Journal of Natural Products
Vol. 49, No. 3, pp. 445-448, May-Jun 1986

SYNTHESIS OF PRATORIMINE

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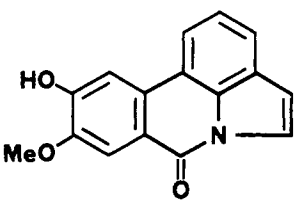
ABSTRACT.—The pyrrolophenanthridone alkaloid pratorimine (**2**) has been synthesized by an unambiguous route.

Pratorimine and pratorinine were first isolated from *Crinum latifolium* and *Crinum pratense* and assigned structures **1** and **2**, respectively, on the basis of ^{1}H-nmr studies (1,2). Furthermore, the synthesis of pratosine (**3**) was described, and its partial demethylation with aqueous piperidine to pratorimine was assumed to involve demethylation of the C(10) methoxyl to produce a compound of structure **1**. Recently we reported revised structures for pratorimine and pratorinine as **2** and **1**, respectively, based on an X-ray diffraction analysis of pratorinine isolated from *Crinum bulbispermum*. The structure of pratorimine was revised on the basis of the identity of the ir spectra of alkaloids isolated from *C. latifolium* and *C. bulbispermum* (3). Ghosal *et al.* (1) appear to have ignored the possibility of demethylation of the C(9) methoxyl group in pratosine (**3**). We therefore decided to settle this structural ambiguity by a synthesis of alkaloid **2**.



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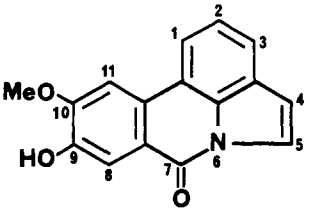

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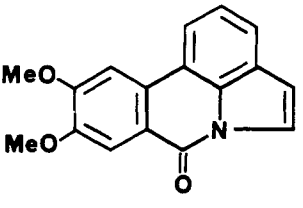
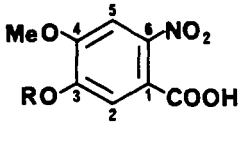


3

RESULTS AND DISCUSSION

Heating methyl 3,4-dimethoxy-6-nitrobenzoate, obtained by methylation and subsequent nitration of veratric acid, with aqueous NaOH gave 3-hydroxy-4-methoxy-6-nitrobenzoic acid (**4**) (4), which was acetylated to give **5**. It has been established that the action of boiling aqueous alkali on 4-nitroveratrole effects exclusively the hydrolysis of the methoxy group in the *p*-position to the nitro group (5). The acid chloride obtained by treatment of **5** with oxalyl chloride was condensed with indoline to afford 1′-(3-acetoxy-4-methoxy-6-nitrobenzoyl)-2′,3′-dihydroindole (**6**) in good yield. The nitroamide **6** appears to exist as two conformers (^{13}C-nmr spectrum) due to restricted rotation. Hydrolysis of **6** gave the corresponding phenol **7**, mp 208-209°. Reduction of the nitro group in **6** using Pd-C and hydrogen gave the amine **8**. Pschorr cyclization of **8** gave the desired phenanthridone **9** in poor yield; the major product was probably the deaminated benzoyl indole as in the case of analogous reactions reported earlier (6,7). Hydrolysis of **9** with methanolic KOH gave the phenol **10**. In an alternative approach, the amides **11** and **12** were prepared with a view to obtain **10** from the phenol **12**. Oxidation of **12** with potassium ferricyanide (8) failed to give the cyclized product. Dehydrogenation of **10** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone afforded **2** which was shown to be identical with pratorimine.



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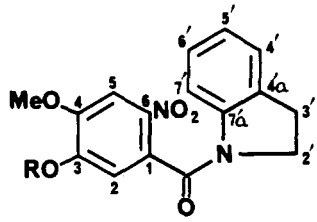

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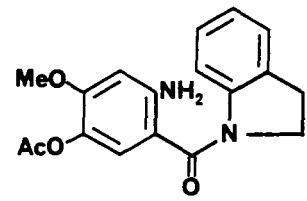

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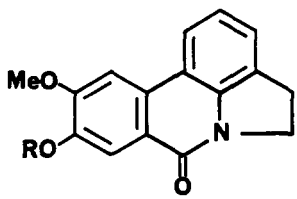

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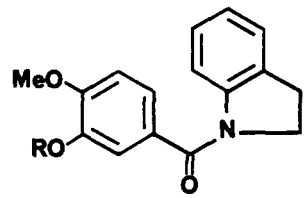

11 R=Ac
12 R=H

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mp's were taken on a microscope hot-stage apparatus and are corrected. Ir spectra were taken on Perkin-Elmer Model 1420 and nmr spectra were recorded on Varian EM-390 90 MHz, JEOL FT models FX-60 and FX-90 Q spectrometers. Chemical shifts are reported in ppm downfield from internal TMS. Mass spectra were obtained by using a Finnegan Quadrupole 4023 spectrometer.

3-HYDROXY-4-METHOXY-6-NITROBENZOIC ACID (**4**).—Methyl-3,4-dimethoxy-6-nitrobenzoate (10 g) was added to 10% NaOH (150 ml) and the yellow-orange solution heated under reflux for 24 h. The mixture was poured over crushed ice, acidified with dilute HCl, the precipitate collected and washed with ice H_2O. The crude acid on crystallization from hot H_2O (50 ml) gave **4** (7.5 g), mp 181-182° [lit. (4), mp 181°]; ir (nujol) 3520, 1640, 1580, 1530 cm^{-1}; ^1H nmr (CD_3COCD_3) δ 7.59 (1H, s, H-5), 7.22 (1H, s, H-2), 7.00 (2H, br, OH), 4.02 (3H, s, OCH_3); ^{13}C nmr (CD_3COCD_3) 166.7 (*C*OOH), 151.4 (C-4), 149.9 (C-3), 141.8 (C-6), 123.0 (C-1), 116.1 (C-2), 108.5 (C-5), 57.0 (OCH_3).

3-ACETOXY-4-METHOXY-6-NITROBENZOIC ACID (**5**).—The carboxylic acid **4** (18 g) was heated with Ac_2O (75 ml) and pyridine (15 ml) at 90° for 2 h. The solution was added to crushed ice, the precipitate collected and crystallized from EtOAc to afford **5** (10.7 g), mp 213-214° (dec.); ir (nujol) 1775, 1700, 1610 cm^{-1}; ^1H nmr (CD_3COCD_3) δ 7.65 (1H, s, H-5), 7.59 (1H, s, H-2), 7.35 (1H, br, *OH*), 4.00 (3H, s, OCH_3), 2.35 (3H, s, $COCH_3$); ^{13}C nmr (CD_3COCD_3+*DMSO-d*$_6$) 168.5 (*C*OCH_3), 165.2 (*C*OOH), 155.1 (C-4), 149.3 (C-3), 142.4 (C-6), 125.7 (C-2), 119.4 (C-1), 109.0 (C-5), 57.4 (OCH_3), 20.3 ($COCH_3$).

1'-(3-ACETOXY-4-METHOXY-6-NITROBENZOYL)-2',3'-DIHYDROINDOLE (**6**).—The carboxylic acid **5** (6 g) in C_6H_6 (60 ml) was heated under reflux with oxalyl chloride (15 ml) for 1 h. The contents were then evaporated under vacuum, and the solidified acid chloride was dissolved in dry Et_2O (150 ml). This solution was added under magnetic stirring to a solution of indoline (5.7 g) in Et_2O (100 ml), during 30 min. The thick precipitate was kept at room temperature for 10 h, collected, and dried (9.8 g). Crystallization from MeOH afforded **6** (7.4 g) as golden yellow plates, mp 176-177°; ir (nujol) 1760, 1640, 1595 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.35 (1H, d, J=8 Hz, H-4'), 7.85 (1H, s, H-5), 7.20 (3H, m, Arm. H), 7.25 (1H, s, H-2), 3.96 (3H, s, OCH_3), 3.76 (2H, t, J=7 Hz, N-CH_2), 3.15 (2H, t, J=7 Hz, Ar-CH_2), 2.31 (3H, s, $COCH_3$). ^{13}C nmr ($CDCl_3$): The major conformer showed: singlets, 167.7 (*C*OCH_3), 163.9 (N-*C*O), 152.0 (C-4), 144.6 (C-3), 142.6 (C-6), 142.3 (C-4'a), 131.8 (C-7'a), 126.5 (C-1); doublets, 127.7, 124.8, 122.4, 117.3, 113.2, 108.6; triplets, 49.5 (N-CH_2), 28.0 (N-CH_2-CH_2); quartets, 56.7 (OCH_3), 20.5 ($COCH_3$). The second conformer showed minor signals at: 152.3, 143.3, 140.7, 133.5, 127.2, 125.8, 124.7, 108.8, 48.3, 26.8. Found: C, 60.52, H, 4.57, N, 7.82. $C_{18}H_{16}N_2O_6$ requires: C, 60.67; H, 4.49; N, 7.86%.

1′-(3-HYDROXY-4-METHOXY-6-NITROBENZOYL)-2′,3′-DIHYDROINDOLE (**7**).—The nitro compound **6** (300 mg) was dissolved in 2.5% methanolic KOH (10 ml) and the deep yellow solution kept at 20° for 2 h. The solution was diluted with H_2O, acidified with dilute HCl, and the precipitate collected. Crystallization from MeOH afforded yellow plates (**7**; 200 mg), mp 208-209°; ^{1}H nmr (CD_3COCD_3) δ 8.21 (1H, d, J=8 Hz, H-4′), 7.8 (1H, s, H-5), 7.2 (3H, m, Arm. H), 7.05 (1H, s, H-2), 4.0 (3H, s, OCH_3), 3.8 (2H, t, J=7 Hz, N-CH_2), 3.15 (2H, t, J=7 Hz, Ar-CH_2). ^{13}C nmr (CD_3SOCD_3): The major conformer showed: singlets, 164.6 (NCO), 153.5 (C-4), 147.8 (C-3), 142.4 (C-6), 135.7 (C-4′a), 132.3 (C-7′a), 127.9 (C-1); doublets; 127.0, 124.9, 124.0, 116.2, 113.4, 108.2; triplets, 48.9 (N-CH_2), 27.4 (NCH_2-CH_2); quartet, 56.3 (OCH_3). The second conformer showed minor signals at: 140.7, 136.4, 133.3, 125.7, 123.3, 112.5, 47.8, 26.2. Found: N, 8.79; $C_{16}H_{14}N_2O_6$ requires: N, 8.91%.

1′-(3-ACETOXY-6-AMINO-4-METHOXYBENZOYL)-2′,3′,-DIHYDROINDOLE (**8**).—The nitrodihydroindole **6** (3 g) in EtOH (210 ml), and 10% Pd-C (300 mg) was hydrogenated in a Parr apparatus at 1 atmosphere until hydrogen uptake was complete. Usual work up gave on crystallization from Et_2O/EtOH the amine **8** (2.4 g), mp 126-127°; ir (nujol) 3480, 3380, 1760, 1630 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 7.36 (1H, d, J=7 Hz, H-4), 7.00 (3H, m, Arm. H), 6.80 (1H, s, H-2), 6.15 (1H, s, H-5), 4.68 (2H, br, NH_2), 3.90 (2H, t, J=7 Hz, N-CH_2), 3.65 (3H, s, OCH_3), 2.95 (2H, t, J=7 Hz, Ar-CH_2), 2.05 (3H, s, $COCH_3$); ^{13}C nmr ($CDCl_3$): singlets, 169.5 (C=O), 168.4 (C=O), 153.9 (C-4), 147.1 (C-6), 142.9 (C-7′a), 132.7 (C-4′a), 130.5 (C-3), 110.5 (C-1); doublets, 127.2, 124.9, 123.8, 123.1, 117.1, 100.4; triplets, 50.9 (CH_2-2′), 28.3 (CH_2-3′); quartets, 55.8 (OCH_3), 20.5 ($COCH_3$). Found: C, 66.18; H, 5.60; $C_{18}H_{18}N_2O_4$ requires: C, 66.26; H, 5.56%.

9-ACETOXY-10-METHOXY-4, 5-DIHYDRO-7-*H*-PYRROLO[3,2,1-de]PHENANTHRIDINE-7-ONE (**9**).—An ice cold solution of $NaNO_2$ (180 mg in 1 ml H_2O) was gradually added during 15 min to a solution of the amine **8** (200 mg) in glacial HOAc (5 ml) and H_2SO_4 (0.5 ml) at 0°. The yellow solution was heated on the steam bath for 3 h. The tarry reaction mixture was diluted with H_2O, extracted with CH_2Cl_2 and the organic layer was washed with ice cold H_2O and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a brown colored gum (80 mg). Three batches of this reaction were combined and chromatographed on a "Chromatotron" on a silica gel covered rotor (9) and eluted with CH_2Cl_2 and CH_2Cl_2 containing 2-5% MeOH. Fractions collected were monitored by uv light. One of the fractions (tlc, $CHCl_3$-5% MeOH Rf 0.3) afforded on crystallization from MeOH, yellowish plates of **9** (25 mg), mp 288-289°; ms, M^+ *m/z* 309.

9-HYDROXY-10-METHOXY-4, 5-DIHYDRO-7-*H*-PYRROLO[3, 2, 1-de]PHENANTHRIDINE-7-ONE (**10**).—The phenanthridine **9** (20 mg) was suspended in MeOH (2 ml) and was heated at 50° for 3 min with 5% methanolic KOH (0.6 ml). The solution was diluted with ice and acidified with 2 N HCl. The MeOH was removed under vacuum and the precipitate collected, washed with H_2O, and dried to give **10** (18 mg). Crystallization from EtOH afforded pale yellow plates, mp 283-284°; ms, M^+ *m/z* 267.

9-HYDROXY-10-METHOXY-7-*H*-PYRROLO-[3,2,1-de]PHENANTHRIDINE-7-ONE (**2**).—The phenol **10** (20 mg) was suspended in dry C_6H_6 (50 ml), and the mixture was heated under reflux with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (400 mg) for 10 h. The mixture was evaporated under vacuum, dissolved in $CHCl_3$, and chromatographed on a "Chromatotron" using a silica gel covered rotor (9). The plate was eluted with $CHCl_3$, and the band (bluish orange in long wave length uv) corresponding to pratorimine was collected. Evaporation and crystallization from MeOH gave colorless crystals of **2** (3 mg), mp 261-262°, mixture mp with pratorimine 262-263°; ms, M^+ *m/z* 265. The ir spectrum (KBr) was superimposable on that of pratorimine.

1′-(3-ACETOXY-4-METHOXYBENZOYL)-2′,3′-DIHYDROINDOLE (**11**).—3-Acetoxy-4-methoxybenzoic acid (1.1 g), C_6H_6 (15 ml), and oxalyl chloride (3 ml) were heated under reflux for 3 h. The contents were evaporated under vacuum, the residue dissolved in Et_2O (50 ml) and added with stirring to a solution of indoline (2 g in 20 ml Et_2O). The precipitate was collected, dried, and crystallized from EtOH to afford colorless needles of **11** (1.2 g), mp 194-195°; ms, M^+ *m/z* 311; ir (nujol) 1770, 1645, 1612 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 7.91 (1H, dd, J=9, 2 Hz, H-6), 7.65 (1H, d, J=2 Hz, H-2), 7.40 (4H, m, Arm. H), 7.01 (1H, d, J=9 Hz, H-5), 3.92 (3H, s, OCH_3), 3.85 (2H, t, J=9 Hz, N-CH_2), 3.25 (2H, t, J=9 Hz, Ar-CH_2), 2.29 (3H, s, $COCH_3$); ^{13}C nmr ($CDCl_3$+CD_3SOCD_3): singlets 168.4 (C=O), 167.0 ($COCH_3$), 154.8 (C-4), 139.2 (C-7′a), 136.4 (C-3), 135.1 (C-4′a), 123.6 (C-1); doublets 129.3, 129.0, 128.1, 125.8, 124.2, 119.5, 111.7; triplets 45.2 (CH_2-2′), 29.1 (CH_2-3′); quartets 56.0 (OCH_3), 20.4 ($COCH_3$).

1′-(3-HYDROXY-4-METHOXYBENZOYL)-2′,3′-DIHYDROINDOLE (**12**).—A solution of **11** (100 mg) in 2.5% methanolic KOH (6 ml) was warmed to 50° for 5 min and left at 20° for 2 h. This solution was acidified with 10% HCl, the MeOH evaporated under vacuum, and the precipitate collected, washed, and dried. Crystallization from EtOH afforded **12** (80 mg) as colorless cubes, mp 145°; ms, M^+ *m/z* 269; ir

(nujol) 3200 (br), 1620, 1590 cm^{-1}; ^1H nmr (CD_3COCD_3) δ 7.82 (1H, dd, J=8, 2 Hz, H-6), 7.22 (6H, m, Arm. H), 4.13 (2H, t, J=8 Hz, N-CH_2), 3.93 (3H, s, OCH_3), 3.15 (2H, t, J=8 Hz, Ar-CH_2); ^{13}C nmr (CD_3COCD_3): singlets 169.0 (C=O), 150.1 (C-4), 147.3 (C-3), 144.3 (C-7'a), 133.5 (C-4'a), 131.2 (C-1); doublets 127.5, 125.6, 124.1, 120.0, 117.6, 115.2, 111.9; triplets 51.4 (CH_2-2'), 29.6 (CH_2-3'); quartet 56.3 (OCH_3).

ACKNOWLEDGMENTS

We wish to thank Professor A.W. Frahm for the ir spectrum of pratorimine.

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Received 4 October 1985