

TOTAL SYNTHESIS OF NEODIHYDROTHEBAINE AND BRACTAZONINE, TWO DIBENZ[d,f]AZONINE ALKALOIDS FROM PAPAVER BRACTEATUM⁺

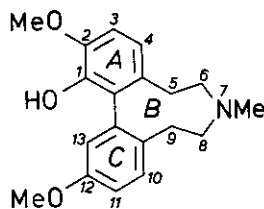
Hubert G.Theuns*[1], Herman B.M.Lenting[2], Cornelis A.Salemink[2], Hitoshi Tanaka[3], Masayoshi Shibata[3], Kazuo Ito[3] and Robert J.J.Ch.Lousberg[4]

[1] Laboratory of Organic Chemistry, Agricultural University, De Dreijen 5, 6703 BC Wageningen, The Netherlands; [2] Organic Chemical Laboratory, State University of Utrecht, Utrecht, The Netherlands; [3] Laboratory of Natural Products Chemistry, Faculty of Pharmacy, Meijo University, Nagoya, Japan; [4] Ministry of Welfare, Health, and Culture, Leidschendam, The Netherlands

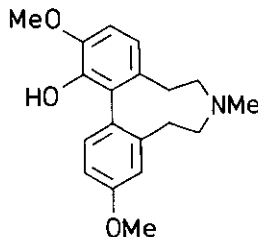
Abstract — The total syntheses of neodihydrothebaine and bractazonine, two dibenz[d,f]azonine alkaloids from Papaver bracteatum, are described.

Neodihydrothebaine is prepared in a total synthesis for the first time. A new and efficient total synthesis of bractazonine is presented.

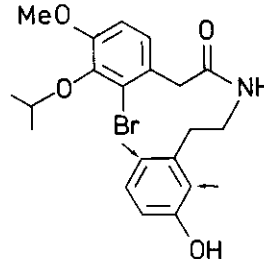
Recently, we reported the structural elucidation of two new dibenz[d,f]azonine alkaloids from Papaver bracteatum^{1,2}. The structures of these alkaloids, neodihydrothebaine 1 and bractazonine 2, were established unambiguously by comparison with some isomeric compounds^{1,2}, and with the synthetic products 1 and 2¹. Neodihydrothebaine 1 was derived from the morphinan alkaloid thebaine in two procedures, while bractazonine 2 was synthesised by a photochemical cyclisation procedure, employing N-(3-hydroxyphenethyl)-2-(2-bromo-3-isopropoxy-4-methoxyphenyl)acetamide 3. In that procedure, the aryl-aryl coupling occurs para, as well as ortho with respect to the phenolic function, present in the ring C precursor.



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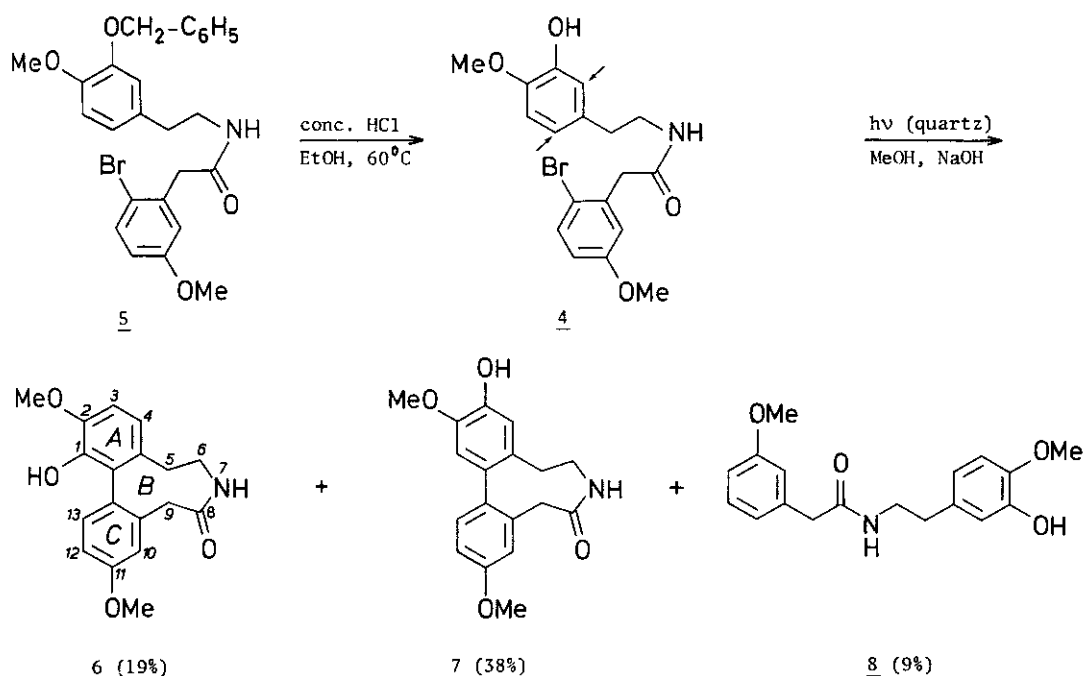
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Therefore it was interesting to develop another total synthesis of bractazonine 2, which would ensure a fixed position of the methoxy substituent of ring C of the latter alkaloid. The procedure, presented here, constitutes a short and efficient pathway to bractazonine 2. Again, we employed the photolytic aryl-aryl coupling reaction, used earlier in the synthesis of the natural alkaloids erybidine³, laurifinine, laurifine and laurifonine⁴. In the substrate (4) for this key step, the bromo substituent is connected to the ring C precursor, and aryl-aryl coupling expectedly takes place at ortho as well as para positions with respect to the phenolic function of the ring A precursor (See Scheme 1). Compound 4 was prepared from 3-benzyloxy-4-methoxyphenethyl-

⁺ Dedicated to Dr.U.Weiss (National Institute of Arthritis and Metabolic Diseases, National Institute of Health, Bethesda, Maryland, U.S.A.) on the occasion of his 70th birthday.

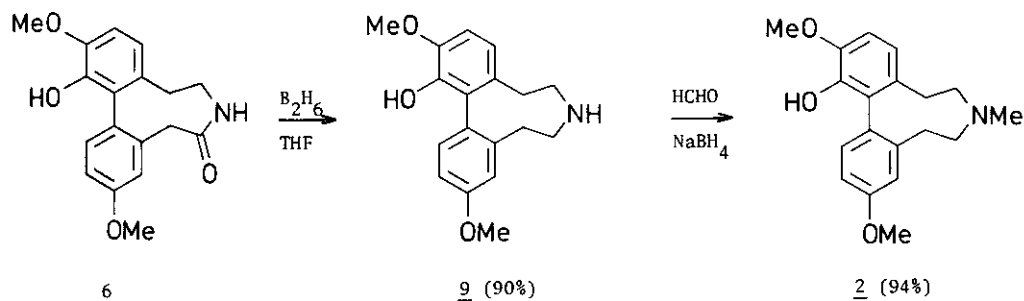
amine⁵ and 2-bromo-5-methoxyphenylacetic acid⁶, through compound 5.

Scheme 1: The photochemical reaction used in the total synthesis of bractazonine



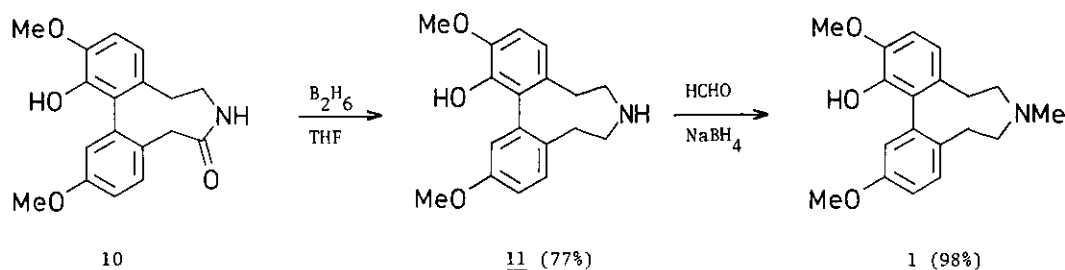
Compound 6 was further converted into bractazonine 2 (overall yield 85%), by reduction of the amide function using in situ prepared diborane, followed by reductive N-methylation (See Scheme 2).

Scheme 2: Final steps in the synthesis of bractazonine 2 from product 6



The first total synthesis of neodihydrothebaine 1 starts with compound 10, a product which was already available from the total synthesis of laurifinine for structural proof⁴. Similar steps, as mentioned above for the synthesis of 2 from 6, gave an excellent yield of neodihydrothebaine 1 (See Scheme 3).

Both synthetic substances 1 and 2 were identical with authentic specimens. By these total syntheses, the substitution patterns of both unusual *Papaver bracteatum* alkaloids are established once more beyond any doubt¹.

Scheme 3: Synthesis of neodihydrothebaine 1 from compound 10

EXPERIMENTAL

Total synthesis of neodihydrothebaine 1. The starting compound for the total synthesis of neodihydrothebaine, 5,6,8,9-tetrahydro-2,12-dimethoxy-1-hydroxy-7H-dibenz[d,f]azonin-8-one 10, was already available as a result of the preparation of laurifinine for definitive structural proof⁴. Reduction of the amide function of the starting compound afforded the secondary amine 11, which was N-methylated to afford neodihydrothebaine 1.

5,6,8,9-Tetrahydro-2,12-dimethoxy-7H-dibenz[d,f]azonin-1-ol 11. To a cold suspension of compound 10⁴ (220 mg) and NaBH₄ (100 mg) in dry THF a solution of BF₃·OEt₂ (0.5 ml) was added dropwise in 15 min. After stirring at room temp. for 6 h, excess diborane was destroyed by slow addition of EtOH. A stream of HCl gas was passed through the mixture, and the volatile materials were removed. The residue was poured into H₂O, treated with aq. NH₃, and extracted with CHCl₃. The CHCl₃ extract was washed with H₂O, dried over Na₂SO₄, and evaporated to afford 11 (161 mg, yield 77%) as a colourless oil. IR ν_{max} (CHCl₃): 3540 cm⁻¹ (OH). ¹H-NMR (CDCl₃): δ 3.80 (3H,s,OMe), 3.92 (3H,s,OMe), 6.69 (1H,d,J=3 Hz,H-13), 6.80 and 6.87 (2H,2 d,J=7 Hz,H-3 and H-4), 6.88 (1H,dd,J=3 and 8 Hz,H-11), 7.17 (1H,d,J=8 Hz,H-10). MS m/z (rel.int.): 299(100),284,257,256,242,226,211.

Neodihydrothebaine 1. A 37% aq. HCHO solution (0.1 ml) was added to a solution of 11 (95 mg) in MeOH (25 ml) and the mixture was stirred at room temp. for 0.5 h. The mixture was cooled to 5-10°C, and NaBH₄ (100 mg) was added in small portions during 10 min. After continued stirring for 30 min. at room temp., the mixture was evaporated to dryness and dissolved in CHCl₃. The CHCl₃ extract was washed with H₂O, dried over Na₂SO₄, and evaporated, to give 1 (97 mg, yield 98%) as a colourless oil. IR ν_{max} (CHCl₃): 3540 cm⁻¹ (OH). This compound was identical (TLC,IR,NMR,MS) with an authentic specimen, prepared from thebaine¹.

Synthesis of bractazonine 2. Bractazonine was synthesised in a procedure involving photolytic aryl coupling of the substrate 4. The synthetic pathway started with 3-benzyloxy-4-methoxyphenethylamine and 2-bromo-5-methoxyphenylacetic acid.

N-(3-Benzyloxy-4-methoxyphenethyl)-2-(2-bromo-5-methoxyphenyl)acetamide 5. Heating of a mixture of 3-benzyloxy-4-methoxyphenethylamine⁵ and 2-bromo-5-methoxyphenylacetic acid⁶ in decaline yielded compound 5 in 64% yield. M.p. 149°C (decomp., from MeOH). Acidification of the basic washings, and CHCl₃ extraction recovered unreacted 2-bromo-5-methoxyphenylacetic acid (36%). ¹H-NMR (CDCl₃): δ 2.63 (2H,t,J=7 Hz,ArCH₂CH₂N), 3.41 (2H,double t,J=6 and 7 Hz,ArCH₂CH₂NH), 3.59 (2H,s,ArCH₂CO), 3.75 (3H,s,OMe), 3.86 (3H,s,OMe), 5.08 (2H,s,ArCH₂O), 5.43 (1H,br t,NH), 6.5-6.9 (6H,m,ArH), 7.2-7.5 (5H,m,ArH). GC/MS m/z (rel.int.): 485(10),483(10),207(3),201(3),199(3),166(8),151(3),150(23),137

(4), 135(4), 121(5), 92(9), 91(100).

N-(3-Hydroxy-4-methoxyphenethyl)-2-(2-bromo-5-methoxyphenyl)acetamide 4. A stirred solution of compound 5 in conc. HCl and EtOH (1:1) was heated at 60°C for 6 h. The volatile materials were removed, H₂O was added, and the mixture was extracted with CHCl₃. The extract was washed with H₂O, dried over Na₂SO₄, and evaporated. The yield of 4 was 100%. M.p. 151°C (decomp., from MeOH). ¹H-NMR (CDCl₃): δ 2.62 (2H, t, J=7 Hz, ArCH₂CH₂N), 3.42 (2H, double t, J=6 and 7 Hz, ArCH₂CH₂NH), 3.61 (2H, s, ArCH₂CO), 3.74 (3H, s, OMe), 3.83 (3H, s, OMe), 5.60 (1H, br t, J=6 Hz, NH), 5.70 (1H, s, OH), 6.4-6.9 (5H, m, ArH), 7.43 (1H, d, J=8.7 Hz, ArH). GC/MS m/z (rel.int.): 395(2), 393(2), 314(3), 201(5), 199(5), 151(13), 150(100), 137(14), 135(10), 91(6).

Photolysis of compound 4. Compound 4 (500 mg) in MeOH (250 ml), containing NaOH (400 mg) was irradiated for 45 min using a 125W high-pressure mercury lamp (Philips HPLN 57236 E/74, from which the outer bulb was removed) in a quartz immersion apparatus, while a stream of nitrogen was passed through the solution. The solvent was removed in vacuo, and the residue was dissolved in H₂O, whereupon Et₂O extraction was performed. The aq. phase was neutralised using conc. HCl, and extracted with CHCl₃. The extract was washed with H₂O, dried over MgSO₄, and evaporated. The crude products from 5 g 4 were separated on a Si-gel column, eluted with CHCl₃, and then with CHCl₃-MeOH (99:1). With CHCl₃ first product 8 was eluted (346 mg), then a mixture of 6 and 8 (754 mg), followed by pure 6 (495 mg). With CHCl₃-MeOH (99:1) product 7 (1.492 g) was collected. The total recovery was ca. 78%. Crystallisation from MeOH afforded the analytically pure compound 6 (749 mg). (See Scheme 1).

5,6,8,9-Tetrahydro-2,11-dimethoxy-1-hydroxy-7H-dibenz[d,f]azonin-8-one 6. M.p. 177°C. ¹H-NMR (CDCl₃): δ 3.86 (3H, s, OMe), 3.90 (3H, s, OMe), 2.1-4.0 (6H, m, 3 CH₂), 4.33 and 5.53 (2H, 2 br s, NH and OH), 6.6-7.2 (5H, m, ArH). In DMSO-d₆ the high field part of the AB-pattern for H-3 and H-4 was found at δ 6.62 (J=8.7 Hz), whereas the low field part appeared at δ 6.92, partly obscured by the other ArH resonances. Addition of (excess) NaOH to the DMSO-d₆ solution gave a much better resolved pattern in ¹H-NMR, and considerable line-sharpening. ¹H-NMR (DMSO-d₆/NaOH): δ 5.73 and 6.48 (2H, AB-pattern, J=7.8 Hz, H-4 and H-3, respectively), 6.69 (1H, dd, J=2.7 and 8.1 Hz, H-12), 7.02 (1H, d, J=8.1 Hz, H-13), 7.09 (1H, d, J=2.7 Hz, H-10). The upfield shifts, observed for H-3 and H-4 upon addition of NaOH to the DMSO-d₆ solution, as well as the decrease of J_{3,4}, are in agreement with literature data on this effect^{7,8}. GC/MS m/z (rel.int.): 314(20), 313(100), 284(50), 257(17), 256(67), 241(24), 225(16), 223(14), 181(12), 153(12), 152(15).

5,6,8,9-Tetrahydro-2,11-dimethoxy-3-hydroxy-7H-dibenz[d,f]azonin-8-one 7. M.p. 255°C. ¹H-NMR (DMSO-d₆): δ 1.7-3.7 (6H, br m, 3 CH₂), 3.75 (3H, s, OMe), 3.78 (3H, s, OMe), 6.62 (2H, s, H-1 and H-4), 6.86 (1H, dd, J=2.7 and 8.7 Hz, H-12), 7.12 (1H, d, J=8.7 Hz, H-13), 7.18 (1H, H-10, obscured by the H-13 resonance), 7.57 (1H, br s, NH), 8.98 (1H, s, OH). GC/MS m/z (rel.int.): 314(20), 313(100), 285(10), 284(52), 256(39), 255(14), 242(18), 241(39), 225(23), 181(10), 152(11).

N-(3-Hydroxy-4-methoxyphenethyl)-2-(3-methoxyphenyl)acetamide 8. Yellowish oil. ¹H-NMR (CDCl₃): δ 2.56 (2H, t, J=7 Hz, ArCH₂CH₂N), 3.35 (2H, double t, J=6 and 7 Hz, ArCH₂CH₂NH), 3.43 (2H, s, ArCH₂CO), 3.70 (3H, s, OMe), 3.77 (3H, s, OMe), 5.97 (1H, t, J=6 Hz, NH), 6.35-7.2 (8H, m, ArH + OH). GC/MS m/z (rel.int.): 315(8), 151(16), 150(100), 137(21), 135(12), 122(10), 121(30).

5,6,8,9-Tetrahydro-2,11-dimethoxy-7H-dibenz[d,f]azonin-1-ol 9. Compound 6 was treated with in situ prepared diborane, as in the synthesis of compound 11. The yield of 9 was 90%. M.p. 212°C. ¹H-NMR (CDCl₃): δ 2.0-3.2 (10H, m), 3.84 (3H, s, OMe), 3.91 (3H, s, OMe), 6.6-6.93 (4H, m, ArH), 7.0-7.2 (1H, m, ArH). GC/MS m/z (rel.int.): 300(21), 299(100), 257(26), 256(13), 255(16), 253(26), 242(12), 240(19), 226(11), 225(36), 223(12).

Bractazonine 2. N-Methylation of compound 9, similar to the synthesis of 1 from 11, gave bractazonine in 94% yield. M.p. 101°C. ¹H-NMR (CDCl₃): δ 2.28 (3H,s,NMe), 2.3 - 2.7 (8H,m,4 CH₂), 3.84 (3H,s,OMe), 3.90 (3H,s,OMe), 5.3 (1H,br s,OH), 6.70 and 6.84 (2H,AB-pattern,J=8.3 Hz,H-3 and H-4), 6.82 (1H,d,J=2.7 Hz,H-10), 6.82 (1H,dd,J=2.7 and 9.2 Hz,H-12), 7.09 (1H,d,J=9.2 Hz,H-13). The Δδ (OMe) observed was 0.068¹. GC/MS m/z (rel.int.): 314(22),313(100),312(14),298(15),296(24),270(27),257(15),256(28),255(32),239(15),225(14),223(30).

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