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STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS—DCXCIII†

A TOTAL SYNTHESIS OF ATHEROLINE BY PHOTOLYSIS

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Abstract—Atheroline (**3**), an oxoaporphine alkaloid, has been synthesised by photolysis of 8-bromo-1-(3-hydroxy-4-methoxybenzoyl)-6,7-dimethoxyisoquinoline (**13**) in the presence of sodium hydroxide.

Atheroline, isolated from *Atherosperma moschatum*,[1] was firstly assigned to a structure of a phenolic oxoaporphine (**1**),[1] which was later revised to **3** by a synthesis of O-ethylatheroline (**2**).[2] Recently Cava and Noguchi synthesised atheroline (**3**) by applying a classical Pschorr reaction and confirmed its structure.[3] Some oxoaporphines have drawn attention from the pharmaceutical point of view.[4] We have several choices for the synthesis of aporphine alkaloids by photolysis, which are the photolytic electrocyclisation of the benzylidene urethane,[5,6] the photolytic cyclodehydrohalogenation,[7,8] and photo-Pschorr reaction.[9,10] Therefore photolysis of the bromobenzylidene urethane (**7**) and phenolic 1-benzoylisoquinoline (**13**), which were derived from 1 - (3 - benzyloxy - 4 - methoxybenzyl) - 8 - bromo - 3,4 - dihydro - 6,7 - dimethoxyisoquinoline (**6**), were investigated. We now report a total synthesis of atheroline (**3**) by photolysis of the benzoylisoquinoline (**13**).

Refluxing N - (5 - bromo - 3,4 - dimethoxyphenethyl)-3-benzyloxy - 4 - methoxyphenylacetamide (**5**) with phosphoryl chloride caused a predominant cyclisation at the *ortho* position to the Br atom to yield **6**. Condensation of the 3,4-dihydroisoquinoline (**6**) with ethyl chloroformate gave, in 89.5% yield, the benzylidene urethane (**7**). Although the product was not crystallisable, the NMR spectrum of the urethane (**7**) showed the signal, which should be attributed to Me due to ethoxycarbonyl group only at 1.35 ppm as triplet with a coupling constant, $J = 7$ Hz. Cava *et al.* reported that all the Me due to ethoxycarbonyl group of the Z-benzylidene urethanes appeared at 0.87–0.80 ppm.[5] The urethane (**7**) thus seemed to be the stereoisomer having E-form about the double bond. However, irradiation of the urethane (**7**) in the presence of sodium sulphite or potassium carbonate in several solvents gave no cyclised compound but a tarry product.

After a solution of the 3,4-dihydroisoquinoline (**6**) in methanol[11] had been allowed to stand at room temperature for 6 days, the 1 - benzoyl - 3,4 - dihydroisoquinoline (**8**) was obtained in 65% yield together with a small amount of 8-bromocorydaldine (**9**) and 3 - benzyloxy - 4 - methoxybenzaldehyde (**10**). The latter two compounds would indicate the formation of the 1,2-dioxetane (**11**) as an intermediate. The 1 - benzoyl - 3,4 - dihydroisoquinoline (**8**) was also obtained in 50% yield together with a trace of 8-bromocorydaldine (**9**) by stirring the 3,4-dihydroisoquinoline (**6**) with manganese dioxide for 16 hr. Refluxing the 1 - benzoyl - 3,4 - dihydroisoquinoline (**8**) with sodium hydroxide afforded, in 45% yield, the 1 - benzoylisoquinoline (**12**), which was debenzylated to the phenolic 1-benzoylisoquinoline (**13**) in 70% yield.

Irradiation of the above phenolic 1-benzoylisoquinoline (**13**) with a 450 W mercury lamp (quartz) gave atheroline (**3**) in 21.9% yield and its position isomer (**14**) in 20.9% yield. The spectral data and m.ps of atheroline and its O-acetate (**4**) were consistent with those of the previously reported data,[3] respectively.

The structure of the position isomer (**14**) was determined as follows. The mass spectrum, *m/e* 337 (M^+), suggested the removal of hydrogen bromide from the starting benzoylisoquinoline (**13**). The phenolic oxoaporphine structure was indicated from the UV [λ_{max} (MeOH) 271, 353 and 412 nm (log ϵ 4.49, 3.94 and 3.97)] and IR spectra [ν_{max} ($CHCl_3$) 3550 (OH) and 1650 cm^{-1} (C=O)]. The NMR spectrum exhibited five aromatic protons at 7.15 (1H, d, J 9 Hz), 7.20 (1H, s), 7.75 (1H, d, J 5.6 Hz), 8.11 (1H, d, J 9 Hz) and 8.85 (1H, d, J 5.6 Hz), indicating the coupling at the *ortho* position to the OH group which belongs to the benzoyl group.

When a solution of the 1-benzoylisoquinoline (**13**) and sodium hydroxide in methanol was irradiated through Vicor filter for 2.6 hr, the ratio of the formation of both oxoaporphines interestingly changed, and atheroline (**3**) and its position isomer (**14**) were obtained in 24% and 2.5% yield, respectively.

Thus, a total synthesis of atheroline has been accomplished and it is of interest that two position isomers were formed by irradiation of the phenolic 8-bromoisoquinoline.

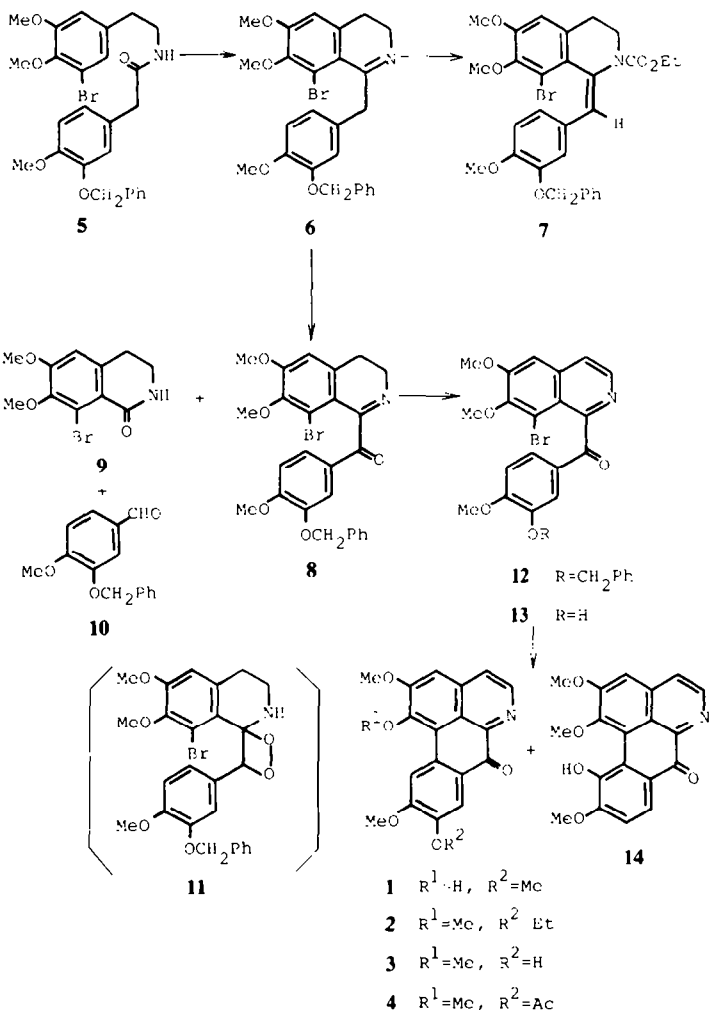
EXPERIMENTAL

All m.ps are uncorrected. The IR, UV and mass spectra were taken with Hitachi 215, Hitachi 124, and Hitachi RMU-7 spectrometers, respectively. The NMR spectra were measured with a JNM-PMX-60 spectrometer.

1 - (3 - Benzyloxy - 4 - methoxybenzyl) - 5 - bromo - 3,4 - dihydro - 6,7 - dimethoxyisoquinoline (**6**)

A mixture of **5**[12] (5 g) and $POCl_3$ (4 g) in dry acetonitrile (100 ml) was refluxed for 1.5 hr and the resulting mixture was evaporated to remove the solvent and reagent. The residue was taken up in

†Part DCXCII, T. Kametani, T. Ohsawa, S. Hirata, M. S. Premila, M. Ihara and K. Fukumoto, *Chem Pharm. Bull.* (Tokyo) **25**, 328 (1977).



Scheme 1.

chloroform, and the extract was washed with 10% ammonia and water. The chloroform extract was dried over Na_2SO_4 and evaporated to give **6** as a yellowish syrup (5 g); IR ($CHCl_3$): 1639 cm^{-1} (C=N); NMR ($CDCl_3$): 3.75 (6H, s, 2 × OMe), 3.80 (3H, s, OMe), 4.29 (2H, s, CH_2), 5.01 (2H, s, OCH_2Ph) and 6.52–6.71 (4H, m, ArH).

1 - (3 - *Benzyloxy* - 4 - *methoxybenzylidene*) - 8 - *bromo* - 2 - *ethoxycarbonyl* - 1,2,3,4 - *tetrahydro* - 6,7 - *dimethoxyisoquinoline* (**7**)

Ethyl chloroformate (5.5 g) was added dropwise to a stirred soln of **6** (1.2 g) and pyridine (3.5 ml) in chloroform (20 ml) at − 5° and the mixture was stirred for 2 hr at room temp. After the addition of chloroform, the resulting mixture was washed with 25% HCl, saturated $NaHCO_3$aq and water. The chloroform layer was dried over Na_2SO_4 and evaporated to give a brown syrup, which was chromatographed on alumina with ether to afford **7** as a yellowish oil (1.15 g); IR ($CHCl_3$): 1680 cm^{-1} (CO); NMR ($CDCl_3$): δ 1.35 (3H, t, J = 7 Hz, CH_2CH_3), 3.75 (3H, s, OMe), 3.82 (3H, s, OMe) and 3.92 (3H, s, OMe); MS *m/e* 569 and 567 (M⁺).

1 - (3 - *Benzyloxy* - 4 - *methoxybenzoyl*) - 8 - *bromo* - 3,4 - *dihydro* - 6,7 - *dimethoxyisoquinoline* (**8**)

(A) A soln of **6** (4.5 g) in MeOH (200 ml) was allowed to stand for 6 days at room temp. After the evaporation of the solvent, the residue was chromatographed on silica gel in benzene. First eluate gave **10** (70 mg), which was identified by TLC and IR and NMR spectral comparisons.

Further elution with MeOH-benzene (1:99 v/v) gave a powder, which was recrystallised from EtOH-chloroform to give **8** as colourless needles (2.85 g), m.p. 152–158°. (Found: C, 59.63; H, 4.51; N, 2.57. $C_{26}H_{24}NO_5Br.0.5H_2O$ requires: C, 60.12; H, 4.85; N, 2.70%). IR ($CHCl_3$): 1660 cm^{-1} (C=O); NMR ($CDCl_3$): δ 3.78 (3H, s, OMe), 3.87 (3H, s, OMe), 3.90 (3H, s, OMe), 5.16 (2H, s, OCH_2Ph) and 6.73 (1H, s, 5-H).

Further elution with MeOH–benzene (3:97 v/v) yielded a powder, which was recrystallised from MeOH–ether to afford **9** as colourless prisms (80 mg), m.p. 197–198°. (Found: C, 46.28; H, 4.20; N, 4.81. $C_{11}H_{12}NO_3Br$ requires: C, 46.15; H, 4.20; N, 4.90%). IR ($CHCl_3$): 1660 cm^{-1} (C=O); NMR ($CDCl_3$): δ 3.80 (3H, s, OMe), 3.88 (3H, s, OMe) and 6.69 (1H, s, 5-H).

(B) To a soln of **6** (2.6 g) in benzene (100 ml), MnO_2 (26 g) was added and the resulting mixture was stirred for 16 hr at room temp. After filtration through celite, the solvent was evaporated and the residue was chromatographed on silica gel to give **8** (1.3 g) and **9** (50 mg), identical with the samples obtained by method A on TLC and IR and NMR spectral comparisons.

1 - (3 - *Benzyloxy* - 4 - *methoxybenzoyl*) - 8 - *bromo* - 6,7 - *dimethoxyisoquinoline* (**12**)

A mixture of the above **8** (1.6 g) and EtOH (90 ml) containing 50% NaOHaq (1 ml) was refluxed for 30 min. After the evaporation of the solvent, the residue was taken up in chloroform. The extract was washed with water, dried over K_2CO_3 and evaporated. The residue was chromatographed on silica gel with benzene to give a powder, which on recrystallisation

from EtOH yielded **12** as colourless needles (700 mg), m.p. 153–154°. (Found: C, 58.97; H, 4.08; N, 2.67. $C_{26}H_{22}NO_5Br.H_2O$ requires: C, 59.32; H, 4.59; N, 2.66%). IR ($CHCl_3$): 1655 cm^{-1} (C=O); NMR ($CDCl_3$): δ 3.86 (6H, s, 2 × OMe), 3.97 (3H, s, OMe), 5.12 (2H, s, $OC\underline{H}_2Ph$), 6.80 (1H, d, J = 8 Hz, 5'-H), 7.10 (1H, s, 5-H), 7.17–7.40 (6H, m, 6'-H and 5 × ArH), 7.47 (1H, d, J = 5.6 Hz, 4-H), 7.62 (1H, d, J = 2 Hz, 1'-H) and 8.35 (1H, d, J = 5.6 Hz, 3-H).

8 - *Bromo* - 1 - (3 - *hydroxy* - 4 - *methoxybenzoyl*) - 6,7 - *dimethoxyisoquinoline* (**13**)

A mixture of the above **12** (450 mg) and conc. HCl (30 ml) in MeOH (30 ml) was refluxed for 1 hr. After evaporation of the solvent, the residue was partitioned between chloroform and 10% ammonia. The chloroform layer was washed with water, dried over Na_2SO_4 and evaporated to give a powder, which on recrystallisation from benzene–chloroform afforded **13** (160 mg) as colourless prisms, m.p. 210–211°. (Found: C, 54.47; H, 3.78; N, 3.31. $C_{19}H_{16}NO_5Br$ requires: C, 54.55; H, 3.83; N, 3.35%). IR ($CHCl_3$): 3550 (OH) and 1660 cm^{-1} (C=O); NMR (dimethyl sulphoxide-d_6): δ 3.82 (6H, s, 2 × OMe), 4.02 (3H, s, OMe), 6.92 (1H, d, J = 8 Hz, 5'-H), 7.13 (1H, dd, J = 8 and 2 Hz, 6'-H), 7.25 (1H, d, J = 2 Hz, 2'-H), 7.63 (1H, s, 5-H), 7.87 (1H, d, J = 5.6 Hz, 4-H) and 8.43 (1H, d, J = 5.6 Hz, 3-H).

Irradiation of the phenolic 1-*benzoylisoquinoline* (**13**).

(A) A soln of the above **13** (240 mg) and NaOH (220 mg) in 90% aqueous MeOH (800 ml) was irradiated with a 450 W mercury lamp (quartz) under a current of N_2 for 27 min. The reaction was monitored by TLC and UV spectroscopy. After the evaporation of the solvent followed by addition of water, the resulting mixture was washed with ether. The aqueous layer was neutralised by addition of crystalline NH_4Cl and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4 and evaporated to give a brown residue, which was purified by column chromatography on silica gel. Elution with MeOH–benzene (2:98 v/v) gave a brown powder, which was rechromatographed on neutral alumina (Woelm, grade III). Elution with chloroform gave a gum, which on recrystallisation from chloroform–hexane afforded **14** (40.4 mg) as a greenish powder, m.p 219–220° (dec.). (Found: C, 65.80; H, 4.30. $C_{19}H_{15}NO_5$. 0.5 H_2O requires: C, 65.89; H, 4.65%). UV (MeOH): 271, 353 and 412 nm (log ϵ 4.49, 3.94 and 3.97); IR ($CHCl_3$) 3550 (OH) and 1650 cm^{-1} (C=O); NMR ($CDCl_3$): δ 3.90 (3H, s, OMe), 4.06 (3H, s, OMe), 4.11 (3H, s, OMe), 7.15 (1H, d, J = 9 Hz, 9-H), 7.20 (1H, s, 3-H), 7.75 (1H, d, J = 5.6 Hz, 4-H), 8.11 (1H, d, J = 9 Hz, 8-H), 8.85 (1H, d, J = 5.6 Hz, 5-H) and 9.29 (1H, s, OH, disappeared with D_2O), MS *m/e* 337 (M^+).

Further elution with MeOH–benzene (2:98 v/v) yielded a brown powder, which on recrystallisation from chloroform–hexane afforded **3** (42.4 mg) as a brown powder, m.p. 250–251° (dec.) [lit.,[3] m.p. 252° (decomp.)]. MS *m/e* 337 (M^+). The IR and UV (EtOH) spectra were consistent with the previous reported data.[3]

(B) A soln of **13** (195.7 mg) and NaOH (200 mg) in 90% aqueous MeOH (800 ml) was irradiated with a 450 W mercury lamp (Vicor filter) under a current of N_2 for 2.6 hr. The same work-up as above gave **14** (3.8 mg), m.p. 219–220° (dec.) and **3** (39 mg), m.p. 250–251° (dec.), identical with the samples, synthesised by method A, respectively, from TLC, UV and IR spectral comparisons.

9 - *Acetoxy* - 1,2,10 - *trimethoxydibenz*[d,e,g]*quinolin* - 7 - *one* (**4**). A soln of **3** (10 mg) and Ac_2O (0.5 ml) in dry pyridine (0.5 ml) was stirred overnight at room temp. After evaporation of the reagents, the residue was taken up in chloroform. The extract was washed with 10% ammonia and water, dried over Na_2SO_4, and evaporated to give a syrup, which was purified by column chromatography on neutral alumina (Woelm; grade III). Elution with chloroform–benzene (1:1 v/v) yielded a yellow powder, which on recrystallisation from chloroform–ether afforded **4** (7 mg) as yellow needles, m.p. 213–217° (dec.) [lit.,[3] m.p. 216–218° (dec.)], whose IR (KBr) and NMR (CF_3CO_2H) spectra were identical with the previously reported data.[3]

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