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

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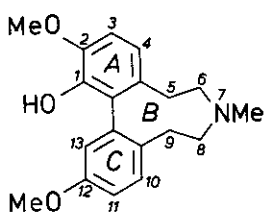
Abstract — The total syntheses of neodihydrothebaine and bractazonine, two dibenz[d,f]azonine alkaloids from Papaver bracteatum, are described. Neodihydrothebaine is prepared in a total synthesis for the first time. A new and efficient total synthesis of bractazonine is presented.

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 2[1]. 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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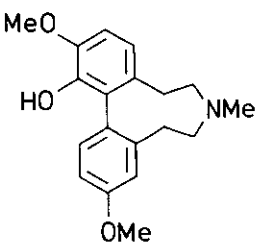

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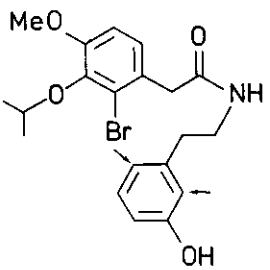

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Therefore it was interesting to develop another total synthesis of bractazonine 2, which would ensure a fixed position of the methoxy substituent of ring C of the latter alkaloid. The procedure, presented here, constitutes a short and efficient pathway to bractazonine 2. Again, we employed the photolytic aryl-aryl coupling reaction, used earlier in the synthesis of the natural alkaloids erybidine[3], laurifinine, laurifine and laurifonine[4]. 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-

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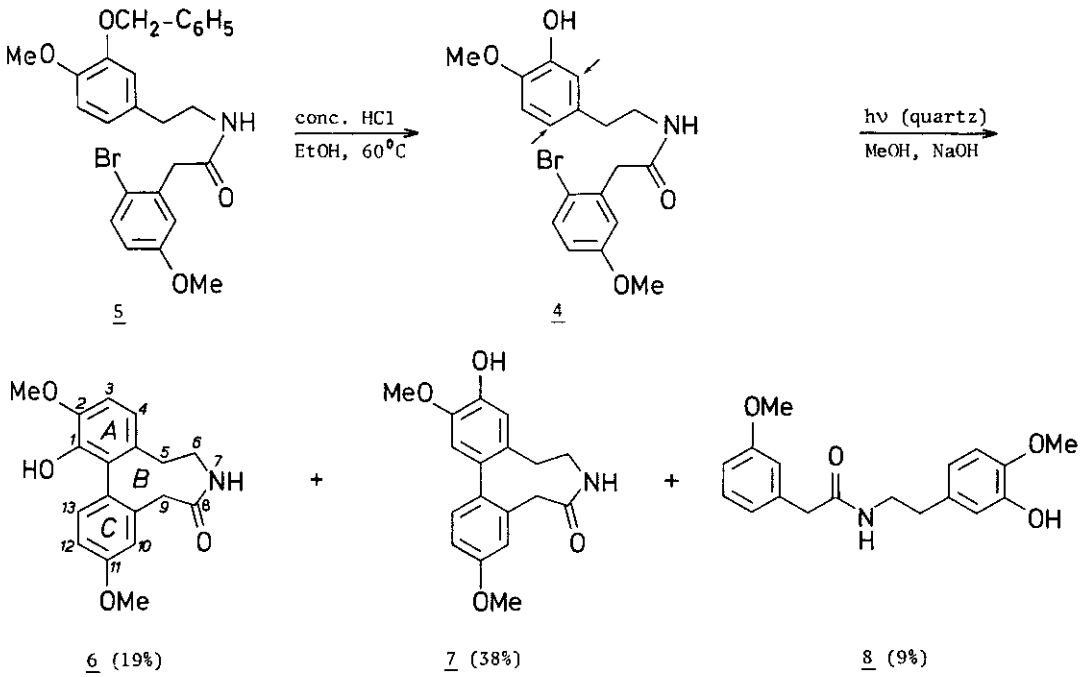
amine[5] and 2-bromo-5-methoxyphenylacetic acid[6], through compound 5.

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

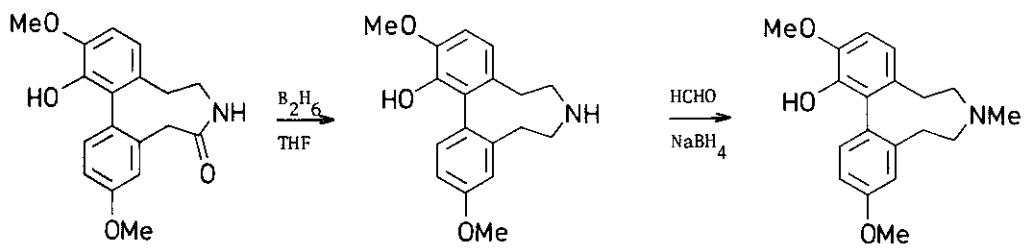


5 4

6 (19%) 7 (38%) 8 (9%)

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

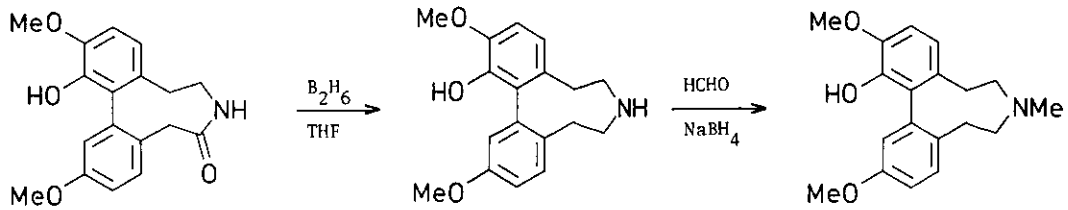


6 9 (90%) 2 (94%)

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 proof[4]. 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 doubt[1].

Scheme 3: Synthesis of neodihydrothebaine 1 from compound 10



10 11 (77%) 1 (98%)

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 proof[4]. 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 10[4] (220 mg) and $NaBH_4$ (100 mg) in dry THF a solution of $BF_3.OEt_2$ (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 H_2O, treated with aq. NH_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, and evaporated to afford 11 (161 mg, yield 77%) as a colourless oil. IR ν_{max} ($CHCl_3$): 3540 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$): 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 $NaBH_4$ (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 $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, and evaporated, to give 1 (97 mg, yield 98%) as a colourless oil. IR ν_{max} ($CHCl_3$): 3540 cm^{-1} (OH). This compound was identical (TLC,IR,NMR,MS) with an authentic specimen, prepared from thebaine[1].

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-methoxyphenethylamine[5] and 2-bromo-5-methoxyphenylacetic acid[6] in decaline yielded compound 5 in 64% yield. M.p. 149°C (decomp., from MeOH). Acidification of the basic washings, and $CHCl_3$ extraction recovered unreacted 2-bromo-5-methoxyphenylacetic acid (36%). ^{1}H-NMR ($CDCl_3$): δ 2.63 (2H,t,J=7 Hz,$ArCH_2CH_2N$), 3.41 (2H,double t,J=6 and 7 Hz,$ArCH_2CH_2NH$), 3.59 (2H,s,$ArCH_2CO$), 3.75 (3H,s,OMe), 3.86 (3H,s,OMe), 5.08 (2H,s,$ArCH_2O$), 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, H_2O was added, and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The yield of 4 was 100%. M.p. 151°C (decomp., from MeOH). ^{1}H-NMR ($CDCl_3$): δ 2.62 (2H,t,J=7 Hz,$ArCH_2CH_2N$), 3.42 (2H,double t,J=6 and 7 Hz,$ArCH_2CH_2NH$), 3.61 (2H,s,$ArCH_2CO$), 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 H_2O, whereupon Et_2O extraction was performed. The aq. phase was neutralised using conc. HCl, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$, and evaporated. The crude products from 5 g 4 were separated on a Si-gel column, eluted with $CHCl_3$, and then with $CHCl_3$-MeOH (99:1). With $CHCl_3$ first product 8 was eluted (346 mg), then a mixture of 6 and 8 (754 mg), followed by pure 6 (495 mg). With $CHCl_3$ - 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. ^{1}H-NMR ($CDCl_3$): δ 3.86 (3H,s,OMe), 3.90 (3H,s,OMe), 2.1 - 4.0 (6H,m,3 CH_2), 4.33 and 5.53 (2H,2 br s,NH and OH), 6.6 - 7.2 (5H,m,ArH). In DMSO-d_6 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-d_6 solution gave a much better resolved pattern in ^{1}H-NMR, and considerable line-sharpening. ^{1}H-NMR (DMSO-d_6/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-d_6 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. ^{1}H-NMR (DMSO-d_6): δ 1.7 - 3.7 (6H,br m,3 CH_2), 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. ^{1}H-NMR ($CDCl_3$): δ 2.56 (2H,t,J=7 Hz,$ArCH_2CH_2N$), 3.35 (2H,double t,J=6 and 7 Hz,$ArCH_2CH_2NH$), 3.43 (2H,s,$ArCH_2CO$), 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. ^{1}H-NMR ($CDCl_3$): 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. ^{1}H-NMR ($CDCl_3$): δ 2.28 (3H,s,NMe), 2.3 - 2.7 (8H,m,4 CH_2), 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 0.068[1]. 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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