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THE SYNTHESIS OF THALMICRINONE, A CONFIRMATION OF STRUCTURE

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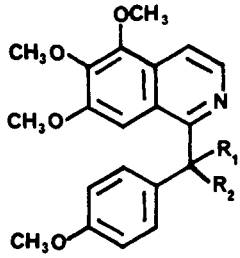
The genus *Thalictrum*, consisting of more than 120 perennial species, is one of the largest genera in the family Ranunculaceae. These species are widespread and are found principally in climatically moderate zones of the northern hemisphere (1). *Thalictrum minus* L. var. *microphyllum* Boiss. is a herb indigenous to Turkey, being found in regions of western Anatolia (2). In 1981, the first report of the alkaloids of this species appeared in the literature, with the isolation and identification of the protoberberine alkaloids berberine, palmatine, jatrorrhizine, and 8-trichloromethyldihydroberberine; the aporphine alkaloid magnoflorine; and the phenanthrene alkaloid thaliglucinone. The bisbenzylisoquinoline alkaloids *O*-methylthalicberine, obaberine, thalrugosine, and thaligosine, and the aporphine-benzylisoquinoline dimeric alkaloids thaliadanine, thalmelatidine, and adiantifoline were also isolated from extracts of roots and rhizomes of the plant (3). Only one year later, a series of three papers appeared describing the isolation and identification of five novel aporphine-benzylisoquinoline dimeric alkaloids including (+)-istanbulamine (2), (+)-bursanine (2), (+)-iznikine (2), (+)-*N*-2′-noradiantifoline (4), and (+)-uskudaramine (5) from extracts of the roots and rhizomes. In 1984, the novel bisbenzylisoquinoline alkaloids (+)-thaligrisine and (+)-thaliphylline were isolated from a root extract along with seven other bisbenzylisoquinoline alkaloids including thalicberine, *O*-methylthalicberine, thaligosine, homoaromoline, thalirugine, obamegine, and aromoline (6).

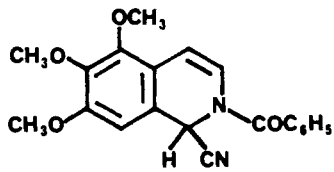
In 1982, the isoquinolone alkaloid thalactamine, the benzylisoquinoline alkaloid takatonine and a new alkaloid, the oxobenzylisoquinoline thalmicrinone (**1**), were isolated from an extract of the leaves of this species (7). The isolation of only 2 mg of thalmicrinone precluded a detailed physicochemical investigation, and its structure was proposed as 1-(4-methoxybenzoyl)-5,6,7-trimethoxyisoquinoline (**1**) based on spectral data (7). This present paper describes the synthesis of 1-(4-methoxybenzoyl)-5,6,7-trimethoxyisoquinoline (**1**), which was found to be identical to thalmicrinone, thus confirming the earlier structural proposal. Synthesis of thalmicrinone (**1**) was achieved via preparation of the Reissert compound 2-benzoyl-1-cyano-5,6,7-trimethoxy-1,2-dihydroisoquinoline (**2**) (8) from 5,6,7-trimethoxyisoquinoline (9).

Subsequent reaction of the Reissert anion (prepared via treatment of the Reissert compound **2** with sodium hydride in dimethylformamide) with *p*-anisaldehyde (10) afforded 4-methoxyphenyl-1-(5,6,7-trimethoxyisoquinolyl) carbinol (**3**). This alcohol underwent facile oxidation with chromic acid (10) to yield 1-(4-methoxybenzoyl)-5,6,7-trimethoxyisoquinoline (**1**), identical to natural thalmicrinone (7) by direct comparison (uv, ir, ^{1}H nmr, ms).

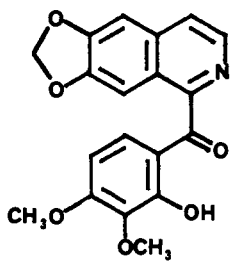
Thalmicrinone (**1**) is only the second oxobenzylisoquinoline alkaloid to have been isolated from a *Thalictrum* species. In 1980, the isolation, identification, and synthesis of rugosinone (**4**), an alkaloid of *Thalictrum rugosum* Ait., was described (10,11). Rugosinone (**4**) was subsequently isolated from *Thalictrum foliolosum* DC. in 1983 (12).



1 $R_1+R_2=O$
3 $R_1=H$, $R_2=OH$



2



4

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were taken on a Fisher-Johns apparatus and are uncorrected. The uv spectra were obtained on a Perkin-Elmer model 552A recording spectrophotometer in MeOH, and the ir spectra were determined on a Perkin-Elmer model 257 recording spectrophotometer in KBr pellets. The ^{1}H-nmr spectra were recorded on a Hitachi Perkin-Elmer model R-24 high resolution spectrometer (60 MHz) or on a JEOL FX-90Q spectrometer in $CDCl_3$ with TMS as the internal standard and chemical shifts reported in δ (ppm) units. The low resolution mass spectra were taken with a Finnigan EI Mass Spectrometer, Spectrel Electronics, interfaced with a Finnigan Incos Data System, Extranuclear Laboratories, Inc. The high resolution mass spectrum was obtained on a Varian MAT, Model CH-5 spectrometer. Alumina (neutral, Brockmann I) (150 mesh) (Aldrich) was used for column chromatography.

PREPARATION OF 2-BENZOYL-1-CYANO-5,6,7-TRIMETHOXYISOQUINOLINE (**2**).—To 5,6,7-trimethoxyisoquinoline (9) (200 mg) (0.91 mmole) in CH_2Cl_2 (20 ml) was added a solution of KCN (544 mg) (8.37 mmole) in H_2O (2.4 ml). Benzoyl chloride (544 mg) (0.45 ml) (3.87 mmole) was added over 0.5 h under N_2 and the mixture allowed to stand at room temperature for 1 h. An additional quantity of KCN (272 mg) (4.19 mmoles) in H_2O (1.2 ml) was added and the mixture kept at room temperature for an additional 4 h. The CH_2Cl_2 layer was separated, partitioned with H_2O (6 ml) twice, 2M HCL (6 ml), 2M NaOH (6 ml), H_2O (6 ml) twice, and dried (anhydrous Na_2SO_4). The CH_2Cl_2 was filtered and evaporated to dryness to leave 2-benzoyl-1-cyano-5,6,7-trimethoxyisoquinoline (**2**) (180 mg) which crystallized from MeOH as colorless needles (141 mg) (44% yield), mp 167-168° [lit. 166-167° (8)]; uv λ max (MeOH) 321 nm (log ε 2.92), 301 (sh) (2.95), 280 (3.03), and 238 (3.69); ir ν max (KBr) 2235 cm^{-1} (C ≡ N), 1670 (C=O), 1630 (C=C), 1605 (Ar), and 1500 (Ar); ^{1}H nmr δ 3.90 (s, 6H, 2ArOC*H*$_3$), 3.95 (s, 3H, ArOC*H*$_3$), δ 6.29 (d, 1H, *J*=8 Hz, H-4), 6.48 (s, 1H, H-1), 6.67 (s, 1H, H-8), 7.53 (m, 5H, benzoyl Ar*H*), and 8.17 (d, 1H, *J*=8 Hz, H-3); ms M^+ *m/z* 350 (72%) for $C_{20}H_{18}O_4N_2$, 335 (5), 323 (3), 321 (3), 307 (5), 291 (3), 245 (28), 219 (38), 204 (19), and 105 (100).

PREPARATION OF 4-METHOXYPHENYL-1-(5,6,7-TRIMETHOXYISOQUINOLYL)CARBINOL (**3**).—To NaH (10 mg) (0.42 mmole) suspended in DMF (1 ml) at −10° was added 2-benzoyl-1-cyano-5,6,7-trimethoxyisoquinoline (**2**) (80 mg) (0.23 mmole) in DMF (4 ml) over a period of 5 min under N_2. After 5 min, *p*-anisaldehyde (70 mg) (0.52 mmole) in DMF (4 ml) was added over 10 min at −10°. The mixture was stirred for 2 h at 0° and then allowed to stand at room temperature for an additional 2 h. The mixture was treated with MeOH (20 ml) and then evaporated to a residue. The residue was dissolved in C_6H_6 (10 ml), partitioned with H_2O (5 ml) twice, then dried (anhydrous $NaSO_4$), filtered, and evaporated. The resulting residue (consisting primarily of the benzoate ester of **3**) was dissolved in EtOH (5 ml) and hydrolyzed with KOH (20 mg) in H_2O (1 ml) under reflux for 3 h. The solution was cooled, evaporated to dryness, and the resulting residue dissolved in 6M HCl (20 ml). The acidic solution was partitioned with Et_2O (20 ml), alkalinized with NH_4OH to pH 8-9 and extracted with Et_2O (30 ml) twice. The combined Et_2O extracts were dried (anhydrous Na_2SO_4), filtered, and the filtrate evaporated to a white residue. The residue was dissolved in petroleum ether-$CHCl_3$ (1:2) (2 ml) and chromatographed over neutral Al_2O_3 (5 g). Elution with the same solvent afforded a residue which upon crystallization from MeOH afforded 4-methoxyphenyl-1-(5,6,7-trimethoxyisoquinolyl) carbinol (**3**) (40 mg)

(44% yield), mp 169-170° (MeOH); uv λ max (MeOH) 335 nm (log ε 3.57), 323 (sh) (3.51), 283 (sh) (3.77), and 242 (4.71); ir ν max (KBr) 3450 cm^{-1}, 1610, 1590, 1510, 1490, 1475, 1430, 1395, 1325, 1305, 1250, 1195, 1175, 1120, 1060, 1035, 1015, 965, and 835; ^1H nmr δ 3.75 (s, 3H, ArOCH_3), 3.78 (s, 3H, ArOCH_3), 3.96 (s, 3H, ArOCH_3), 4.01 (s, 3H, ArOCH_3), 6.14 (s, 1H, H-α), 6.82 (d, 2H, J=9 Hz, H-3′+H-5′), 6.91 (s, 1H, H-8), 7.25 (d, 2H, J=9 Hz, H-2′+H-6′), 7.84 (d, 1H, J=5.7 Hz, H-4), and 8.42 (d, 1H, J=5.7 Hz, H-3); ms, M^+ *m/z* 355 (100%) for $C_{20}H_{21}O_5N$, 340 (8), 338 (52), 324 (42), 322 (45), 248 (42), 219 (78), and 121 (83).

PREPARATION OF 1-(4-METHOXYBENZOYL)-5,6,7-TRIMETHOXYISOQUINOLINE (THALMICRINONE) (**1**).—To 4-methoxyphenyl-1-(5,6,7-trimethoxyisoquinolyl) carbinol (**3**) (30 mg) (0.0845 mmole) in HOAc (2 ml) was added a solution of Na_2CrO_4 (36 mg) (0.22 mmole) in HOAc (2 ml). The mixture was heated for 3 min on a steam bath, diluted with H_2O (10 ml), alkalinized with NH_4OH to pH 8-9 and partitioned with Et_2O (10 ml) three times. The Et_2O extracts were combined, partitioned with H_2O (30 ml), dried (anhydrous Na_2SO_4), filtered, and evaporated to afford a residue. Treatment of the residue with MeOH afforded 1-(4-methoxybenzoyl)-5,6,7-trimethoxyisoquinoline (**1**) as white crystals (10 mg) (34%), mp 145° (MeOH); uv 340 nm (sh) (log ε 3.49), 296 (sh) (4.02), 291 (4.04), and 235 (4.45); ir ν max (KBr) 1650 cm^{-1} (s), 1600 (s), 1585, 1575, 1555, 1505, 1475 (s), 1465, 1450, 1430, 1405, 1375, 1325, 1305, 1280 (s), 1255 (s), 1195, 1175, 1160, 1125, 1050, 1025 (s), 970, 930 (s), 890, 875, 830 (s), 800, 785, 765, and 735; ^1H nmr δ 3.88 (s, 3H, ArOCH_3), 3.93 (s, 3H, ArOCH_3), 4.02 (s, 3H, ArOCH_3), 4.07 (s, 3H, ArOCH_3), 6.95 (d, 2H, J=9 Hz, H-3′+H-5′), 7.37 (s, 1H, H-8), 7.95 (d, 2H, J=9 Hz, H-2′+H-6′), 7.97 (d, 1H, J=5 Hz, H-4), and 8.47 (d, 1H, J=5 Hz, H-3); ms M^+ *m/z* 353 (90%) (measured 353.1263, calcd 353.1263 for $C_{20}H_{19}O_5N$), 338 (64), 325 (56), 322 (58), 310 (32), 295 (10), 294 (16), 280 (12), 279 (10), 278 (14), 267 (6), 264 (8), 252 (12), 224 (7), 176 (14), and 135 (100).

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