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Photochemical Synthesis of 8*H*-Benzo[*g*]-1,3-benzodioxolo-[6,5,4-*de*]quinolin-8-one (Liriodenine) via 7-Methyl-6,7-dihydro-5*H*-benzo[*g*]-1,3-benzodioxolo[6,5,4-*de*]quinoline

Surachai Nimgirawath[A] *and Walter C. Taylor*[B]

[A] Department of Chemistry, Silpakorn University, Nakorn Pathom, Thailand.
[B] Department of Organic Chemistry, University of Sydney, N.S.W. 2006.

Abstract

Irradiation of ethyl (*Z*)-1-(2-bromobenzylidene)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (4) afforded ethyl 6,7-dihydro-5*H*-benzo[*g*]-1,3-benzodioxolo[6,5,4-*de*]quinoline-7-carboxylate (5), the reduction of which with lithium aluminium hydride–aluminium chloride gave the 7-methyl derivative (6). Oxidation of (6) with lead tetraacetate afforded liriodenine (8*H*-benzo[*g*]-1,3-benzodioxolo[6,5,4-*de*]quinolin-8-one) (1) in moderate yield.

Liriodenine (8*H*-benzo[*g*]-1,3-benzodioxolo[6,5,4-*de*]quinolin-8-one) (1), the first 7-oxoaporphine alkaloid to be fully characterized,[1] has been found to occur in a number of plant families.[2] The total synthesis of liriodenine, by means of the Pschorr cyclization, was reported[1] in 1961. Liriodenine is a broad-spectrum antimicrobial agent being active against gram-positive bacteria and yeast-like and filamentous fungi.[3,4] It also exhibits cytoxic inhibitory activity *in vitro* against cells derived from human carcinoma of the nasopharynx.[5] In view of these biological activities and in connection with other studies, we decided to undertake an alternative synthesis of liriodenine in which the formation of the C-ring was achieved by photochemical means. The synthesis is outlined in Scheme 1.

Reaction of 2-bromo-ω-diazoacetophenone with 2-(3,4-methylenedioxyphenyl)-ethylamine in the presence of silver oxide afforded the amide (2) in good yield. The Bischler–Napieralski cyclization was smoothly effected with phosphorus oxychloride in acetonitrile and the dihydroisoquinoline (3) was obtained in excellent yield. This was treated with ethyl chloroformate and pyridine to give the stilbene (4) in which a *trans* configuration of the two benzene rings was assigned on the basis of u.v. and n.m.r. spectroscopic results. Thus, the methyl protons of the ethoxycarbonyl function resonated unusually upfield at δ 0·83; this must result from a shielding

[1] Taylor, W. I., *Tetrahedron*, 1961, **14**, 42.
[2] Guinaudeau, H., Leboeuf, M., and Cavé, A., *J. Nat. Prod.*, 1979, **42**, 325.
[3] Chen, C. R., Beal, J. L., Doskotch, R. W., Mitscher, L. A., and Svoboda, G. H., *Lloydia*, 1974, **37**, 493.
[4] Hufford, C. D., Funderburk, M. J., Morgan, J. M., and Robertson, L. W., *J. Pharm. Sci.*, 1975, **64**, 789.
[5] Warthen, D., Gooden, E. L., and Jacobson, M., *J. Pharm. Sci.*, 1969, **58**, 637.

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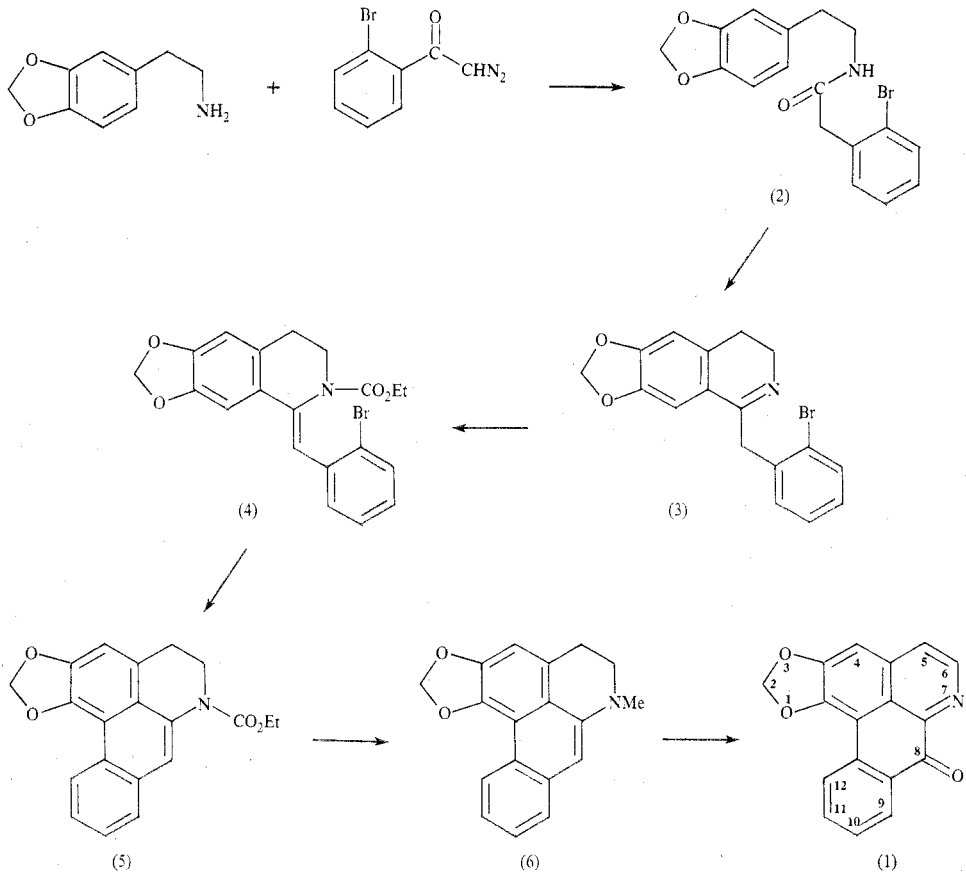
effect by an aromatic ring which can operate only in the *trans* configuration. Irradiation of (4) in 20% t-butyl alcohol/benzene in the presence of potassium t-butoxide gave the corresponding dehydroaporphine, ethyl 6,7-dihydro-5*H*-benzo[*g*]-1,3-benzodioxolo[6,5,4-*de*]quinoline-7-carboxylate (5), in 35% yield. The u.v. spectrum of (5), with a strong band at 257 nm in particular, was diagnostic of a dehydroaporphine system.[6] The n.m.r. spectrum of (5) had a one-proton multiplet at δ 8·88–9·08 which was assigned to H 11. Reduction of (5) with lithium aluminium hydride–aluminium chloride afforded the 7-methyl derivative (6), a natural alkaloid isolated from *Nelumbo nucifera* Gaern (Nymphaeaceae),[7] *Colubrina faralaotra* R. Capuron (Rhamnaceae)[8] and *Stephania sasakii* Hayata (Menispermaceae).[9] The spectral data of (6) were entirely consistent with those of the natural material.[8,9] Since the



Scheme 1

[6] Shamma, M., 'The Isoquinoline Alkaloids' p. 225 (Academic Press: New York 1972).
[7] Kunitomo, J., Yoshikawa, Y., Tanaka, S., Imori, Y., Isoi, K., Masada, Y., Hashimoto, K., and Inoue, T., *Phytochemistry*, 1973, **12**, 699.
[8] Guinaudeau, H., Leboeuf, M., Debray, M., Cavé, A., and Paris, R. R., *Planta Med.*, 1975, **27**, 304.
[9] Kunitomo, J., Murakami, Y., Oshikata, M., Shingu, T., Lu, S.-T., Chen, I.-S., and Akasu, M., *Yakugaku Zasshi*, 1981, **101**, 431.

only synthesis of (6) has involved dehydration of ushinsunine with phosphorus oxychloride and pyridine,[10] the present work constitutes a total synthesis of this alkaloid. Finally, oxidation of (6) with lead tetraacetate afforded liriodenine in 27% yield. In a recent report a 61% yield of liriodenine was claimed by the oxidation of the dihydro derivative of (6) with Fremy's salt.[11] This reagent was not tested in the present work.

Experimental

Melting points were determined on a Kofler hot-stage microscope 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 spectrophotometer. Mass spectra were obtained at 70 eV with an A.E.I. MS 902 mass spectrometer. ^{1}H nuclear magnetic resonance spectra were measured in deuterochloroform solutions on a Varian A60 or Varian EM360A 60 MHz instrument. Analyses were performed by the Australian Microanalytical Service, Melbourne.

2-(3,4-Methylenedioxyphenyl)ethylamine

A solution of 3,4-methylenedioxy-β-nitrostyrene (40 g) in tetrahydrofuran (1·5 l.) was added dropwise to a stirred suspension of lithium aluminium hydride (30 g) in tetrahydrofuran (300 ml) and the reaction mixture was stirred overnight at room temperature. Wet ether (500 ml) was then added followed by dropwise addition of water (30 ml), 15% sodium hydroxide (30 ml) and then water (100 ml). The resulting precipitate was filtered and washed with ether. The filtrate and washings were washed with water, brine and dried over potassium carbonate. Removal of the solvent left an oil which was distilled to give the amine as a colourless oil (22 g, 64%), b.p. 106–110°/1 mm (lit.[12] 146–148°/10 mm). N.m.r. δ 1·47, bs, NH_2; 2·45–3·05, m, $ArCH_2CH_2$; 5·88, s, OCH_2O; 6·45–6·85, m, 3ArH.

2-Bromo-ω-diazoacetophenone

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 (generated from 40 g of *N*-nitrosomethylurea) at 0°. The reaction mixture was then left to stand overnight at room temperature and the solvent removed under vacuum to give a yellow oil (21 g, 93%) which was satisfactory to use in the next step. A small portion of the diazoketone was crystallized from light petroleum at 0° to give yellow needles, m.p. 41–42° (lit.[13] 42–43°). N.m.r. δ 5·70, s, $COCHN_2$; 7·13–7·73, m, 4ArH.

N-[*2-(3,4-Methylenedioxyphenyl)ethyl*]-*2-bromophenylacetamide* (*2*)

Silver oxide (0·5 g) was added portionwise over 20 min to a stirred solution of 2-bromo-ω-diazoacetophenone (4·5 g) and 2-(3,4-methylenedioxyphenyl)ethylamine (3·3 g) in dry dioxan (75 ml) at 60° and the reaction mixture was stirred for 1½ h longer at 60–70°. Silver oxide (0·5 g) was added, the reaction mixture refluxed for ½ h and then filtered hot. The filtrate was evaporated to give a crystalline solid which was recrystallized from ethanol to give colourless needles of the *amide* (2) (6·0 g, 83%), m.p. 128–130° (Found: C, 56·4; H, 4·6; Br, 22·0; N, 3·8. $C_{17}H_{16}BrNO_3$ requires C, 56·4; H, 4·4; Br, 22·1; N, 3·9%). N.m.r. δ 2·67, t, *J* 6 Hz, $ArCH_2CH_2$; 3·38, t, *J* 6 Hz, $ArCH_2CH_2$; 3·67, s, $ArCH_2CO$; 5·30–5·70, bs, NH; 5·91, s, OCH_2O; 6·50, d, *J* 8 Hz, ArH; 6·60, s, ArH, 6·70, d, *J* 8 Hz, ArH; 7·10–7·70, m, 4ArH. Mass spectrum *m/z* 361 (2%), 171 (5), 169 (5), 149 (10), 148 (100), 135 (11), 32 (55), 30 (11).

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[13] Hoermann, W. D., and Fahr, E., *Justus Liebigs Ann. Chem.*, 1963, **663**, 1.

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

The cyclization method of Cleaver *et al.*[14] was used.

A solution of the amide (2) (4 g) and phosphorus oxychloride (12 g) in dry acetonitrile (150 ml) was refluxed for 3 h and the excess reagent and solvent were removed under vacuum. The residue was shaken with chloroform (100 ml) and dilute sodium hydroxide (100 ml). The washed and dried chloroform layer was then evaporated to give a yellow-brown oil which crystallized from ethanol as pale yellow prisms of the *dihydroisoquinoline* (3) (3·5 g, 92%), m.p. 121–123° (Found: C, 59·2; H, 4·1; Br, 23·2; N, 4·1. $C_{17}H_{14}BrNO_2$ requires C, 59·3; H, 4·1; Br, 23·2; N, 4·1%). λ_{max} 215(sh), 230(sh), 318 nm; log ε 3·46, 3·36, 2·91. ν_{max} (Nujol) 1635, 1600, 1565, 1496, 1310, 1275, 1260, 1190, 1120, 1095, 1060, 1040, 990, 955, 890, 865, 780, 755, 750 cm^{-1}. N.m.r. δ 2·40–2·80, m, $ArCH_2CH_2N$; 3·50–3·87, m, $ArCH_2CH_2N$; 4·12, s, $ArCH_2$; 5·95, s, OCH_2O; 6·67, s, H5; 6·90, s, H8; 7·05–7·70, m, 4ArH. Mass spectrum *m/z* 345 (2%), 343 (3), 265 (16), 264 (100), 263 (16), 262 (19), 234 (10), 206 (15), 205 (6), 204 (11), 102 (6), 89 (8), 63 (6), 44 (33), 43 (11).

Ethyl (Z)-1-(2-Bromobenzylidene)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (4)

A solution of ethyl chloroformate (18 g) in chloroform (40 ml) was added dropwise over 30 min to a stirred solution of the dihydroisoquinoline (3) (6 g) in pyridine (20 ml) and chloroform (60 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 (100 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 crystallized from ethanol as almost colourless plates of the *stilbene* (4) (6·0 g, 83%), m.p. 164–166° (Found: C, 57·5; H, 4·4; Br, 19·0; N, 3·4. $C_{20}H_{18}BrNO_4$ requires C, 57·7; H, 4·4; Br, 19·2; N, 3·4%). λ_{max} 295, 322(sh) nm; log ε 4·10, 4·03. ν_{max} ($CHCl_3$) 3000–2750, 2930, 2895, 1690, 1635, 1620, 1500, 1480, 1450, 1430, 1405, 1380, 1330, 1250–1180, 1160, 1150, 1115, 1065, 1040, 1020, 940, 890, 860, 845, 710 cm^{-1}. N.m.r. δ 0·83, t, *J* 7 Hz, Me; 2·70–3·10, m, $ArCH_2CH_2$; 3·73, q, *J* 7 Hz, CH_2CH_3; 3·75–4·10, m, $ArCH_2CH_2$; 5·97, s, OCH_2O; 6·61, s, ArH; 6·93, s, ArH; 7·00–7·75, m, 4ArH, =CH. Mass spectrum *m/z* 417 (26%), 415 (26), 388 (15), 386 (15), 264 (21), 263 (100), 262 (13), 205 (6), 204 (14), 102 (6), 91 (5), 82 (5), 80 (6), 45 (5), 44 (80), 43 (9).

Ethyl 6,7-Dihydro-5H-benzo[g]-1,3-benzodioxolo[6,5,4-de]quinoline-7-carboxylate (5)

A solution of the stilbene (4) (0·5 g) and potassium t-butoxide (0·6 g) in t-butyl alcohol (50 ml) and benzene (200 ml) was irradiated (under nitrogen) for 60 h with a 125-W medium-pressure mercury lamp with a Pyrex filter. The solvent was then removed under vacuum 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* (5) which was recrystallized from ethanol to give golden-yellow needles (0·15 g, 35%), m.p. 172° (Found: C, 71·3; H, 5·2; N, 4·2. $C_{20}H_{17}NO_4$ requires C, 71·6; H, 5·1; N, 4·2%). λ_{max} 257, 278, 289, 322, 332, 358, 377 nm; log ε 4·78, 4·10, 4·01, 4·06, 4·07, 3·55, 3·58. ν_{max} ($CHCl_3$) 3030–2950, 2930, 2900–2875, 1670, 1630, 1610–1600, 1530, 1445, 1420, 1390, 1360, 1320, 1240–1200, 1145, 1110, 1060, 1020, 940, 930, 880, 855 cm^{-1}. N.m.r. δ 1·32, t, *J* 7 Hz, Me; 3·14, t, *J* 6 Hz, $ArCH_2CH_2$; 4·06, t, *J* 6 Hz, $ArCH_2CH_2$; 4·31, q, *J* 7 Hz, CH_2CH_3; 6·20, s, OCH_2O; 7·00, s, H4; 7·40–7·85, m, 4ArH; 8·88–9·05, m, H12.

7-Methyl-6,7-dihydro-5H-benzo[g]-1,3-benzodioxolo[6,5,4-de]quinoline (6)

A mixture of the ester (5) (80 mg), lithium aluminium hydride (30 mg) and aluminium chloride (40 mg) in dry tetrahydrofuran (10 ml) was heated on a steam bath under reflux for 1 h. Water was added dropwise followed by dilute ammonium hydroxide. Chloroform extraction afforded the base (6) which was recrystallized from methanol as pale greenish needles (50 mg), m.p. 86–88°. λ_{max} 256(sh), 263, 333, 388, 395(sh) nm; log ε 4·64, 4·67, 4·07, 3·60, 3·57. ν_{max} ($CHCl_3$) 3000–2780, 1620, 1605–1585, 1530, 1470, 1440, 1425, 1410, 1340, 1310, 1275, 1240, 1190, 1120, 1080, 1055, 1040, 990, 970, 940, 850, 830, 815 cm^{-1}. N.m.r. δ 3·07, s, NMe; 3·10–3·50, m, $ArCH_2CH_2$; 6·20, s, OCH_2O; 6·56, s, ArH; 6·94, s, ArH; 7·20–7·70, m, 3ArH; 8·80–8·95, m, H12.

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Liriodenine (*8*H-*Benzo*[g]-*1,3-benzodioxolo*[*6,5,4*-de]*quinolin-8-one*) (*1*)

A solution of the base (6) (60 mg) in acetic acid (6 ml) was stirred with lead tetraacetate (240 mg of 85% lead tetraacetate moistened with acetic acid) at room temperature for 16 h. The mixture was then poured into dilute sulfuric acid and the mixture extracted with chloroform (10 × 5 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 2% methanol/chloroform gave liriodenine as pale yellow needles (16 mg, 27%), m.p. 281–283° undepressed on admixture with an authentic sample. The spectral data of the synthetic compound were identical to those reported for natural liriodenine.[15]

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[15] Shamma, M., 'The Isoquinoline Alkaloids' Ch. 13 (Academic Press: New York 1972).