HETEROCYCLES, Vol. 55, No. 2, 2001, pp. 371 - 376, Received, 11th November, 2000

A SYNTHESIS OF BIPOWINE AND BIPOWINONE

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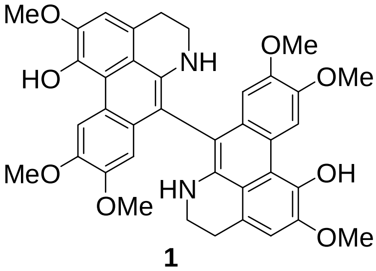
Abstract- Various oxidizing agents were investigated for the synthesis of bipowine (**1**) and bipowinone (**2**), two symmetrical dimeric aporphine alkaloids, from the oxidative coupling of dehydroaporphine (**3**).

Dimeric aporphine alkaloids[1-5] are a small group of natural alkaloids isolated from plants of the family Annonaceae. There are two types of linkages between the two aporphine units i.e. C4-C7 and C7-C7. Bipowine (**1**) and bipowinone (**2**) are the two representative of the symmetrical 7,7'-bisaporphine alkaloids isolated from the Indonesian annonaceous plant *Popowia pisocarpa.* [2]

The dimerization of aporphine and dehydroaporphine alkaloids to the corresponding 7,7'-bisaporphines has been achieved. Various reagents utilized to effect such dimerization include I_2/C_2H_5OH,[6] $Hg(NO_3)_2/CH_3CN$,[7] $Hg(OAc)_2/CH_3OH$,[7] NCS/base and air.[2,8] Bipowinone (**2**) has been previously obtained from the oxidation of wilsonirine (dihydro derivative of **3**) with NCS followed by reaction with sodium ethoxide, but in a very low yield (1.6%)[2] the main product was later found to be pancoridine (**4**).[8] However, no satisfactory methods for the synthesis of **2** have so far been reported. In this study various oxidizing agents were investigated for the oxidative dimerization of dehydroaporphine alkaloid. In this paper we report the synthesis of bipowine (**1**) and bipowinone (**2**).



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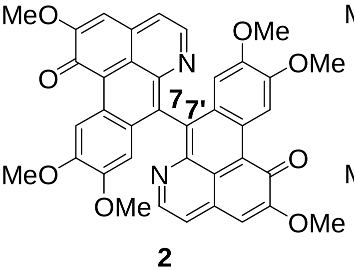

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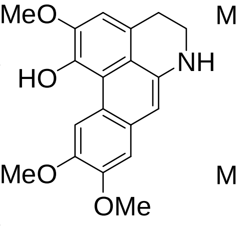

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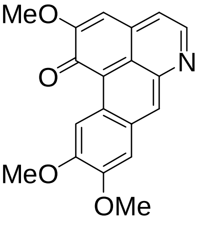

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6a,7-Dehydronorthaliporphine (**3**) was used in our study of the oxidative coupling reaction. This dehydroaporphine alkaloid was obtained[9] from hydrogenation of pancoridine (**4**)[9,10] using PtO_2 as catalyst.

The reaction of dehydroaporphine (**3**) with various oxidizing agents is shown in Table I.

Table I "The reaction of **3** with various oxidizing agents[a)]"

Entry	Oxidizing agents (equivalent)	Reaction Time	Products (%)	
			1	**2**
1	$Hg(OAc)_2$ (0.6)	15 min	60	trace
2	$Hg(OAc)_2$ (2.7)	3 h	-	68
3	$PhI(OAc)_2$ (0.6)	5 min	53	trace
4	$PhI(OAc)_2$ (2.6)	5 min	-	74
5	air	48 h	58	-

"a) The reaction was carried out in dichloromethane at rt"

$Hg(OAc)_2$ could be used to oxidise **3** to the dimeric bipowine (**1**) and bipowinone (**2**) depending on the ratio of the oxidizing agent and the duration of the reaction. More significantly, we have found that the above dimerization process can be conveniently effected by (diacetoxyiodo)benzene [$PhI(OAc)_2$]. Hypervalent iodine compounds[11-13] have recently been utilized in many organic functional group transformations. The relatively low toxicity of hypervalent iodine compounds[11i] as compared to the mercury compounds makes the above finding very attractive.

Table II "Formation of **2** by the oxidation of **1**[a)]"

Entry	Oxidizing agent (equivalent)	Reaction time	Product (**2**) (%)
1	$Hg(OAc)_2$ (4.2)	3 h	quantitative yield
2	$PhI(OAc)_2$ (4.1)	5 min	73
3	Ag_2O (4.3)	10 min	90

"a) The reaction was carried out in dichloromethane at rt"

Furthermore, we have also found that bipowine (**1**) was easily oxidized to bipowinone (**2**) by excess amount of $Hg(OAc)_2$, $PhI(OAc)_2$, and Ag_2O. The results are summarized in Table II. Reaction of **3** with Ag_2O[14] gave pancoridine (**4**) in 53% yield and bipowinone (**2**) in 28% yield. In addition, when [bis(trifluoroacetoxy)iodo]benzene was used as oxidizing agent, only 12% of **2** was obtained together with 12% of pancoridine (**4**).

In conclusion, the formation of bipowine and bipowinone could be adjusted according to the experimental procedure and we have introduced the use of $PhI(OAc)_2$ in the oxidative dimerization of the dehydroaporphine alkaloid to the corresponding bisaporphine alkaloid.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were taken at 300 or 400 MHz as specified and ^{13}C NMR at 100 MHz. Tetramethylsilane was used as the internal standard, and chemical shifts are reported as δ_H (ppm) or δ_C (ppm). MS spectra were obtained by electron impact technique (EI).

6a,7-Dehydronorthaliporphine (**3**) was prepared according to Cava's procedure[9] and exhibited the following data. mp 197°C (decomp) (ether) (lit.,[9] mp 198°-199°C); IR (KBr): ν_{max} 3460 (NH), 3327 cm^{-1} (OH); ^1H NMR (300 MHz, acetone d_6): δ (ppm) 3.13-3.17 (m, 2H, C-4, CH_2-CH_2-NH), 3.38-3.42 (m, 2H, C-5, CH_2-CH_2-NH), 3.88, 3.89, 4.01 (3s, 9H, 3xOCH_3), 6.63 (s, 1H, C-8-Ar*H*), 7.01 (s, 1H, C-7-=C*H*), 7.11 (t, 1H, J = 0.9 Hz, C-3-Ar*H*), 9.27 (s, 1H, C-11-Ar*H*); MS: m/z 325 (M^+,100), 310 (54).

Formation of bipowine (1) by oxidation of 6a,7-dehydronorthaliporphine (3)

a) By air oxidation:

A solution of **3** (140 mg, 0.43 mmol) in dichloromethane-methanol (9:1, 150 mL) was oxidized by bubbling air at rt until starting materials were consumed (2 days, monitored by TLC). The solution was evaporated to dryness and the crude product so obtained was purified by column chromatography (Al_2O_3, neutral) using dichloromethane as eluting solvent to give bipowine as a pale yellow solid, which was recrystallized from chloroform-acetone to yield **1** (80 mg, 58%). mp 250-252°C (decomp) (lit.,[2] mp > 249 °C); IR (KBr): ν_{max} 3467 (NH), 3388 cm^{-1} (OH); UV: λ_{max} MeOH (log ε) 207 (4.40), 266 (4.82), 335 (4.16), 389 (3.90) nm, λ_{max} MeOH+NaOH 216, 263, 355, 398, 496 nm, λ_{max} MeOH+HCl 205, 263, 293, 338, 356, 374 nm; ^1H NMR (400 MHz, $CDCl_3$): δ 3.09-3.34 (m, 4H, CH_2-CH_2NH), 3.49, 4.05, 4.07 (3s, 9H, 3xOCH_3), 6.65 (s, 1H, C-8-Ar*H*), 6.86 (s, 1H, O*H*), 7.03 (s, 1H, C-3-Ar*H*), 9.33 (s, 1H, C-11-Ar*H*), ^{13}C NMR (100 MHz, $CDCl_3$-CD_3OD) : δ 143.6 (C-1), 119.8 (C-1a), 117.8 (C-1b), 148.9 (C-2), 110.6 (C-3), 125.1 (C-3a), 30.7 (C-4), 49.2 (C-5), 141.1 (C-6a), 128.4 (C-7), 138.7 (C-7a), 104.1 (C-8), 145.4 (C-9), 143.6 (C-10), 109.2 (C-11), 119.5 (C-11a), 55.3, 55.8, 56.9 (OCH_3-2, 3, 10); MS : m/z 648 (M^+, 89), 633 (33), 325 (92), 324 (100), 310 (68), 292 (39), 290 (69).

b) By oxidation with mercuric acetate:

$Hg(OAc)_2$ (16.0 mg, 0.05 mmol) was added to a solution of **3** (28.9 mg, 0.09 mmol) in dichloromethane (3 mL). The mixture was allowed to stir at rt for 15 min, then filtered. Removal of dichloromethane gave a residue, which was chromatographed on aluminum oxide (neutral) and eluted with dichloromethane to give **1** (17.2 mg, 60%).

c) By oxidation with diacetoxyiodobenzene:

Diacetoxyiodobenzene (17.7 mg, 0.05 mmol) was added to a solution of **3** (29.3 mg, 0.09 mmol) in dichloromethane (3 mL). The mixture was stirred for 5 min at rt, then water was added and the mixture was extracted with dichloromethane (2x20 mL). The dichloromethane extract was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was purified by column chromatography (Al_2O_3, neutral) using dichloromethane as eluting solvent to give **1** (15.5 mg, 53%).

Bipowinone (2) from 6a,7-dehydronorthaliporphine (3)

a) By oxidation with mercuric acetate:

$Hg(OAc)_2$ (70.0 mg, 0.22 mmol) was added to a solution of **3** (26.8 mg, 0.08 mmol) in dichloromethane (3 mL). The mixture was allowed to stir for 3 h at rt. Removal of dichloromethane gave the residue which was chromatographed on aluminum oxide (neutral) and eluted with dichloromethane to afford an orange-red solid (18 mg, 68%), which was crystallized from dichloromethane-acetone to give **2**. mp 292 °C (decomp) (lit.,[2] mp > 295 °C); IR (KBr): ν_{max} 1626 cm^{-1} (C=O); UV: λ_{max} MeOH (log ε) 237 (4.72), 278 (4.42), 288 (4.37), 300 (4.29), 411 (4.26), 476 (4.23), 502 (4.20) nm, λ_{max} MeOH+HCl 204, 250, 432, 496 nm; ^1H NMR (400 MHz, $CDCl_3$) : δ 3.36, 4.05, 4.20 (3s, 9H, 3xOCH_3-9, 2, 10) 6.44 (s, 1H, C-8-Ar*H*), 6.89 (s, 1H, C-3-Ar*H*), 7.45, 8.66 (AB, J_{AB} = 4.4 Hz, 2H, C*H*=C*H*N), 9.91 (s, 1H, C-11-Ar*H*), ^{13}C NMR ($CDCl_3$-CD_3OD) : δ 180.8 (C-1), 131.8 (C-1a), 120.5 (C-1b), 156.1 (C-2), 105.4 (C-3), 141.8 (C-3a), 121.1 (C-4), 149.7 (C-5), 156.3 (C-6a), 131.6 (C-7), 135.1 (C-7a), 105.3 (C-8), 150.5 (C-9), 144.4 (C-10), 107.5 (C-11), 120.3 (C-11a), 55.4, 56.0, 56.4 (OCH_3-2, 3, 10); MS: m/z 640 (M^+, 17), 625 (25), 609 (15), 321 (57), 320 (18), 307 (23), 290 (100).

b) By oxidation with diacetoxyiodobenzene:

Diacetoxyiodobenzene (69.8 mg, 0.22 mmol) was added to a solution of **3** (27.4 mg, 0.08 mmol) in dichloromethane (3 mL). The mixture was stirred for 5 min at rt. Water was added and the mixture was extracted with dichloromethane (2x20 mL). The dichloromethane extract was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was purified by column chromatography (Al_2O_3; neutral) using dichloromethane as eluting solvent to give **2** as an orange-red solid (20.1 mg, 74%).

Oxidation of bipowine (**1**) **to bipowinone** (**2**)

a) By oxidation with mercuric acetate:

$Hg(OAc)_2$ (36.7 mg, 0.12 mmol) was added to a solution of **1** (17.7 mg, 0.03 mmol) in dichloromethane (3 mL). The mixture was allowed to stir for 3 h at rt, then filtered. Removal of dichloromethane gave a residue which was chromatographed on aluminum oxide (neutral) and eluted with 1% methanol-dichloromethane to give **2** (quantitative yield).

b) By oxidation with diacetoxyiodobenzene:

Diacetoxyiodobenzene (36.1 mg, 0.11 mmol) was added to a solution of **1** (17.4 mg, 0.03 mmol) in dichloromethane (3 mL). The mixture was stirred for 5 min at rt. Water was added and the mixture was extracted with dichloromethane (2x20 mL). The dichloromethane extract was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was purified by column chromatography (Al_2O_3; neutral) using 1% methanol-dichloromethane as eluting solvent to give **2** (12.5 mg, 73%).

c) By oxidation with silver oxide:

Silver(I) oxide (27.1 mg, 0.12 mmol) was added to a solution of **1** (17.7 mg, 0.03 mmol) in dichloromethane (3 mL). The solution was allowed to stir for 10 min at rt, then filtered. Removal of dichloromethane gave a residue which was chromatographed on aluminum oxide (neutral) and eluted with 1% methanol-dichloromethane to give **2** (15.8 mg, 90%).

Pancoridine (**4**)

Silver(I) oxide (53.3 mg, 0.23 mmol) was added to a solution of **3** (28.8 mg, 0.09 mmol) in dichloromethane (3 mL). The mixture was allowed to stir for 30 min at rt, then filtered. Removal of dichloromethane gave a residue which was chromatographed on aluminum oxide (neutral) and eluted with dichloromethane to give **4** (15.2 mg, 53%) and **2** (8.0 mg, 28%). Pancoridine (**4**); mp (dichloromethane-hexane) 233-234 °C (decomp)(lit.,[9] 214-215°C, lit.,[10] 236-238 °C); FTIR (KBr) : ν_{max} 1626 cm^{-1} (C=O); UV: λ_{max} MeOH (log ε), 203(4.09), 232(4.59), 243(4.52), 285(4.15), 402(4.02), 466(3.92) nm, λ_{max} MeOH+HCl, 203, 243, 277, 295, 419, 485 nm; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 4.03, 4.09, 4.15 (3s, 9H, 3xOCH_3), 6.78 (s, 1H, C-3-Ar*H*), 6.89 (s, 1H, C-8-Ar*H*), 7.45, 8.66 (AB, J_{ab}= 4.3Hz, 2H,C*H* =C*H* N), 8.70 (s, 1H, C-7-Ar*H*), 9.51 (s, 1H, C-11-Ar*H*), ^{13}C NMR ($CDCl_3$-CD_3OD), δ 180.4(C-1), 132.0(C-1a),135.1(C-1b),156.3(C-2), 106.7(C-3), 141.4(C-3a), 121.0(C-4), 150.0(C-5), 156.5(C-6a),104.8(C-7), 135.1(C-7a), 107.1(C-8), 150.3(C-9), 144.6(C-10), 106.7(C-11), 131.7(C-11a), 56.4, 55.9, 55.86. (OCH_3-2,3,10); MS: m/z 321(M^{+},73.80), 290(100.00).

ACKNOWLEDGEMENT

We are grateful to the Thailand Research Fund (TRF) for the generous support of our research programme. We also acknowledge the facilities provided by the PERCH programme.

REFERENCES

1. A. Jossang, M. Leboeuf, A. Cavé, T. Sévenet, and K. Padmawinata, *J. Nat. Prod.*, 1984, **47**, 504.
2. A. Jossang, M. Leboeuf, A. Cavé, and T. Sévenet, *J. Nat. Prod.,* 1986, **49**, 1028.
3. G. Arango, D. Cortes, and A. Cavé, *Phytochemistry*, 1987, **26**, 1227.
4. O. Laprévote, F. Roblot, R. Hocquemiller, and A. Cavé, *J. Nat. Prod.*, 1987, **50**, 984.
5. D. Cortes, D. Davoust, A. H. A. Hadi, S. H. Myint, R. Hocquemiller, and A. Cavé, *J. Nat. Prod.*, 1990, **53**, 862.
6. M. Gerecke, R. Borer, and A. Brossi, *Hel. Chim. Acta*, 1975, **58**, 185.
7. L. Castedo, R. Riguera, J. M. Sáa, and R. Suau, *Heterocycles*, 1977, **6,** 677.
8. A. Jossang, M. Leboeuf, and A. Cavé, *Heterocycles*, 1987, **26**, 2191.
9. M. P. Cava, I. Noguchi, and K. T. Buck, *J. Org. Chem*., 1973, **38**, 2394.
10. S. M. Kupchan and A. J. Liepa, *J. Am. Chem. Soc.*,1973, **95**, 4062.
11. For some reviews, see: a) T. Wirth and U. H. Hirt, *Synthesis*, 1999, 1271. b) P. J. Stang and V. V. Zhdankin, *Chem. Rev.*, 1996, **96**, 1123. c) V. V. Zhdankin and P. J. Stang, *Tetrahedron*, 1998, **54**, 10927. d) T. Umemoto, *Chem. Rev.*, 1996, **96**, 1757. e) A. Varvoglis, *Tetrahedron,* 1997, **53**, 1179. f) A. Varvoglis and S. Spyroudis, *Synlett*, 1998, 221. g) D. F. Banks, *Chem. Rev.*, 1966, **66**, 242. For some books, see: h) A. Varvoglis, '*The Organic Chemistry of Polycoordinated Iodine*,' VCH, New

York, 1992. i) A. Varvoglis, '*Hypervalent Iodine in Organic Synthesis,*' Academic Press, London, 1997. j) J. P. Fine, '*Ligand Coupling Reactions with Heteroatomic Compounds*,' Pergamon Press, Oxford, 1998.

12. S. V. Ley, O. Schucht, A. W. Thomas, and P. J. Murray, *J. Chem. Soc., Perkin Trans. 1,* 1999, 1251.
13. S. V. Ley, A. W. Thomas, and H. Finch, *J. Chem. Soc., Perkin Trans. 1,* 1999, 669.
14. S. R. Angle, D. O. Arnaiz, J. P. Boyce, R. P. Fruos, M. S. Louie, H. L. Mattson-Arnaiz, J. D. Rainier, K. D. Turnbull, and W. Yang, *J. Org. Chem*., 1994, **59**, 6322.