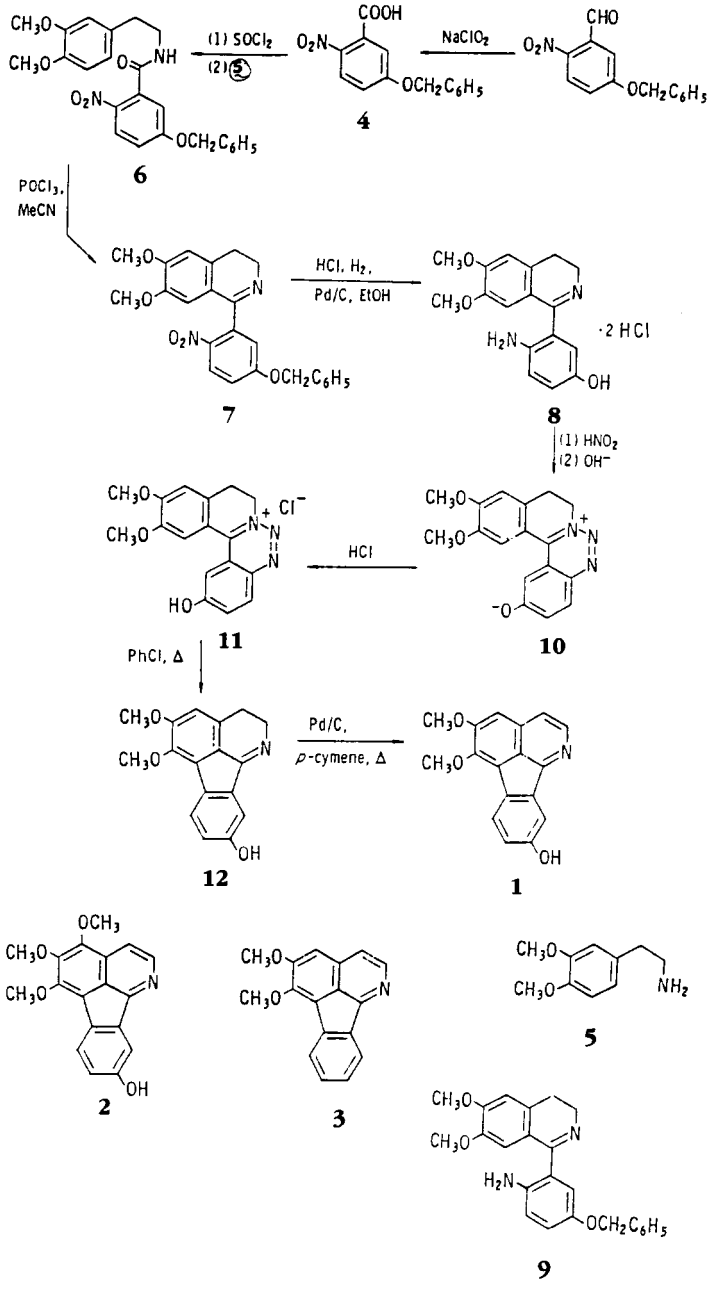
Diazotization of **8** in 1 *N* H_2SO_4, followed by adjustment of the reaction to pH 8 and extraction with $CHCl_3$ gave the triazinium dipole **10** (80% yield); treatment of the extract with conc. HCl and crystallization from $CHCl_3$/MeOH gave dark orange crystals of the triazinium chloride **11**, mp 213-215° (dec.). Thermolysis of **11** in chlorobenzene produced dihydrotelitoxine [**12**], mp 250-251° (dec.), in 28% yield, accompanied by a small amount of telitoxine [**1**]. Dehydrogenation of **12** gave a 45% yield of **1**, mp 269-271° (dec.), identical (ms, ^1H nmr, tlc) to isolated telitoxine (1).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points are uncorrected. Ir spectra were recorded on a Perkin-Elmer 1420 instrument and uv spectra were measured on a Beckman DU-50 or Hewlett-Packard 8450A UV-Vis spectrophotometer. ^1H-nmr spectra were recorded at 200 or 360 MHz, as noted, on a WP 200 or WM 360 Bruker spectrometer; chemical shifts are in ppm. Mass spectra were recorded on a Kratos-MS 9/50 mass spectrometer at 70 eV.

2-NITRO-5-BENZYLOXYBENZOIC ACID [**4**].—2-Nitro-5-benzyloxybenzaldehyde (8,12) (51.4 g) was partially dissolved at room temperature in a mixture of *t*-BuOH (200 ml), H_2O (100 ml), and sulfamic acid (24 g). A solution of $NaClO_2$ (23 g [Ventron, 80%]) in H_2O (200 ml) was added dropwise with stirring over 30 min. The temperature rose to 65° and all solid dissolved. The reaction was stirred an addi-

[1]Similar selectivity has been observed in hydrazine-Raney nickel reductions of benzyloxy-substituted aromatic nitro compounds (11).



SCHEME 1

tional 60 min without cooling, the temperature gradually falling to 35°. The mixture was extracted with Et_2O (500 ml), and the organic layer was washed several times with dilute $NaHCO_3$ solution until no more acid was removed, adding H_2O as necessary to dissolve the only slightly soluble Na salt. Acidification of the aqueous extracts and filtration yielded **4** (36.8 g, 67%), mp 141-143°, unchanged by recrystallization of a sample from $CHCl_3$/hexane [reported 143-144° (10)].

N-(3,4-DIMETHOXYPHENETHYL)-2-NITRO-5-BENZYLOXYBENZAMIDE [**6**].—A solution of **4** (27 g) in $SOCl_2$ (36 ml) was refluxed 45 min. The $SOCl_2$ was stripped on a rotary evaporator, some $CHCl_3$ [note: all $CHCl_3$ was passed through neutral grade 1 alumina to remove EtOH] was added, and the solvent was again removed. The residual acid chloride, dissolved in $CHCl_3$ (200 ml) was added dropwise over 10 min with vigorous stirring to a mixture of 3,4-dimethoxyphenethylamine [**5**] (18 g) in $CHCl_3$ (250 ml),

and K_2CO_3 (29 g) in H_2O (350 ml). The reaction was stirred 30 min, and the organic layer was separated, washed with dil. HCl, dil. K_2CO_3, dried ($MgSO_4$), and evaporated. Crystallization (C_6H_6/$CHCl_3$/hexane) gave 40.7 g (93%), mp 140-146°. A sample purified by column chromatography on neutral alumina in $CHCl_3$ and recrystallization from C_6H_6/hexane had mp 140-142°.

^{1}H nmr (360 MHz, $CDCl_3$) δ 8.11 (1H, d, J=9.1 Hz), 7.02 (1H, dd, J=9.1 and 2.7 Hz), 6.93 (1H, d, J=2.7 Hz), 7.40 (5H, benzyl spike), 6.81 (s, 3 aromatic H), 5.68 (1H, broad s, NH), 5.13 (2H, s), 3.88 (3H, s), 3.85 (3H, s), 3.74 (2H, q, J=6.7 Hz), 2.93 (2H, t, J=6.7 Hz); ir 1640 (C=O), 3290 cm-1 (N-H); hrms *m/z* calcd. for $C_{24}H_{24}N_2O_6$ 436.1626, found 436.1625.

1-(2-NITRO-5-BENZYLOXYPHENYL)-6,7-DIMETHOXY-3,4-DIHYDROISOQUINOLINE [**7**].—Amide **6** (33.4 g) was dissolved in 180 ml dry MeCN; $POCl_3$ (30 ml) was added, and the reaction was refluxed 3h. After cooling, the mixture was poured slowly (vigorous exotherm) into a mixture of H_2O (300 ml) and conc. NH_4OH (300 ml). The product rapidly precipitated. After 30 min cooling, the product was filtered, washed with H_2O, dried, and purified by column chromatography on neutral alumina in $CHCl_3$ and recrystallization from $CHCl_3$/hexane. Yield 30.1 g (94%), mp 174-176°; ^{1}H nmr (360 MHz, $CDCl_3$) δ 8.15 (1H, d, J=8 Hz), 7.40 (5H, m), 7.11 (1H, d, J=3 Hz), 7.10 (1H, dd, J=3 & 8 Hz), 6.77 (1H, s), 6.30 (1H, s), 5.19 (2H, s), 3.87 (2H, t, J=7.5 Hz), 2.84 (2H, t, J=7.5 Hz), 3.93 (3H, s), 3.63 (3H, s); hrms *m/z* calcd for $C_{24}H_{22}N_2O_5$ 418.1521, found 418.1534.

1-(2-AMINO-5-HYDROXYPHENYL)-6,7-DIMETHOXY-3,4-DIHYDROISOQUINOLINE DIHYDROCHLORIDE [**8**].—Compound **7** (15 g) was dissolved in 95% EtOH (200 ml) and conc. HCl (20 ml), 10% Pd/C (0.5 g) was cautiously added, and the reaction was hydrogenated at 40 psi for 3 h at 50°. Filtration and evaporation of solvent yielded a yellow gum that solidified on standing. The product was slurried with Et_2O containing a small amount of EtOH and filtered, yielding tan-yellow crystals of the *bis*-hydrochloride. Recrystallization (EtOH/Et_2O) gave 9.6 g (72%), mp 166-168° (darkening gradually with decomposition). ^{1}H nmr of **8** free amine (360 MHz, $CDCl_3$) δ 6.79 (1H, s), 6.76 (1H, s), ~6.77 (1H, unresolved), 6.71 (1H, d, J=2.7 Hz), 6.62 (1H, d, J=8.6 Hz), 3.95 (3H, s), 3.78 (2H, t, J=7 Hz), ~3.78 (2H, broad s, D_2O-exchanged, NH_2), 3.72 (3H, s), 2.77 (2H, t, J=7 Hz), 1.74 (1H, s, D_2O-exchanged, OH); hrms *m/z* calcd for $C_{17}H_{18}N_2O_3$ 298.1311, found 298.1318.

1-(2-AMINO-5-BENZYLOXYPHENYL)-6,7-DIMETHOXY-3,4-DIHYDROISOQUINOLINE [**9**].—To a partial solution of **7** (21 g) in 95% EtOH (500 ml) was added 85% hydrazine hydrate (10 ml) and then cautiously 10% Pd/C (4 g), and the reaction was warmed gently on the steam bath. After 30 min, N_2 evolution was complete, and the starting material had dissolved. Filtration and cooling gave a precipitate of **9**, which separated completely after addition of some Et_2O, yield 10.8 g (55%). Purification by filtration through alumina in $CHCl_3$ and recrystallization from $CHCl_3$/hexane gave yellow crystals, mp 144-146°. Concentration of the filtrates gave debenzylated material (**8** free base) as a gum [crude yield 5.4 g (36%)].

Spectral data for **9** are: ^{1}H nmr (200 MHz, $CDCl_3$) δ 7.35 (5H, benzyl spike), 6.71-6.91 (5H, unresolved aromatic H), 4.93 (2H, s), 4.70 (2H, broad, NH_2), 3.95 (3H, s), 3.69 (3H, s), 3.82 (2H, t, J=~7 Hz), 2.70 (2H, t, J=~7Hz); hrms *m/z* calcd for $C_{24}H_{24}N_2O_3$ 388.1779, found 388.1782.

8,9-DIHYDRO-2-HYDROXY-11,12-DIMETHOXYISOQUINO [2,1-C] [1,2,3] BENZOTRIAZIN-7-IUM CHLORIDE [**11**].—Compound **8** (0.264 g) was purified as the free base by passage through a short Si gel column with $CHCl_3$/2% MeOH. It was dissolved in 1*N* H_2SO_4 (10 ml), and the solution was cooled to 0° and diazotized by adding 0.130 g $NaNO_2$. The reaction was then basified with 1*N* NaOH to pH 8, and the triazinium dipole was extracted into $CHCl_3$. The $CHCl_3$ extract was washed with distilled H_2O, dried over Na_2SO_4, and evaporated to dryness, yielding 0.208 g (80%). Treatment of the dipole with a small amount of conc. HCl, followed by crystallization from $CHCl_3$/MeOH gave dark orange crystals of **11**, mp 213-215° (dec.); ^{1}H nmr (360 MHz, $CDCl_3$) δ 9.16 (1H, d, J=2.3 Hz), 8.48 (1H, d, J=9.0 Hz), 8.05 (1H, dd, J=9.0 and 2.3 Hz), 7.81 (1H, s), 6.99 (1H, s), 5.01 (2H, t), 4.36 (3H, s), 4.09 (3H, s), 3.36 (2H, t); ir no diazonium band at ~2200 cm-1; uv λ max (EtOH) 266 nm (log ε 4.48), 283 (4.40), 378 (4.33), 489 (4.09); hrms *m/z* calcd for $C_{17}H_{15}N_3O_3$ (M+-HCl) 309.1107, found 309.1127; *Anal.* calcd for $C_{17}H_{16}N_3O_3Cl$ C 59.03, H 4.67, N 12.16, Cl 10.26, found C 58.88, H 4.63, N 12.10, Cl 10.59%.

5,6-DIMETHOXY-2,3-DIHYDROINDENO [1,2,3-IJ] ISOQUINOLIN-9-OL (DIHYDROTELITOXINE) [**12**].—A solution of the triazinium chloride **11** (0.319 g) in chlorobenzene (70 ml) was refluxed 1 h under N_2. Column chromatography on Si gel with $CHCl_3$/2% MeOH and crystallization of the second fraction from $CHCl_3$/MeOH gave dihydrotelitoxine (72 mg, 28%), mp 250-251° (dec.). Traces of telitoxine were also isolated; ^{1}H nmr (200 MHz, $CDCl_3$+CD_3OD) δ 7.60 (1H, d, J=8.2 Hz), 7.10 (1H, d, J=2 Hz), 6.85 (1H, dd, J=8 and 2 Hz), 6.40 (1H, s), 4.06 (2H, t, J=8 Hz), 3.86 (6H, s), 2.73 (2H, t, J=8 Hz); uv λ max (MeOH) 220 nm (log ε 4.23), 225 (4.24), 244 (4.36), 263 (4.62), 281 (4.13), 288 (4.10), 309 sh (3.45), 352 (3.32); hrms *m/z* calcd for $C_{17}H_{15}NO_3$ 281.1047, found 281.1047.

5,6-DIMETHOXYINDENO[1,2,3-IJ]ISOQUINOLIN-9-OL (TELITOXINE) [**1**].—A mixture of **12** (48 mg) and 10% Pd/C (80 mg) in *p*-cymene (70 ml) was refluxed 8 h. After filtration of the mixture, the solvent was evaporated, and the residue was purified by column chromatography on Si gel with $CHCl_3$/2% MeOH as eluent, giving telitoxine [**1**] (21 mg, 45%), mp 269-271° (dec.) [reported 273-275° (1)]; ^1H nmr [360 MHz, $(CD_3)_2CO$] δ 8.52 (1H, d, J=6 Hz), 7.85 (1H, d, J=8 Hz), 7.51-7.52 (2H, m), 7.19 (1H, s), 6.94 (1H, dd, J=8 and 2 Hz), 4.06 (3H, s), 4.05 (3H, s); uv λ max (MeOH) 245 nm (log ε 4.34), 266 sh (3.92), 279 (4.08), 289 (4.07), 300 (4.04), 323 (3.12), 352 (2.89), 370 (3.31)[2]; hrms *m/z* calcd for $C_{17}H_{13}NO_3$ 279.0891, found 279.0896.

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