# Synthesis of 2,3,10,11-Tetraalkoxy-substituted Tetrahydrobenzo[*a*]naphtho[1,2-*g*]quinolizines

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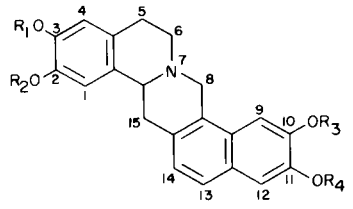
Four 2,3,10,11-tetraalkoxy-substituted 5,6,15,15a-tetrahydro-8*H*-benzo[*a*]naphtho[1,2-*g*]-quinolizines were prepared by the Pictet-Spengler cyclization of the respective 1-(6,7-dialkoxy-2-naphthylmethyl)-6,7-dialkoxy-1,2,3,4-tetrahydroisoquinolines. The latter compounds were obtained by a chemical reduction of the corresponding dihydro compounds, which, in turn, were formed by a Bischler-Napieralski cyclization of the appropriate amides.

Synthesis of 2,3,10,11-tetraalkoxy-5,6,15,15a-tetrahydro-8*H*-benzo[*a*]naphtho[1,2-*g*]quinolizines (I), the second class of model compounds for our triangulation pharmacophore study (1), is presented as follows:



I

Series a: $R_1 = R_2 = R_3 = R_4 = CH_3$
b: $R_1 + R_2 = R_3 + R_4 = CH_2$
c: $R_1 = R_2 = CH_3$; $R_3 + R_4 = CH_2$
d: $R_1 + R_2 = CH_2$; $R_3 = R_4 = CH_3$

Treatment of 6,7-dimethoxy-2-naphthaleneacetyl chloride (IIa), prepared from the corresponding acid (1), with 3,4-dimethoxyphenethylamine (IIIa) in aqueous base gave the substituted amide IVa in 95% yield. Bischler-Napieralski cyclization of IVa with phosphorus pentachloride in chloroform yielded 1-(6,7-dimethoxy-2-naphthylmethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (Va). An oxidized by-product VIa was also formed and identified during the isolation and purification of Va.

Reduction of the dihydroisoquinoline Va with zinc and aqueous acetic acid (2) gave the tetrahydroisoquinoline VIIa, isolated as its hydrochloride. Treatment of VIIa with formaldehyde under the Pictet-Spengler's condition cyclized it to 2,3,10,11-tetramethoxy-5,6,15,15a-tetrahydro-8*H*-benzo[*a*]naphtho[1,2-*g*]quinolizine (Ia), m.p. 238-240°. Nmr study of Ia ruled out the possibility of formation of the kinetically less favorable (3) isomer VIIIa. The mass spectra fragmentation pattern of Ia corresponds exactly to that of the tetrahydroberberine group of alkaloids (4,5), which further confirms the structural assignment. The hydrochloride, m.p. 283-285°, and methiodide IXa, m.p. 273-275° were also prepared.

The corresponding methylenedioxy analogs (series b) and the mixed dimethoxy-methylenedioxy analogs (series c and d) were prepared in a similar fashion. The intermediate homopiperonylamine (IIIb) was obtained by diborane reduction of homopiperonylnitrile (6). Biological activity of these compounds is currently being evaluated.

## EXPERIMENTAL

All melting points were taken on a Thomas-Hoover melting point apparatus. The nmr spectra were determined on a Varian A-60 spectrometer. The mass spectra data were obtained with a Varian Mat CH-4B mass Spectrometer. Infrared spectra were taken on a Perkin Elmer Infracord. The ultraviolet absorption spectra were determined with a Beckman DK-2 spectrometer.

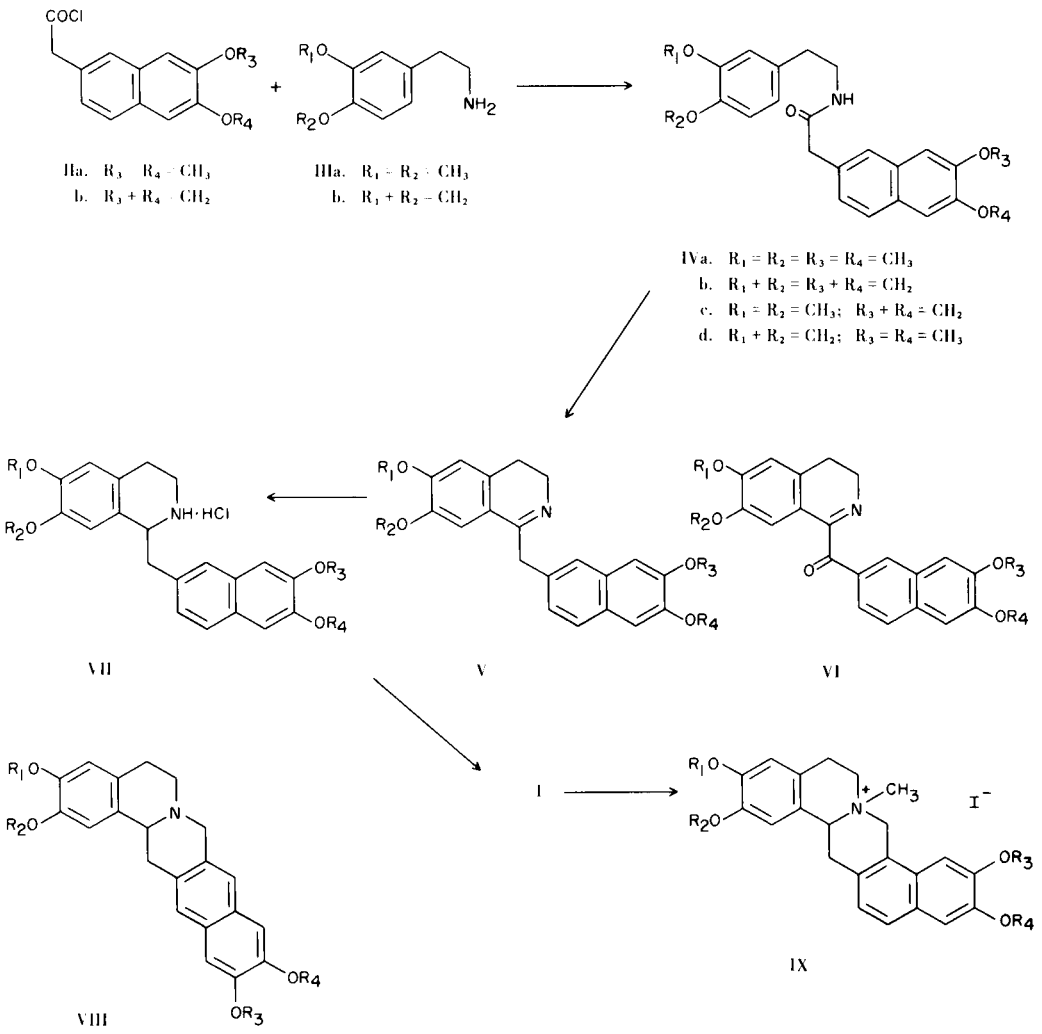
Homopiperonylamine (IIIb).

To a stirred solution of 8.2 g. (0.05 mole) of homopiperonylnitrile (6) in 230 ml. of dry tetrahydrofuran cooled in an ice bath was added dropwise 150 ml. of 1 *M* diborane in tetrahydrofuran. After the addition was complete, the mixture was stirred at 0° for 15 minutes, then at room temperature for 15 minutes, and finally refluxed for 5 hours. The reaction mixture was cooled in an ice bath, after which was decomposed cautiously with 30 ml. of ethanol followed by the addition of 100 ml. of 11% ethanolic hydrogen chloride. After being allowed to stir for 13 hours at room temperature, the mixture was filtered and the white solid washed with ethanol and ether to give, after drying, 8.3 g. (83% yield) of the hydrochloride salt of IIIb, m.p. 210-212° dec. An analytical sample was prepared by recrystallization from butanol, m.p. 210-212° dec.

*Anal.* Calcd. for $C_9H_{11}NO_2$·HCl: C, 53.60; H, 6.00; N, 6.95. Found: C, 53.22; H, 5.81; N, 6.63.

*N*-[2-(3,4-Dimethoxyphenethyl)]-6,7-dimethoxy-2-naphthaleneacetamide (IVa).

To an ice-cooled solution of 12 g. (0.05 mole) of 6,7-dimethoxy-2-naphthaleneacetic acid (1) in 75 ml. of dry chloroform was




added dropwise, with stirring, 27 g. (0.23 mole) of thionyl chloride. The mixture was gradually warmed to room temperature, then heated at 50° on a water bath for 2 hours and allowed to stand overnight at room temperature. Solvent and excess thionyl chloride were removed under reduced pressure. The residue (*ca.* 15 g. of IIa) was dissolved in 450 ml. of ether and the resulting solution was added dropwise, with cooling, to a stirred mixture of 12 g. (0.07 mole) of 3,4-dimethoxyphenethylamine in 100 ml. of ether and 300 ml. of 1 *N* potassium hydroxide. The mixture was stirred in an ice bath for 2 hours and the solid collected by filtration. It was washed successively with water, ether, and petroleum ether, then dried to give 20 g. (95% yield) of IVa, m.p. 134-136°. An analytical sample was prepared by recrystallization from ethanol-water, m.p. 136-138°.

*Anal.* Calcd. for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.52; H, 6.90; N, 3.54.

The following analogous compounds in series IVb-d were prepared in a similar fashion.

*N*-[2-(3,4-Methylenedioxyphenethyl)]-6,7-methylenedioxy-2-naphthaleneacetamide (IVb).

This compound was prepared in 94% yield; m.p. 170-172°.

*Anal.* Calcd. for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07; N, 3.71. Found: C, 70.25; H, 5.06; N, 3.61.

*N*-[2-(3,4-Dimethoxyphenethyl)]-6,7-methylenedioxy-2-naphthaleneacetamide (IVc).

This compound was prepared in 80% yield; m.p. 180-181°.

*Anal.* Calcd. for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. Found: C, 70.09; H, 6.08; N, 3.62.

*N*-[2-(3,4-Methylenedioxyphenethyl)]-6,7-dimethoxy-2-naphthaleneacetamide (IVd).

This compound was prepared in 95% yield, m.p. 187-189°.

*Anal.* Calcd. for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. Found: C, 70.27; H, 5.93; N, 3.63.

1-(6,7-Dimethoxy-2-naphthylmethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (Va).

A solution of 16 g. (0.039 mole) of IVa in 150 ml. of dry chloroform was added slowly into a cold, stirred suspension of 16.1 g. (0.077 mole) of phosphorus pentachloride in 60 ml. of chloroform under nitrogen. The mixture was stirred in an ice bath for 2 hours and then at room temperature for 3 days. (A brown

solution was obtained initially and the hydrochloride salt of the product started to separate as a yellow solid after *ca.* 1 hour). The reaction mixture was poured into 200 g. of ice and extracted with chloroform (2 x 150 ml.). The *p*H of the aqueous layer was adjusted to 8 with aqueous ammonia and the resulting solution extracted with chloroform (4 x 350 ml.). The combined chloroform extract was washed with aqueous ammonia and water, and dried (potassium carbonate). Evaporation of the solvent yielded 23 g. of a solid m.p. 160-210°, which consisted of a mixture of the desired product Va and a minor by-product VIa in the ratio of 3:1. Fractional recrystallizations from a mixture of ethanol-water followed by methanol-water gave *6,7-dimethoxy-2-naphthyl 6,7-dimethoxy-3,4-dihydroisoquinolyl ketone* (VIa) as the less soluble product, m.p. 213-214°; $\nu$ max 1660 $cm^{-1}$ (conjugated carbonyl).

*Anal.* Calcd. for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45; mol. wt., 405.46. Found: C, 70.85; H, 5.95; N, 3.42; m/e 405 ($M^+$).

A more soluble product Va, m.p. 173-175°, was obtained in 70% yield.

*Anal.* Calcd. for $C_{24}H_{25}NO_4 \cdot H_2O$: C, 70.40; H, 6.65; N, 3.42; mol. wt. 391.47 + 18.02. Found: C, 70.47; H, 6.48; N, 3.44; m/e 391 ($M^+$-$H_2O$).

The following analogous compounds in series Vb-d were prepared in a similar manner:

1-(6,7-Methylenedioxy-2-naphthylamethyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (Vb).

This compound was prepared in 90% yield, m.p. 193-195° dec. (HCl salt).

*Anal.* Calcd. for $C_{22}H_{17}NO_4 \cdot HCl$: C, 66.75; H, 4.58; N, 3.54. Found: C, 66.90; H, 4.45; N, 3.55.

1-(6,7-Methylenedioxy-2-naphthylmethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (Vc).

This compound was prepared in 81% yield, m.p. 215-217° dec. (HCl salt).

*Anal.* Calcd. for $C_{23}H_{21}NO_4 \cdot HCl \cdot H_2O$: C, 64.26; H, 5.63; N, 3.26. Found: C, 64.01; H, 5.42; N, 3.27.

1-(6,7-Dimethoxy-2-naphthylmethyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (Vd).

This compound was prepared in 75% yield, m.p. 205-207° dec. (HCl salt).

*Anal.* Calcd. for $C_{23}H_{21}NO_4 \cdot HCl \cdot H_2O$: C, 64.26; H, 5.63; N, 3.26. Found: C, 64.52; H, 5.34; N, 3.15.

1-(6,7-Dimethoxy-2-naphthylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (VIIa).

To a solution of 23 g. (0.06 mole) of Va in 500 ml. of 50% aqueous acetic acid was added 50 g. of zinc dust followed by 8 g. of concentrated hydrochloric acid. The mixture was heated on a steam bath for 10 hours with stirring and then cooled. Excess zinc dust was filtered and the cake was washed with 4 x 100 ml. of hot water. The combined filtrate and washings were cooled in an ice bath and basified with 400 ml. of concentrated aqueous ammonia. The resulting mixture was extracted with chloroform (4 x 350 ml.). The chloroform extract was washed with water and dried (potassium carbonate). The solvent was removed *in vacuo* and the residue was dissolved in 80 ml. of ethanol. To this was added 20 g. of 11% ethanolic hydrogen chloride. The resulting solution was poured into 500 ml. of ether with stirring. The precipitated hydrochloride salt of the tetrahydroisoquinoline was collected by filtration to yield 21 g., m.p. 233° dec. (softened at 160°). Recrystallization from a mixture of methanol and ether gave 18 g. (78% yield) of pure VIIa, m.p. 233-235° dec.

*Anal.* Calcd. for $C_{24}H_{27}NO_4 \cdot HCl$: C, 67.05; H, 6.56; N, 3.26. Found: C, 66.68; H, 6.44; N, 3.12.

The following analogous compounds in series VIIb-d were prepared in a similar manner:

1-(6,7-Methylenedioxy-2-naphthylmethyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (VIIb).

This compound was prepared in 70% yield, m.p. 266-268° dec.

*Anal.* Calcd. for $C_{22}H_{19}NO_4 \cdot HCl$: C, 66.41; H, 5.07; N, 3.52. Found: C, 66.25; H, 4.98; N, 3.73.

1-(6,7-Methylenedioxy-2-naphthylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (VIIc).

This compound was prepared in 70% yield as a monohydrate, m.p. 185-187° dec.

*Anal.* Calcd. for $C_{23}H_{23}NO_4 \cdot HCl \cdot H_2O$: C, 63.96; H, 6.07; N, 3.24. Found: C, 64.19; H, 5.78; N, 3.25.

1-(6,7-Dimethoxy-2-naphthylmethyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (VIId).

This compound was prepared in 69% yield, m.p. 253-255° dec.

*Anal.* Calcd. for $C_{23}H_{23}NO_4 \cdot HCl$: C, 66.74; H, 5.84; N, 3.38. Found: C, 66.78; H, 5.82; N, 3.19.

2,3,10,11-Tetramethoxy-5,6,16,16a-tetrahydro-8*H*-benzo[*a*]naphtho[1,2-*g*]quinolizine (Ia).

To a stirred aqueous solution of 19 g. (0.044 mole) of VIIa in 450 ml. of hot water was slowly added 160 ml. of 40% aqueous formaldehyde followed by 2 ml. of concentrated hydrochloric acid. The mixture was heated on a steam bath with continuous stirring for 1 hour, after which it was stirred overnight and was then allowed to stand at room temperature for 3 days. The reaction mixture was diluted with 400 ml. of water and the *p*H of the solution was adjusted to 8 with aqueous ammonia. It was extracted with 5 x 300 ml. of chloroform and the extract washed with water, treated with charcoal, and dried (potassium carbonate). The solution was evaporated *in vacuo* to a brown syrup. This was triturated with 20 ml. of methanol. The resulting pale yellow solid was collected by filtration to give 6.8 g. (38% yield) of Ia, m.p. 238-240°. An analytical sample was obtained by recrystallization from methanol as fine, yellow crystals, m.p. 238-240°; $\lambda$ max (ethanol) 237 (log $\epsilon$ 4.56), 280 (log $\epsilon$ 3.65), 311 (log $\epsilon$ 3.12) and 325 nm (log $\epsilon$ 3.38); nmr: $J_{H_{13}, H_{14}}$: 7.5 cps. m/e: 405 ($M^+$), 390, 214, 199, 190.

*Anal.* Calcd. for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found: C, 73.94; H, 6.43; N, 3.48.

The *hydrochloride salt of Ia* melted at 283-285° dec.

*Anal.* Calcd. for $C_{25}H_{27}NO_4 \cdot HCl$: C, 67.94; H, 6.39; N, 3.17. Found: C, 67.87; H, 6.62; N, 3.14.

The *methiodide IXa* was prepared in 84% yield, m.p. 273-275°.

*Anal.* Calcd. for $C_{26}H_{30}INO_4$: C, 57.04; H, 5.52; N, 2.56. Found: C, 56.79; H, 5.46; N, 2.49.

The following analogous compounds in series Ib-d were prepared in a similar fashion.

2,3:10,11-Bis(methylenedioxy)-5,6,15,15a-tetrahydro-8*H*-benzo[*a*]naphtho[1,2-*g*]quinolizine (Ib).

This compound was prepared in 70% yield, m.p. 237-238°; $\lambda$ max (ethanol) 233 (log $\epsilon$ 4.87), 267 (log $\epsilon$ 3.96), 276 (log $\epsilon$ 3.99) 288 (log $\epsilon$ 4.02), 314 (log $\epsilon$ 3.72), 322 (log $\epsilon$ 3.72) and 329 nm (log $\epsilon$ 3.88). m/e: 373 ($M^+$), 198, 174.

*Anal.* Calcd. for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75.

Found: C, 74.29; H, 5.26; N, 3.81.

The *hydrochloride salt of Ib* melted at 305-307° dec.

*Anal.* Calcd. for $C_{23}H_{19}NO_4 \cdot HCl \cdot H_2O$: C, 64.56; H, 5.18; N, 3.27. Found: C, 64.22; H, 5.14; N, 3.12.

2,3-Dimethoxy-10,11-methylenedioxy-5,6,15,15a-tetrahydro-8*H*-benzo[*a*]naphtho[1,2-*g*]quinolizine (Ic).

This compound was prepared as its hydrochloride salt in 30% yield, m.p. 270-272°.

*Anal.* Calcd. for $C_{24}H_{23}NO_4 \cdot HCl \cdot \frac{1}{2}H_2O$: C, 66.28; H, 5.79; N, 3.22. Found: C, 66.32; H, 6.05; N, 2.99.

10,11-Dimethoxy-2,3-methylenedioxy-5,6,15,15a-tetrahydro-8*H*-benzo[*a*]naphtho[1,2-*g*]quinolizine [2,3-Dimethoxy-7,8,13b,14-tetrahydro-5*H*-[1,3]benzodioxolo[5,6-*a*]naphtho[1,2-*g*]quinolizine] (Id).

This compound was prepared in 35% yield, m.p. 208-210°.

*Anal.* Calcd. for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 74.37; H, 6.12; N, 3.59.

The *hydrochloride salt of Id* melted at 281-283° dec.

*Anal.* Calcd. for $C_{24}H_{23}NO_4 \cdot HCl$: C, 67.68; H, 5.68; N, 3.29. Found: C, 67.51; H, 5.89; N, 3.27.

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