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Syntheses of Heliparvifoline and *O*-Demethylpteleine

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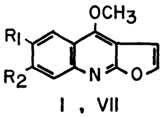
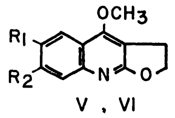
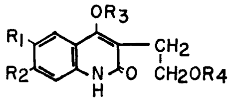
Synopsis. 2,3-Dihydroheliparvifoline (Va) was obtained from 4-methoxy-3-benzyloxyaniline by condensation with diethyl (2-benzyloxyethyl)-malonate, and by subsequent methylation, debenzylation, and then cyclodehydration. Benzyl ether of Va was dehydrogenated and then treated with hydrochloric acid to give heliparvifoline.

Recently, heliparvifoline was isolated from the leaves and twigs of *Helietta parvifolia* Benth (Rutaceae).[1] Its structure was proposed to be 4,6-dimethoxy-7-hydroxyfuro[2,3-*b*]quinoline (Ia) on the basis of the spectral data. However, the synthesis of Ia has not yet been reported. Although *O*-demethylpteleine (Ib) has not yet been found in any natural source, it is considered valuable to synthesize this substance, because it may be expected to occur in nature and to be an intermediate in medicosmine synthesis.[2] Govindachari and his co-workers attempted to synthesize Ib, but they merely obtained benzyl ether of Ib.[3] In previous papers,[4,5] the present author reported the syntheses of some furoquinoline alkaloids through the corresponding dihydrofuroquinolines as key intermediates.

The present paper will describe convenient syntheses of Ia and Ib from 3-benzyloxy-4-methoxyaniline. The condensation of an aniline derivative and diethyl (2-benzyloxyethyl)-malonate without a solvent gave the 4-hydroxy-2-quinolone derivatives (IIa, b), which were methylated with diazomethane into 4-methoxy compounds (IIIa, b). The catalytic debenzylation of IIIa and IIIb using 5% Pd–C gave 3-(2-hydroxyethyl)-4-methoxy-2-quinolone derivatives (IVa, b). The IR spectra of IVa and IVb indicated the presence of a hydroxyl group (*ca.* 3500 cm^{-1}), and the NMR spectra of IVa and IVb indicated the complate debenzylation and exhibited a signal for one proton of the hydroxyl group which easily disappeared upon deuterium exchange. The cyclodehydration of IVa and IVb with polyphosphate ester yielded 2,3-dihydrofuro[2,3-*b*]quinoline derivatives (Va, b). The structures of Va and Vb were assigned on the basis of their NMR spectra, which showed signals at δ *ca.* 3.42(t) and 4.58(t) ppm attributable to two methylene protons of a dihydrofuran-ring system. Since the dehydrogenation of Va and Vb with DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) was unsuccessful, Va and Vb were treated with benzyl chloride to give benzyl ether (VIa,b), whose IR spectra indicated the absence of the hydroxyl group, and their NMR spectra showed signals characteristic of a benzyl group. VIa and VIb were then treated with DDQ in dry toluene to give the corresponding dehydro compounds (VIIa,b). The structures of VIIa and VIIb were assigned on the basis of their NMR spectra, which showed signals at δ 7.04 (d) and 7.62 (d) ppm attributable to the 2,3-protons of a furan-ring system. The debenzylation of VIIa and VIIb with ethanol-hydrochloric acid gave furo[2,3-*b*]quinoline derivatives (Ia; heliparvifoline and Ib; *O*-demethylpteleine). The synthetic heliparvifoline (Ia) was shown to be identical with a natural specimen by a mixed-melting-point determination and by a comparison of the IR, UV, and NMR spectra.


I , VII


V , VI


II , R_3=H , R_4=CH_2Ph
III , R_3=CH_3 , R_4=CH_2Ph
IV , R_3=CH_3 , R_4=H

	I, IV, V		II, III, VI, VII	
	R_1	R_2	R_1	R_2
a	OCH_3	OH	OCH_3	OCH_2Ph
b	OH	H	OCH_2Ph	H

Experimental*

3-(2-Benzyloxyethyl)-4-hydroxy-2-quinolones (IIa, b). A mixture of 3-benzyloxy-4-methoxyaniline (4.2 g) or 4-benzyloxyaniline (3.5 g) and diethyl (2-benzyloxyethyl)-malonate (6.3 g) was heated under reduced pressure (*ca.* 70 mmHg). The temperature was then raised to 180 °C over a period of 30 min, maintained at that temperature for a further 30 min, and then raised and kept at 250 °C for 30 min. The cooled reaction mixture was subsequently dissolved in chloroform. The chloroform solution was treated in a way similar to that described in previous papers.[4,5] IIa: Mp 185—186 °C (pale yellow plates from EtOH) (yield, 58.0%). Found: C, 72.08; H, 5.99; N, 3.21%. Calcd for $C_{26}H_{25}O_5N$: C, 72.37; H, 5.84; N, 3.25%. IR (cm^{-1}, Nujol): 3200, 1650. NMR ($CDCl_3$): δ 3.14, 3.82 ppm (both 2H, t, J=5.0 Hz, **CH_2–CH_2**), 3.93 (3H, s, **OCH_3**), 4.66, 5.20 (both 2H, s, **CH_2**Ph), 6.85 (1H, s, arom-**H**), 7.2—7.5 (11H, m, arom-**H** and 2×CH_2**Ph**), 9.68 (1H, br, **OH**), 12.04 (1H, br, **NH**). IIb: Mp 190.5—191.5 °C (pale yellow needles from ethyl acetate) (yield, 88.5%). Found: C, 74.73; H, 5.72; N, 3.50%. Calcd for $C_{25}H_{23}O_4N$: C, 74.79; H, 5.78; N, 3.49%. IR (Nujol); 3400, 1650. NMR ($CDCl_3$): δ 3.20, 3.90 (both 2H, t, J=5.3 Hz, **CH_2–CH_2**), 4.67, 5.15 (both 2H, s, **CH_2**Ph), 7.28, 7.38 (both 5H, s, CH_2**Ph**) 7.2—7.6 (3H, m, arom-**H**), 9.75 (1H, br, **OH**), 12.00 (1H, br, **NH**).

3-(2-Benzyloxyethyl)-4-methoxy-2-quinolones (IIIa, b). Prepared by the usual diazomethane method: IIIa: Mp 175—176 °C (colorless plates from ethyl acetate) (yield, 81.0%). Found: C, 72.52; H, 6.16; N, 3.08%. Calcd for $C_{27}H_{27}O_5N$: C, 72.79; H, 6.11; N, 3.14%. IR (Nujol): 1660. NMR ($CDCl_3$): δ 3.92, 3.94 (both 3H, **OCH_3**), 3.06, 3.82 (both 2H, t, J=6.8 Hz, **CH_2–CH_2**), 4.51, 5.18 (both 2H, s, **CH_2**Ph), 6.8—7.5 (12H, m, arom-**H** and CH_2**Ph**),

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* All the melting points are uncorrected.

12.46 (1H, s, **NH**). IIIb: Mp 163—165 °C (pale yellow needles from EtOH) (yield, 90.5%). Found: C, 75.08; H, 6.01; N, 3.45%. Calcd for $C_{26}H_{25}O_4N$: C, 75.16; H, 6.07; N, 3.37%. IR (Nujol): 1650. NMR ($CDCl_3$): δ 3.87 (3H, s, $\mathbf{OCH_3}$), 3.07, 3.83 (both 2H, t, J=7.2 Hz, $\mathbf{CH_2}$–$\mathbf{CH_2}$), 4.55, 5.12 (both 2H, s, $\mathbf{CH_2}$Ph), 7.24, 7.40 (both 5H, s, CH_2**Ph**), 7.0—7.5 (3H, m, arom-**H**), 12.25 (1H, br, **NH**).

3-(2-Hydroxyethyl)-4-methoxy-2-quinolones (IVa, b). To a hydrogen-saturated solution of Pd-C (5%, 2.0 g) in abs ethanol 100 ml, IIIa or IIIb (5.0 g) was added; the mixture was then stirred for 3 h at *ca.* 60 °C in an atmosphere of hydrogen. After the catalyst had been filtered off, the residue was recrystallized from ethanol to give 1.7 g (62.7%) of IVa or 1.8 g (63.6%) of IVb. IVa: Mp 217—219 °C. Found: C, 58.80; H, 5.69; N, 5.27%. Calcd for $C_{13}H_{15}O_5N$: C, 58.86; H, 5.70; N, 5.28%. IR (Nujol): 3500, 3200, 1650. NMR (DMSO-d_6): δ 3.87, 3.91 (both 3H, s, $\mathbf{OCH_3}$), 2.77, 3.65 (both 2H, t, J=7.0 Hz, $\mathbf{CH_2}$–$\mathbf{CH_2}$), 6.85, 7.06 (both 1H, s, C_8–**H** and C_5–**H**), 8.28, 9.80, 11.40 (each 1H, br, **OH** and **NH**). IVb: Mp 227—229 °C (colorless needles from EtOH). Found: C, 61.04; H, 5.65; N, 6.24%. Calcd for $C_{12}H_{13}O_4N$: C, 61.27; H, 5.57; N, 5.96%. IR (Nujol): 3600, 3200, 1655. NMR (DMSO-d_6): δ 3.86 (3H, s, $\mathbf{OCH_3}$), 2.70, 3.57 (both 2H, t, J=6.0 Hz, $\mathbf{CH_2}$–$\mathbf{CH_2}$), 4.66 (1H, t, J=5.25 Hz, CH_2OH), 6.8—7.4 (3H, m, arom-**H**), 9.38 (1H, s, **OH**), 11.45 (1H, s, **NH**).

*2,3-Dihydrofuro[2,3-*b*]quinolines (Va, b).* A mixture of IVa or IVb (1.0 g) and polyphosphate ester (15 g) was heated at 120—130 °C for 2.5 h. The cooled mixture was then poured into water, and the insoluble materials were filtered off. The aq. solution was neutralized with ammonia. The precipitate was collected, washed with water, and recrystallized to give Va or Vb. Va: Mp 320 °C (dec, pale green needles from EtOH) (yield, 42.2%). Found: C, 63.30; H, 5.29; N, 5.47%. Calcd for $C_{13}H_{13}O_4N$: C, 63.15; H, 5.30; N, 5.67%. IR (Nujol): 3400, 1630, 1490. NMR (DMSO-d_6): δ 3.60, 4.50 (both 2H, t, J=7.8 Hz, $\mathbf{CH_2}$–$\mathbf{CH_2}$), 3.85, 4.18 (both 3H, s, $\mathbf{OCH_3}$), 6.93, 7.23 (both 1H, s, C_8–**H** and C_5–**H**), 9.55 (1H, br, **OH**). Vb: Mp 288—290 °C (colorless needles from EtOH) (yield, 67.7%). Found: C, 66.46; H, 5.07; N, 6.50%. Calcd for $C_{12}H_{11}O_3N$: C, 66.35; H, 5.10; N, 6.45%. IR (Nujol): 3450, 1630, 1520. NMR (DMSO-d_6): δ 3.60, 4.50 (both 2H, t, J=7.5 Hz, $\mathbf{CH_2}$–$\mathbf{CH_2}$), 4.15 (3H, s, $\mathbf{OCH_3}$), 6.95—7.55 (3H, m, arom-**H**), 9.45 (1H, s, **OH**).

*Benzyl Ether of 2,3-Dihydrofuro[2,3-*b*]quinolines (VIa, b).* To a sodium ethoxide solution prepared from metallic sodium (140 mg) and abs. ethanol (100 ml), Va (1.0 g) or Vb (0.9 g), and benzyl chloride (0.7 g) were added, after which the mixture was refluxed for 8 h in an atmosphere of nitrogen. After the mixture had then been evaporated under a vacuum, the residue was extracted with chloroform. The chloroform solution was washed with a sodium hydroxide solution and water, and then extracted with a 6M hydrochloric acid solution. The acidic solution was neutralized with ammonia and extracted with chloroform. After the solvent had been evaporated, the residue was recrystallized to give VIa or VIb. VIa: Mp 177—179 °C (colorless plates from EtOH) (yield, 60.2%). Found: C, 71.23; H, 5.61; N, 4.05%. Calcd for $C_{20}H_{19}O_4N$: C, 71.20; H, 5.68; N, 4.15%. NMR ($CDCl_3$): δ 3.90, 4.09 (both 3H, s, $\mathbf{OCH_3}$), 3.51, 4.49 (both 2H, t, J=8.8 Hz, $\mathbf{CH_2}$–$\mathbf{CH_2}$), 4.44 (2H, s, $\mathbf{CH_2}$Ph), 7.14 (7H, m, arom-**H** and CH_2**Ph**). VIb: Mp 182—184 °C (colorless plates from EtOH) (yield, 63.5%). Found: C, 74.02; H, 5.52; N, 4.40%. Calcd for $C_{19}H_{17}O_3N$: C, 74.25; H, 5.58; N, 4.56%. NMR ($CDCl_3$): δ 4.10 (3H, s, $\mathbf{OCH_3}$), 3.50, 4.50 (both 2H, t, J=8.0 Hz, $\mathbf{CH_2}$–$\mathbf{CH_2}$), 5.07 (2H, s, $\mathbf{CH_2}$Ph), 7.38 (5H, s, CH_2**Ph**), 7.0—8.0 (3H, m, arom-**H**).

*Benzyl Ether of Furo[2,3-*b*]quinolines (VIIa, b).* To a solution of VIa or VIb (1.0 g) in dry toluene (150 ml), DDQ (2.0 g) was added; the mixture was then stirred under reflux for 16 h in an atmosphere of nitrogen. The mixture was filtered, and the filtrate was washed with water and extracted with 6M hydrochloric acid. After the acidic solution had been neutralized with ammonia, the resulting precipitate was collected and recrystallized to give VIIa or VIIb. The product was purified by means of chromatography on Wakogel C-200 (10% $CHCl_3$–C_6H_6). VIIa: Mp 186—187 °C (pale yellow needles from EtOH) (yield, 42.4%). Found: C, 71.43; H, 5.25; N, 4.20%. Calcd for $C_{20}H_{17}O_4N$: C, 71.63; H, 5.11; N, 4.18%. NMR ($CDCl_3$): δ 3.97, 4.35 (both 3H, s, $\mathbf{OCH_3}$), 6.96, 7.50 (both 1H, d, J=2.4 Hz, C_3–**H** and C_2–**H**), 5.27 (2H, s, $\mathbf{CH_2}$Ph), 7.44 (7H, m, arom-**H** and CH_2**Ph**). VIIb: Mp 193—194.5 °C (colorless needles from EtOH) (yield, 32.6%). Found: C, 74.68; H, 5.20; N, 4.79%. Calcd for $C_{19}H_{15}O_3N$: C, 74.74; H, 4.95; N, 4.59%. NMR ($CDCl_3$): δ 4.40 (3H, s, $\mathbf{OCH_3}$), 7.01, 7.57 (both 1H, d, J=3.0 Hz, C_3–**H** and C_2–**H**), 5.16 (2H, s, $\mathbf{CH_2}$Ph), 7.95 (1H, d, J=9.0 Hz, arom-**H**), 7.2—7.6 (7H, m, arom-**H** and CH_2**Ph**).

Heliparvifoline (Ia) and O*-Demethylpteleine (Ib).* A mixture of VIIa or VIIb (0.5 g) and ethanol-hydrochloric acid (1 : 1, 50 ml) was treated by a method similar to that described in previous papers.[4,5] The precipitate was collected and recrystallized to give 4,6-dimethoxy-7-hydroxyfuro[2,3-*b*]quinoline (heliparvifoline, Ia) and 6-hydroxy-4-methoxyfuro[2,3-*b*]quinoline (*O*-demethylpteleine, Ib). Ia: Mp 243—245 °C (lit,[1] 245—246 °C; a mixed melting point with natural heliparvifoline was not depressed.) (pale yellow cubic from MeOH) (yield, 76.5%). Found: C, 63.55; H, 4.48; N, 5.65%. Calcd for $C_{13}H_{11}O_4N$: C, 63.67; H, 4.42; N, 5.71%. IR (Nujol): 3500, 1630, 1490. NMR (DMSO-d_6): δ 3.94, 4.38 (both 3H, s, $\mathbf{OCH_3}$), 7.06 (1H, d, J=2.4 Hz, C_3–**H**), 7.52 (1H, d, J=2.4 Hz, C_2–**H**), 7.20 (1H, s, C_8–**H**), 7.40 (1H, s, C_5–**H**), 7.70 (1H, s, **OH**, disappeared with D_2O). Ib: mp 216—217 °C (pale yellow prisms from EtOH–C_6H_6) (yield, 51.7%). Found: C, 66.75; H, 4.30; N, 6.44%. Calcd for $C_{12}H_9O_3N$: C, 66.97; H, 4.22; N, 6.51%. NMR (DMSO-d_6): δ 4.41 (3H, s, $\mathbf{OCH_3}$), 7.14 (1H, d, J=2.4 Hz, C_3–**H**), 7.68 (1H, d, J=8.0 Hz, arom-**H**), 7.90 (1H, d, J=2.4 Hz, C_2–**H**), 6.7—7.4 (2H, m, arom-**H**), 9.60 (1H, br, **OH**, disappeared with D_2O).

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