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PHOTOCHEMICAL SYNTHESIS OF ATHEROSPERMIDINE

SURACHAI NIMGIRAWATH[a] and WALTER C. TAYLOR[b]

a.Department of Chemistry, Faculty of Science, Silpakorn University, Nakorn Pathom 73000, Thailand.

b.Department of Organic Chemistry, the University of Sydney, N.S.W. 2006, Australia.

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Abstract

Irradiation of (Z)-1-(2-bromobenzylidene)-2-alkoxycarbonyl-5-methoxy-6, 7-methylenedioxy-1, 2, 3, 4-tetrahydroisoquinolines (6 and 7) afforded 6-alkoxycarbonyl-3-methoxy-1, 2-methylenedioxy-4, 5, 6, 7-tetrahydrodibenzo [d e, g] quinoline (8 and 9). Reduction of (8) or (9) with lithium aluminium hydride-aluminium chloride followed by oxidation with lead tetraacetate afforded atherospermidine (1) in low yield.

Introduction

Atherospermidine (1)*, the third example of a naturally occurring 7-oxoaporphine, was isolated by Bick *et al.*[1] from *Atherosperma moschatum* Labill (Monimiaceae) and also by Harris and Geissman[2] from *Guatteria psilopus* Mart. (Annonaceae). Atherospermidine was shown to be 3-methoxyliriodenine by unambiguous syntheses using the Pschorr cyclisation as the key step in low yields[3, 4]. In connection with other studies, we decided to undertake a photochemical synthesis of atherospermidine and now report the result of our investigation.

Results and Discussion

2-Bromo-ω-diazoacetophenone (2)[5], prepared in almost quantitative yield from 2-bromobenzoyl chloride and diazomethane, reacted with 2-(2-methoxy-3, 4-methylenedioxyphenyl) ethylamine (3)[6] in the presence of silver oxide to give the amide (4) in good yield. The Bischler-Napieralski cyclisation of (4) was smoothly effected with phosphorus oxychloride in dry acetonitrile and the dihydroisoquinoline (5) was obtained in excellent yield. Treatment of (5) with ethyl chloroformate and pyridine afforded the stilbene derivative (6). The *trans* configuration was assigned on the bases of u.v. and n.m.r. spectroscopic results. The stilbene (6) had in its u.v. spectrum an absorption maximum at 300 nm, logε 4.07, which is characteristic of a *trans*-stilbene system[6]. Moreover, in the n.m.r. spectrum the methyl protons of the ethoxycarbonyl

* The systematic name of atherospermidine is 3-methoxy-1, 2-methylenedioxy-7-oxodibenzo [*d e, g*] quinoline.

group resonated as a triplet at δ 0.81 (J = 7 Hz); this unusually upfield position must result from a shielding effect by an aromatic ring which can operate only in the *trans* configuration[6]. Similarly, treatment of (5) with methyl chloroformate and pyridine afforded the stilbene (7). The *trans* configuration was also assigned on the bases of u.v. (λ_{max} 300 nm, log 4.07) and n.m.r. spectral data. In the n.m.r. spectrum the protons of the methoxycarbonyl group resonated as a singlet at δ 3.21 due to the shielding effect of the *D*-ring.

Irradiation of the stilbene (6) in 20% *tert*-butyl alcohol-benzene in the presence of potassium *tert*-butoxide afforded the dehydroaporphine (8) in 28% yield. The u.v. spectrum of (8), namely λ_{max} 262, 284sh, 320, 332, 352, 370 nm, log ε 4.70, 4.22, 3.98, 3.98, 3.31, 3.23, is indicative of a highly conjugated system and the band at 262 nm is diagnostic of a dehydroaporphine[6], In the n.m.r. spectrum, a multiplet of one proton at δ 9.00-8.85, assigned to H_{11}, also supported the assigned structure. Similarly, irradiation of the stilbene (7) afforded the dehydroaporphine (9) in 27% yield.

Reduction of either (8) or (9) with lithium aluminium hydride-aluminium chloride followed by oxidation with lead tetraacetate afforded atherospermidine in low yield, the spectroscopic properties of which were identical to those of the natural alkaloid.

Experimental

Melting points were determined on a Kofler hot-stage microscope or a Thomas-Hoover melting point apparatus and are uncorrected. Ultraviolet spectra were measured in 95% ethanol on a Perkin-Elmer 402 spectrophotometer or on a Shimadzu UV-240 spectrophotometer and infrared spectra on a Perkin-Elmer 221 or Jasco IRA-1 spectrophotometer. ^1H nuclear magnetic resonance spectra were measured in deuterochloroform solutions on a Varian A60 or Varian EM360A 60 MHz instrument. Mass spectra were measured at 70 eV with an A.E.I. MS 902 mass spectrometer. Analyses were performed by the Australian Microanalytical Service, Melbourne.

2-Bromo-ω-diazoacetophenone (2)

A solution of 2-bromobenzoyl chloride (22 g) in ether (50 ml) was added over 10 min with vigorous stirring to an ethereal solution of diazomethane (from 40 g of *N*-nitrosomethylurea) at 0°. The reaction mixture was then left to stand overnight at room temperature and the solvent removed *in vacuo* to give a yellow oil (21 g; 93%) which was satisfactory to use in the next step. A small portion of the diazoketone was crystallised from light petroleum at 0^0 to give yellow needles, m.p. 41-42° (lit[5]. m.p. 42-43°). N.m.r. δ 5.70, *s*, $COCHN_2$; 7.13-7.73, *m*, 4 x ArH.

N-2-(2'-Methoxy-3, 4'-methylenedioxyphenyl) ethyl-2-bromophenylacetamide (4)

Silver oxide (0.5 g) was added portionwise over 15 min to a stirred solution of

2-bromo-ω-diazoacetophenone (4.5 g) and 2-(2′-methoxy-3′, 4′-methylenedioxyphenyl) ethylamine (3.9 g) in dry dioxan (100 ml) at 60° and the reaction mixture stirred at 60-70° for 1 h longer. Silver oxide (0.5 g) was then added and the mixture refluxed for 20 min and filtered hot. The solvent was removed *in vacuo* to give a red oil which was taken up in benzene and filtered through an alumina column (200 g) eluted with a large volume of ether. Recrystallisation from ethanol afforded the *amide* as colourless needles (6.0 g; 76%), m.p. 152-153°. (Found: C, 55.1; H, 4.9; N, 3.9; Br, 20.1. $C_{18}H_{18}BrNO_4$ requires C, 55.1; H, 4.6; N, 3.6; Br, 20.4%). λ_{max} 280 nm, log ε 3.11; ν_{max} 3450-3360, 3000, 2940, 2885, 1665, 1630, 1515, 1480, 1465, 1435, 1355, 1255, 1070, 1030, 975, 930 cm^{-1}. N.m.r. δ 7.70-7.00, *m*, 4 x ArH; 6.40, *s*, 2 x ArH; 5.90, *s*, OCH_2O; 5.70-5.40, *m*, NH; 3.90, *s*, OCH_3; 3.65, *s*, $ArCH_2CO$; 3.65-3.20, *m*, $ArCH_2CH_2N$; 2.78-2.57, *m*, $ArCH_2$. Mass spectrum m/e 391 (M^+, <1), 179 (12), 178 (100), 165 (22), 44 (26), 40 (22), 32 (28), 30 (8), 29 (12), 28 (30).

1-(2-Bromobenzyl)-5-methoxy-6, 7-methylenedioxy-3, 4-dihydroisoquinoline (5)

A solution of the amide (4) (2 g) and phosphorus oxychloride (6 g) in dry acetonitrile (50 ml) was refluxed for 3 h and the solvent and excess reagent were removed *in vacuo*. The residue was shaken with chloroform (50 ml) and dilute sodium hydroxide (50 ml). The washed and dried chloroform layer was then evaporated to give a yellow-brown oil which crystallised from methanol as pale yellow *prisms* (1.7 g; 89%), m.p. 135-137° (Found: C, 57.4; H, 4.3; N, 3.8; Br, 21.3. $C_{18}H_{16}BrNO_3$ requires C, 57.8; H, 4.3; N, 3.7; Br, 21.4%). λ_{max} 220 sh, 290, 316sh nm, log ε 4.48, 3.85, 3.63, λ_{max} ($EtOH/H^+$) 225sh, 245sh, 350 nm, log 4.36, 4.09, 3.97. ν_{max} 3000, 2990-2910, 2890-2875, 2840, 1630, 1595, 1560, 1495, 1470-1460, 1435, 1390, 1350, 1330, 1200; 1245-1200, 1155, 1120, 1080, 1050, 1030, 990, 955, 930, 900, 885, 840, 810, 740-715 cm^{-1}. N.m.r. δ 7.75-6.85, *m*, 4 x ArH; 6.71, *s*, ArH; 5.91, *s*, OCH_2O; 4.10, *s (b)*, $ArCH_2C = N$; 4.00, *s*, OCH_3; 3.85-3.50, *m*, $ArCH_2CH_2N$; 2.85-2.45, *m*, $ArCH_2$. Mass spectrum m/e 375 (5), 374 (5), 373 (M^+, 5), 372 (5), 295 (20), 294 (100), (293 (9), 292 (9), 278 (18), 147 (8), 83 (6), 45 (17), 44 (34), 43 (8), 40 (29), 32 (76), 31 (29), 29 (21), 28 (7).

(Z)-1-(2-Bromobenzylidene)-2-ethoxycarbonyl-5-methoxy-6, 7-methylenedioxy-1, 2, 3, 4-tetrahydroisoquinoline (6)

A solution of ethyl chloroformate (6 g) in chloroform (25 ml) was added dropwise over 20 min to a stirred solution of the dihydroisoquinoline (5) (2 g) in chloroform (20 ml) and pyridine (10 ml) at 0-5°. The solution was then stirred overnight at room temperature. The resulting red solution was poured into ice-cold 5*N* hydrochloric acid (40 ml) and the organic layer washed with 5*N* hydrochloric acid, water, brine and then dried. Removal of the solvent left a yellow oil which crystallised from ethanol as colourless prisms of the *stilbene* (6) (1.9 g; 80%), m.p. 213-15° (Found: C, 56.4; H, 4.7; N, 3.0; Br, 17.7. $C_{21}H_{20}BrNO_5$ requires C, 56.5; H, 4.5; N, 3.1; Br, 17.9%). λ_{max}

252sh, 300 nm, logε 4.12, 4.07; ν_{max} 2995-2980, 2930, 2900-2860, 1680, 1610, 1495, 1470, 1450, 1420, 1400, 1340, 1280, 1260, 1240-1220, 1180, 1145, 1120, 1090, 1070, 1050, 970, 940, 895, 865, 835 cm^{-1}. N.m.r. δ 7.75-6.90, *m*, CH=C and 5 x ArH; 5.95, *s*, OCH_2O; 4.10-3.85, *m*, $ArCH_2CH_2N$; 4.00, *s*, OCH_3; 3.73, *q* (*J* = 7 Hz), $COOCH_2$; 2.97-2.70, *m*, $ArCH_2$; 0.81, *t* (*J* = 7 Hz) $COOCH_2CH_3$. Mass spectrum m/e 447 (6), 445 (M^+, 7), 416 (18), 414 (18), 371 (6), 299 (5), 294 (22), 293 (100), 292 (11), 83 (8), 82 (10), 80 (7), 45 (11), 44 (65), 43 (11), 40 (51), 32 (73), 31 (8), 29 (45), 28 (47).

(Z)-1-(2-Bromobenzylidene)-2-methoxycarbonyl-5-methoxy-6, 7-methylenedioxy-1, 2, 3, 4-tetrahydroisoquinoline (7)

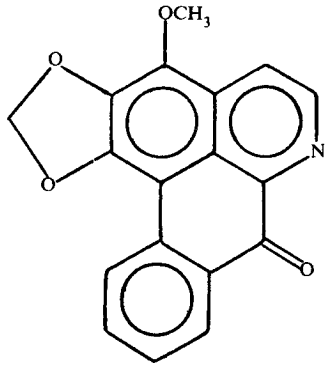
The stilbene (7) was prepared in exactly the same manner as that used for the stilbene (6) in 82% yield. It crystallised from ethanol as colourless *prisms*, m.p. 205-206° (Found: C, 55.3; H, 4.2; N, 3.0; Br, 18.2. $C_{20}H_{18}BrNO_5$ requires C, 55.6; H, 4.2; N, 3.2; Br, 18.5%). λ_{max} 222sh, 252sh, 300 nm, logε 4.50, 4.10, 4.07; ν_{max} 2960, 2900, 1690, 1620, 1500-1440, 1400, 1340, 1280-1200, 1150, 1100, 1060, 970, 950 cm^{-1}. N.m.r. δ 7.68-7.05, *m*, 4 x ArH; 7.00 and 6.90, 2 *singlets*, H_8 and CH=C; 5.90, *s*, OCH_2O; 4.00, *s*, OCH_3; 4.05-3.70, *m*, $ArCH_2CH_2N$; 3.21, *s*, $COOCH_3$; 2.90-2.65, *m*, $ArCH_2$.

6-Ethoxycarbonyl-3-methoxy-1, 2-methylenedioxy-4, 5, 6, 7-tetrahydrodibenzo [d e, g] quinoline (N-Ethoxycarbonyldehydronorstephalagine) (8)

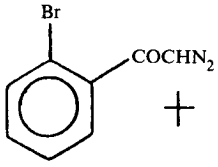
A solution of the stilbene (6) (0.5 g) and potassium *tert*-butoxide (0.6 g) in *tert*-butyl alcohol (50 ml) and benzene (200 ml) was irradiated for 50 h with a 125W medium pressure mercury lamp with a Pyrex filter under a nitrogen atmosphere. The solvent was then removed *in vacuo* and the residue shaken with chloroform (150 ml) and dilute hydrochloric acid (30 ml). The washed and dried chloroform layer was chromatographed on alumina (15 g) packed in benzene. Elution with ethyl acetate-benzene (1 : 1) afforded the dehydroaporphine which was recrystallised from ethanol to give golden-yellow *needles* (0.11 g; 28%), m.p. 138-140° (Found: M, 366.1296. $C_{21}H_{19}NO_5$ requires M, 366.1296). λ_{max} 262, 284sh, 320, 332, 352, 370 nm, logε 4.70, 4.22, 3.98, 3.98, 3.31, 3.23; ν_{max} 3000-2970, 2940, 1685, 1610, 1600, 1540, 1490, 1455, 1420, 1390, 1365, 1325, 1250-1200; 1190, 1160, 1130, 1080, 1060, 1020, 980, 940 cm^{-1}. N.m.r. 9.00-8.85, *m*, H_{11}; 7.85-7.30, *m*, 4 x ArH; 6.23, *s*, OCH_2O; 4.29, *q* (*J* = 7 Hz), $COOCH_2$; 4.09, *s*, OCH_3; 4.02, *t* (*J* = 6 Hz), $ArCH_2CH_2N$; 3.09, *t* (*J* = 6 Hz), $ArCH_2$; 1.32, *t* (*J* = 7 Hz), $COOCH_2CH_3$.

6-Methoxycarbonyl-3-methoxy-1, 2-methylenedioxy-4, 5, 6, 7-tetrahydrodibenzo [d e, g] quinoline (N-Methoxycarbonyldehydrostephalagine) (9)

A solution of the stilbene (7) (0.5 g) and potassium *tert*-butoxide (0.6 g) in *tert*-butyl alcohol (50 ml) and benzene (200 ml) was irradiated as above for 60 h. Workup as above afforded the dehydroaporphine (9) in 27% yield as yellow brown *prisms* m.p. 170-172°, from ethanol, (Found: M, 351.1089. $C_{20}H_{17}NO_5$ requires M, 351.1061).



(1)



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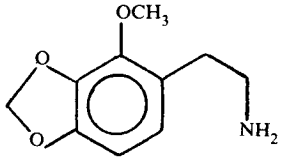

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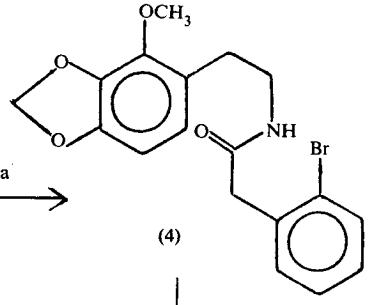

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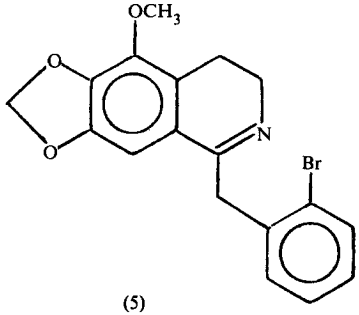

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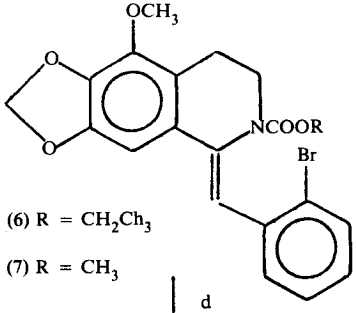
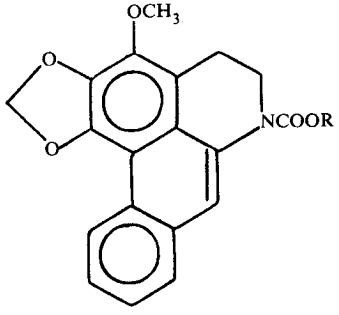


(6) R = CH_2Ch_3

(7) R = CH_3



Scheme : (a) : Ag_2O; (b) $POCl_3$
(c) : ClCOOR/py; (d) : hν/*t*-BuOK

λ_{max} 263, 285sh, 320, 333, 352, 370 nm, log ε 4.74, 4.21, 4.02, 4.02, 3.34, 3.25; ν_{max} 3050, 2950, 2880, 1690, 1630, 1610, 1600, 1585, 1540, 1495-1490, 1460, 1440, 1425, 1380, 1330, 1255, 1245, 1210, 1180, 1165, 1150, 1135, 1090, 1065, 1015, 1000, 950, 940, 885, 860, 830 cm^{-1}. N.m.r. δ 9.10-8.80, *m*, H_{11}; 7.85-7.40, *m*, 4 x ArH; 6.20, *s*, OCH_2O; 4.07, *s*, OCH_3; 4.15-3.90, *m*, $ArCH_2CH_2N$; 3.81, *s*, $COOCH_3$; 3.25-2.95, *m*, $ArCH_2$.

Atherospermidine (1)

A mixture of the dehydroaporphine (8) (80 mg), lithium aluminium hydride (30 mg), aluminium chloride (40 mg) and dry tetrahydrofuran (10 ml) was refluxed for 1 h. Water was added dropwise followed by dilute ammonia. Chloroform extraction afforded a brown oil which was taken up in acetic acid (10 ml) and stirred with lead tetraacetate (250 mg of 85% lead tetraacetate moistened with acetic acid) at room temperature for 24 h. The mixture was then poured into dilute sulphuric acid and extracted with chloroform (3 × 15 ml). The washed and dried chloroform extract was evaporated to give a dark oil which was purified by thin layer chromatography on silica gel; elution with 5% methanol-chloroform gave atherospermidine as fine yellow needles (15 mg), m.p. 274-275° (dec.). The spectral data of the synthetic compound were dentical to those reported for natural atherospermidine[7]. Similarly, reduction of the dehydroaporphine (9) with lithium aluminium hydride-aluminium chloride followed by oxidation with lead tetraacetate as above also afforded atherospermidine in comparable yield.

Acknowledgement

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บทคัดย่อ

การฉายรังสี *(Z)* - 1 - (2 - bromobenzylidene) - 2 - alkoxycarbonyl - 5 - methoxy - 6, 7 - methylenedioxy - 1,2,3,4 - tetrahydroisoquinolines (6 และ 7) ทำให้ได้ 6 - alkoxycarbonyl - 3 - methoxy - 1, 2 - methylenedioxy - 4,5,6,7, - tetrahydrodibenzo *[d e, g]* quinoline (8 และ 9) การรีดิวซ์ 8 และ 9 ด้วย ลิเธียม อะลูมิเนียม คลอไรด์ ตามด้วยการออกซิไดส์ด้วย ตะกั่ว เททราอะซีเตท ทำให้เกิด atherospermidine (1) ในปริมาณผลผลิตปานกลาง