SYNTHESIS OF BENZO[5,6]CYCLOHEPT[1,2,3,ij]ISOQUINOLINES AS RIGID CONGENERS OF TETRAHYDROPAPAVEROLINE

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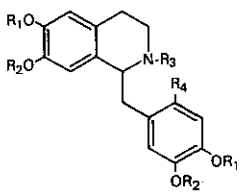
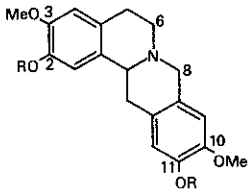
ABSTRACT: The synthesis of several 5,6,9,10-tetraoxygenated 1,2,3,7,12,12a-hexahydrobenzo[5,6]cyclohept[1,2,3-ij]isoquinolines from (±)-coreximine (3) and its diacetate 4 is described. The secondary amine 8 afforded upon N-methylation the isoquinoline 7, previously obtained by Kametani et al through a different route. Aromatization of 8 afforded the aromatic isoquinoline 10 and O-demethylation of 8 with refluxing 48% HBr gave 9, a tetracyclic analog of tetrahydropapaveroline (THP).

Racemic tetrahydropapaveroline (THP; 2) and its optical isomers are mammalian alkaloids, originating *in vivo* from dopamine.[1,2] Racemic THP, and particularly its S-(-)-enantiomer inhibit the binding of radioligands to catecholamine receptors in the CNS[3] and were found highly active in the binding to β-adrenergic and dopaminergic receptors from rat cerebral cortex.[4] Rigid arrangements of the THP molecule prepared in the aporphine,[5] pavinan,[6] isopavinan[6] and berbine series,[5] were considerably less active or even inactive in these or similar assay systems. We considered the methylene isosteres of the cularine alkaloids represented by 7, which were first investigated by Kametani and his school,[7] an interesting ring system to explore in further pursuing the fixed arrangements of THP. We now wish to report the preparation of the 5,6,9,10-tetrahydroxy substituted nor compound 9, an analog of THP with the benzyl group conformationally restricted by a methylene group bridging the 6'-8 positions of THP. This system appeared accessible by initial fission of the N-C_8 berbine bond with a chloroformate, as achieved earlier by Hanaoka and collaborators in their synthesis of (±)-canadine.[8] When (±)-coreximine (3) and the corresponding diacetate (4) were treated in this manner, the following results were obtained.

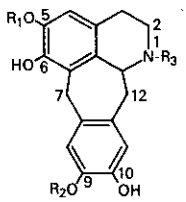
Acylation of (±)-coreximine (3), readily prepared from N-norreticuline[9] (1) by the method of Kametani and collaborators,[10] followed by treatment of its O-diacetate 4 with ethyl chloroformate in refluxing chloroform afforded the crystalline carbamate 5 (82%). Refluxing of 5 in ethanol in



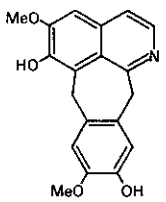
1: R_1 = H, R_2 = Me, R_3 = R_4 = H
2: R_1 = R_2 = R_3 = R_4 = H
5: R_1 = Ac, R_2 = Me, R_3 = CO_2Et, R_4 = CH_2Cl



3: R = H
4: R = Ac



6: R_1 = R_2 = Me, R_3 = CO_2Et
7: R_1 = R_2 = R_3 = Me
8: R_1 = R_2 = Me, R_3 = H
9: R_1 = R_2 = R_3 = H



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the presence of 2% aqueous NaOH provided the diphenolic carbamate 6 (65%), which was converted into Kametani's base 7 by reduction with LAH in refluxing THF (76%). The base 7 of mp 182°C proved identical by spectral comparision with data recorded for a sample prepared by a different route.[12] The mechanism for the formation of the tetracyclic unit is probably initiated through the formation of quinone methide intermediates and their subsequent cyclization as already discussed.[7] Although the ethyl chloroformate route seemed convenient to prepare N-methylated compounds, attempted removal of the N-carbethoxy group with refluxing 48% HBr[13] afforded decomposition products. Hydrazinolysis,[14] although successful, proved unsatisfactory and suggested the following variation which was adopted successfully.

Refluxing (±)-coreximine (3) with 2,2,2-trichloroethyl chloroformate in ethanol, afforded the base 8 in 21% yield, after treatment of the crude reaction products with Zn/NH_4Cl in boiling ethanol and chromatographic purification. Reductive N-methylation of 8 afforded 7 and aromatization in boiling toluene in the presence of Pd/C gave the fully aromatic isoquinoline 10, as shown by spectral analysis. O-Demethylation of 8 with 48% HBr then afforded the tetrahydroxy substituted compound 9, a tetracyclic analog of THP. The biological data of 9 will be reported elsewhere.

EXPERIMENTAL

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed by the Section on Microanalytical Services and Instrumentation of this laboratory, UV spectra were measured in EtOH using a Hewlett Packard 8450A spectrophotometer. IR spectra were determined using Beckman 4230 instrument. ^{1}H NMR spectra were obtained on a Varian HR-220 spectrometer with Me_4Si as the internal reference. Intermediate-range pH strips (pH 0-6 and 5-10) from Aldrich Chemical Company, Inc. Milwaukee, were used for pH determinations. Chemical ionization mass spectra (CI-MS) were determined by using a Finnigan 1015D spectrometer with a Model 6000 data collection system. Electron ionization mass spectra (EI-MS) were obtained with a Hitachi Perkin-Elmer RMU-6E spectrometer (70 ev). ^{13}C-NMR were obtained on a JEOL JNM-FX 60 FT NMR spectrometer. Thin-layer chromatography plates were purchased from Analtech, Inc., Newark, DE. Solvent systems used for TLC (silica gel) were as follows: (A) $CHCl_3$: MeOH (9.8 : 0.2); (B) $CHCl_3$: MeOH : concentrated aqueous NH_3 (9.5 : 0.4 : 0.1); (C) $CHCl_3$: MeOH : concentrated aqueous NH_3 (9.0 : 0.8 : 0.2); (D) $CHCl_3$: MeOH : concentrated aqueous NH_3 (8.5 : 1.3 : 0.2).

1-(5'-Acetoxy-2'-chloromethyl-4'-methoxybenzyl)-N-ethoxycarbonyl-6-methoxy-7-acetoxy-1,2,3,4-tetrahydroisoquinoline (5):

A mixture of 4[10] (8.53 g, 20.7 mol) in EtOH free $CHCl_3$ (400 ml) and ethyl chloroformate (500 ml) was refluxed for 49 h until the TLC (system A) showed the absence of 4 in the reaction mixture. The reaction mixture was cooled and concentrated *in vacuo* to afford an oily residue, which was treated with 2% aqueous HCl solution (100 ml) and extracted with ether (3 x 100 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated to leave an oil, which was digested with ether to afford 5 (8.5 g, 82%); mp 127°C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (OAc), 1690 (N-C=O), 1590 (aromatic) and 1510; ^{1}H NMR ($CDCl_3$): (for the mixture of rotamers) δ 1.07 & 1.20 (2t, each 3 H, $CH_2\underline{CH_3}$), 1.52 (s, 1 H, OH, exchanges with D_2O), 2.20 (s, 6 H, 2 x OAc), 2.64-4.50 (m, 8 H, 4 x CH_2), 3.72 (s, 3 H, OMe), 3.74 (s, 3 H, OMe), 5.06 (m, 1 H, Ar-CH-N) 6.09-6.72 (m, 4 H, 4 x Ar-H); CI-MS m/e 522 (M^+ +1); Anal. Calcd. for $C_{26}H_{30}NO_8Cl$: C, 60.05; H, 5.81; N, 2.69; Cl, 6.81. Found: C, 59.68; H, 5.77; N, 2.67; Cl, 6.87%.

1,2,3,7,12,12a-Hexahydro-6,10-dihydroxy-5,9-dimethoxybenzo-[5,6]-cyclohepta-(1,2,3-ij)-(N-ethoxycarbonyl)isoquinoline (6):

From 5: To a stirred solution of 5 (200 mg, 0.38 mmol) in EtOH (10 ml) under argon was added 2% aqueous NaOH solution (2 ml). The reaction mixture was refluxed for 26 h, then concentrated under reduced pressure to remove EtOH. The aqueous layer was acidified with 2% aqueous HCl (20 ml) and extracted with $CHCl_3$ (3 x 15 ml). The combined organic layer was dried ($MgSO_4$) and

evaporated to leave a residue, which was purified by flash column chromatography over silica gel, using CH_2Cl_2 : MeOH (9.925 : 0.075) to afford 6 (100 mg, 65%): mp 122°C; IR ν_{max}^{KBr} cm^{-1}: 3410 (OH), 1680 (N-C=O), 1615 (aromatic) and 1520; ^1H NMR ($CDCl_3$) : (for the mixture of rotamers) δ 1.33 (t, 3 H, $CH_2\underline{CH_3}$), 1.62 (s, 1 H, OH, exchanges with D_2O), 2.72-4.46 (m, 10 H, 5 x CH_2), 4.08 (s, 3 H, OMe), 4.12 (s, 3 H, OMe), 5.68 & 5.90 (2 bs, each 1 H, 2 x OH) 6.17 (m, 1 H, Ar-CH-N), 6.08 (s, 1 H, Ar-H), 7.02 (s, 1 H, Ar-H) and 7.10 (s, 1 H, Ar-H); EI-MS m/e 399 (M^+); Anal. Calcd. for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.30; N, 3.50. Found: C, 66.47; H, 5.95; N, 3.29%.

From 3: A mixture of 3 (1.9 g, 5.8 mmol) in EtOH free $CHCl_3$ (20 ml) and excess of ethyl chloroformate (70 ml) was refluxed for 41 h until TLC (system B) showed the absence of 3 in reaction mixture. The reaction mixture was concentrated in vacuo to leave an oily residue which was treated with 2% aqueous HCl solution (50 ml) and extracted with $CHCl_3$ (3 x 20 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to residue, which was purified by using flash column chromatography over silica gel (CH_2Cl_2 : MeOH : 9.925 : 0.075) to afford a nearly pure solid residue. It was crystallized from a mixture of CH_2Cl_2- Et_2O to afford 6 (1.0 g, 43%), mp 122°C; IR (KBr) was superimposable with that of the sample prepared from 5 as described above.

1,2,3,7,12,12a-Hexahydro-6,10-dihydroxy-5,9-dimethoxybenzo-[5,6]-cyclohept-(1,2,3,-ij)-N-methylisoquinoline (7):

A solution of 6 (600 mg, 0.66 mmol) in THF (15 ml) was added dropwise to a refluxing mixture of LAH (250 mg, 12.5 mmol) in THF (50 ml) and the resulting mixture was refluxed for 7 h until TLC (system C) showed the absence of 6 in the reaction mixture. The reaction mixture was cooled, cautiously treated with 1 ml of concentrated aqueous NH_3. The reaction mixture was stirred for 0.5 h and filtered. The bluish gray solid was dissolved in 10% aqueous NaOH solution and rendered acidic with 37% HCl (pH 1) and then basic with concentrated aqueous NH_3 (pH 9). The mixture was shaken with $CHCl_3$ (50 ml) and the resulting emulsion was filtered through celite (10 g). The celite was extracted with 20 ml of $CHCl_3$, filtered, and washed with boiling $CHCl_3$ (4 x 10 ml). The combined $CHCl_3$ extracts were separated and washed with H_2O (50 ml), dried (Na_2SO_4) and concentrated to leave a residue, which was crystallized with $CHCl_3$ to afford 7 (392 mg, 76%): mp 182°C (lit.[12] 182-183°C); IR ($CHCl_3$) was superimposable with that of the authentic sample.

1,2,3,7,12,12a-Hexahydro-6,10-dihydroxy-5,9-dimethoxybenzo-[5,6]-cyclohept-(1,2,3,-ij)-isoquinoline (8):

From 6: A solution of 6 (85 mg, 0.21 mmol) in 95% hydrazine (5 ml) and 64% hydrazine (5 ml) was refluxed under N_2 atmosphere for 93 h until TLC (system D) showed the absence of 6 in the reaction mixture). The reaction mixture was cooled and concentrated under reduced pressure to leave a residue, which was dissolved in 2% aqueous HCl solution (20 ml) and washed with ether (3

x 5 ml). The aqueous acidic layer was basified with concentrated aqueous NH_3 (pH 9) and extracted with a mixture of $CHCl_3$: isopropanol (3:1) (3 x 10 ml). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to leave a residue (52 mg). Preparative thin layer chromatography over silica gel with a mixture of $CHCl_3$: MeOH : concentrated aqueous NH_3 (8.5 : 1.3 : 0.2) gave a pure fraction (25 mg), which was crystallized from acetone-Et_2O to afford 8 as white crystals (20 mg, 29%): mp 197°C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH) and 1620 (aromatic); ^1H NMR ($CDCl_3$ + $(CD_3)_2SO$): δ 3.00 (s, 2 H, CH_2), 3.02 (s, 2 H, CH_2), 3.75 (s, 6 H, 2 x OMe), 3.93 (m, 4 H, 2 x CH_2), 4.27 (m, 1 H, Ar-CH-N), 6.31 (s, 1 H, Ar-H), 6.35 (s, 1 H, Ar-H) and 6.51 (s, 1 H, Ar-H); EI-MS m/e 327 (M^+); ^{13}C-NMR $(CD_3)_2SO$): δ 28.8 (C_7), 29.8 (C_3), 40.0 (C_{12},C_2), 43.7 (C_{12a}), 55.8 (2 x OMe), 109.7 (C_4), 114.0 (C_{11}), 117.5 (C_8), 125.0 (C_{3a}), 125.2 (C_{7a}), 127.4 (C_{6a}), 129.4 (C_{11a}), 130.3 (C_{6b}), 140.2 (C_6), 144.4 (C_{10}), 145.0 (C_9) and 145.5 (C_5); hydrochloride salt, mp 248°C (dec.); Anal. Calcd for $C_{19}H_{22}NO_4Cl$: C, 62.72, H, 6.08, N, 3.84, Cl, 9.74. Found: C, 62.37; H, 5.92; N, 3.70, Cl, 9.46%.

From 3: To a well stirred mixture of coreximine (3) (6.52 g, 20 mmol), EtOH free $CHCl_3$ (100 ml), anhydrous $KHCO_3$ (22.0 g, 0.67 mol), was added 2,2,2-trichloroethyl chloroformate (100 ml) dropwise during 10 min under an argon atmosphere. The reaction mixture was refluxed for 5 h, cooled and 2% aqueous HCl solution (100 ml) was added. The aqueous acidic layer was separated and extracted with $CHCl_3$ (4 x 100 ml). The combined organic layer was washed with water (3 x 100 ml), dried ($MgSO_4$) and the solvent was evaporated in vacuo to afforded a foam (8.1 g), CI-MS m/e 502 (M^++1).

Ammonium chloride (22.25 g) was added to a solution of the above foam (7.6 g) in 95% EtOH (585 ml) and the mixture was heated to reflux. Zinc powder (7.3 g, 111 mg. at.) was added to the reaction mixture in portions during 3 h and it was refluxed for 20 h until TLC (system C) showed the absence of the starting material in the reaction mixture. After cooling the Zn was filtered and washed with 95% EtOH (3 x 10 ml). The filtrate was concentrated in vacuo to a residue which was taken up in saturated Na_2SO_4 solution (100 ml) and extracted with a mixture of $CHCl_3$: isopropanol (3:1) (5 x 50 ml). The combined organic layer was evaporated and the residue partitioned between 2% aqueous HCl solution (100 ml) and $CHCl_3$ (3 x 50 ml). The aqueous acidic layer was basified with concentrated aqueous NH_3 (pH 9) and extracted with a mixture of $CHCl_3$: isopropanol (3:1) (3 x 50 ml). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to leave a solid (4.1 g), which was purified by flash column chromatography over silica gel (120 g) using $CHCl_3$: MeOH : NH_4OH (9.0 : 0.8 : 0.2), to afford a nearly pure solid (1.5 g). Crystallization from acetone-Et_2O afforded 8 (1.3 g, 21%), mp 197°C; identical (mp, IR, NMR, MS) with the product synthesized as described above.

1,2,3,7,12,12a-Hexahydro-6,10-dihydroxy-5,9-dimethoxybenzo-[5,6]-cyclohept-(1,2,3,-ij)-N-methylisoquinoline (7):

Reductive N-methylation of 8 (100 mg) with 37% HCHO (4 ml), EtOH (10 ml) and $NaCNBH_3$ (100

mg, 2.1 mmol) afforded after chromatographic separation of the basic materials on silica gel, compound 7 (10 mg, 10%), identical (mp, IR, NMR, MS) with the material prepared earlier.

12,12a-Dihydro-6,10-dihydroxy-5,9-dimethoxybenzo-[5,6]-cyclohept-(1,2,3-ij)-isoquinoline (10):

A mixture of Pd-C (475 mg) in toluene (10 ml) was refluxed for 30 min under an argon atmosphere. A solution of 8 (100 mg, 0.30 mmol) in hot toluene (30 ml) was then added to the reaction mixture and the mixture was refluxed for 2.5 h until TLC (system C) showed the absence of starting material in the reaction mixture. The cooled reaction mixture was filtered and the filtrate was concentrated to afford a residue, which was crystallized with acetone to afford 10 (50 mg, 51%): mp 259°C; UV λ_{max}^{EtOH} nm (log e): 239 (7.57), 284 (6.73), 323 (6.53) and 334 (6.57); IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 1620 (aromatic) and 1515; ^1H NMR (CD_3OD): δ 2.12 (s, 1 H, OH, 3.76 (s, 3H, OMe), 3.96 (s, 3 H, OMe), 4.48 (bs, 1 H, OH), 6.76 (s, 1 H, Ar-H), 6.84 (s, 1 H, Ar-H), 7.04 (s, 1 H, Ar-H), 7.25 (d, 1 H, J = 9Hz, Ar-H) and 7.88 (d, 1 H, J = 9Hz, Ar-H); CI-MS m/e 324 (M^++1); hydrochloride salt, mp 200°C (d). Anal. Calcd. for $C_{19}H_{18}NO_4Cl$: C, 63.42, H, 5.04, N, 3.89, Cl, 9.85. Found C, 63.45, H, 5.96, N, 3.51, Cl, 9.55%.

1,2,3,7,12,12a-Hexahydro-5,6,9,10-tetrahydroxybenzo-[5,6]-cyclohept(1,2,3-ij)-isoquinoline hydrobromide (9.HBr):

A mixture of 8 (100 mg, 0.30 mmol) and 15 ml of 48% aqueous HBr was heated to solution and refluxed for 1.5 h under an argon atmosphere. The cooled reaction mixture was evaporated to dryness and the solid residue was crystallized from EtOH to afford 9.HBr (70 mg, 61%): mp 275°C (dec); IR ν_{max}^{KBr} cm^{-1}; 3460 (OH) and 1615 (aromatic); ^1H NMR ($(CD_3)_2SO$): δ 2.35 (s, 4 H, 4 x OH), 3.15 (m, 6 H, 3 x CH_2), 3.62 (s, 2 H, Ar-CH_2-Ar), 4.48 (m, 1 H, Ar-CH-N), 6.28 (s, 1 H, Ar-H), 6.30 (s, 1 H, Ar-H) and 6.34 (s, 1 H, Ar-H), EI-MS m/e 299 (M^+); Anal. Calcd. for $C_{17}H_{18}NO_4Br$: C, 53.68; H, 4.77; N, 3.68; Br, 21.03, Found: C, 53.29; H, 5.10; N, 3.73; Br, 21.28%.

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