SYNTHESIS OF HETEROCYCLES THROUGH RING CLOSURE OF 2-(SUBSTITUTED)AMINO-1-PHENYLPROPANOLS

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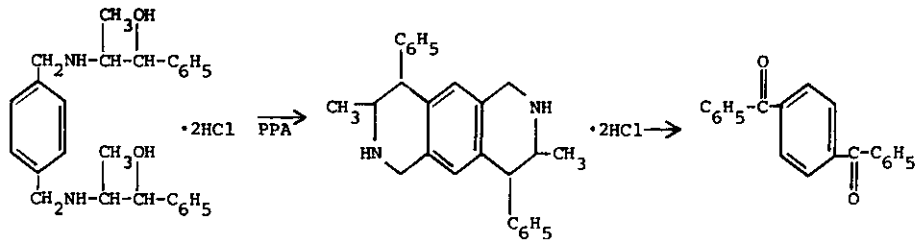
The cyclization of 2-(substituted)amino-1-phenylpropanols in 48% hydrobromic acid or polyphosphoric acid to a variety of nitrogen-containing heterocycles is described.

The facile preparation of 4-phenyl-1,2,3,4-tetrahydroisoquinolines by the 48% hydrobromic acid or polyphosphoric acid (PPA) catalyzed cyclization of 2-benzylamino-1-phenylethanols and related compounds along with a discussion of the scope, limitations, and possible mechanism of the reaction was described previously (1,2).

This publication summarizes the extensions of this cyclization to other nitrogen-containing heterocycles which were conducted in these laboratories. Experimental details are included for transformations not previously reported.

1. Pyrido[3,4-g]isoquinolines

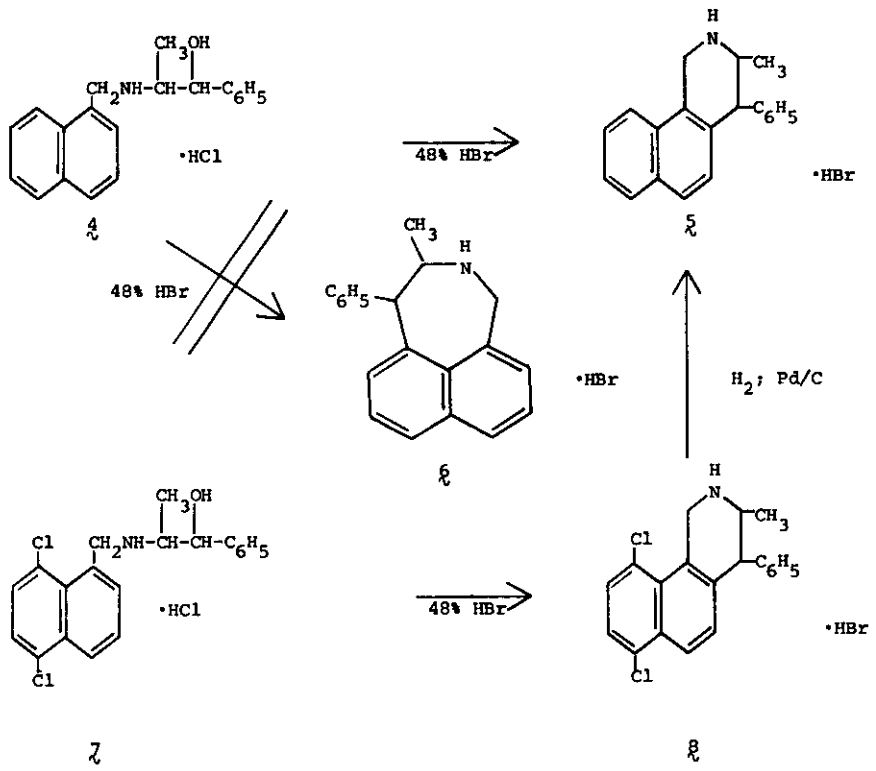
Cyclization of the bis-compound 1 in PPA afforded the pyrido[3,4-g]isoquinoline (2), the linear structure of which was proven by an oxidation-decarboxylation sequence to p-dibenzoylbenzene (3) (3). This apparently was the first reported example of the pyrido[3,4-g]isoquinoline ring system.



1 2 3

2. Benz[h]isoquinolines

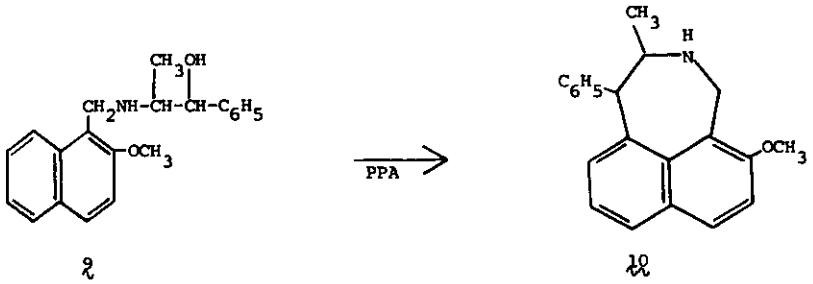
Treatment of the naphthyl compound 4 with refluxing 48% HBr afforded the benz[h]isoquinoline 5 in 93% yield (4). To prove that annelation occurred to the 2-position rather than the 8-position (to yield 6), the dichloro compound 7 with HBr was converted to 8 (5) which upon hydrogenolysis in the presence of palladium-on-carbon gave 5, thus providing an unequivocal route to this compound (6).



4 5 6 7 8

3. Naphth[1,8-cd]azepines

As stated above, cyclization of the 1-substituted naphthyl compound 4, in which the 2-position of the ring contained no substituent, gave the benz[h]isoquinoline 5. In an instance where the 2-position of the naphthalene ring contained a substituent, cyclization to the naphth[1,8-cd]-azepine was observed as is demonstrated in the transformation of 9 → 10 in PPA at 90-95° (6).



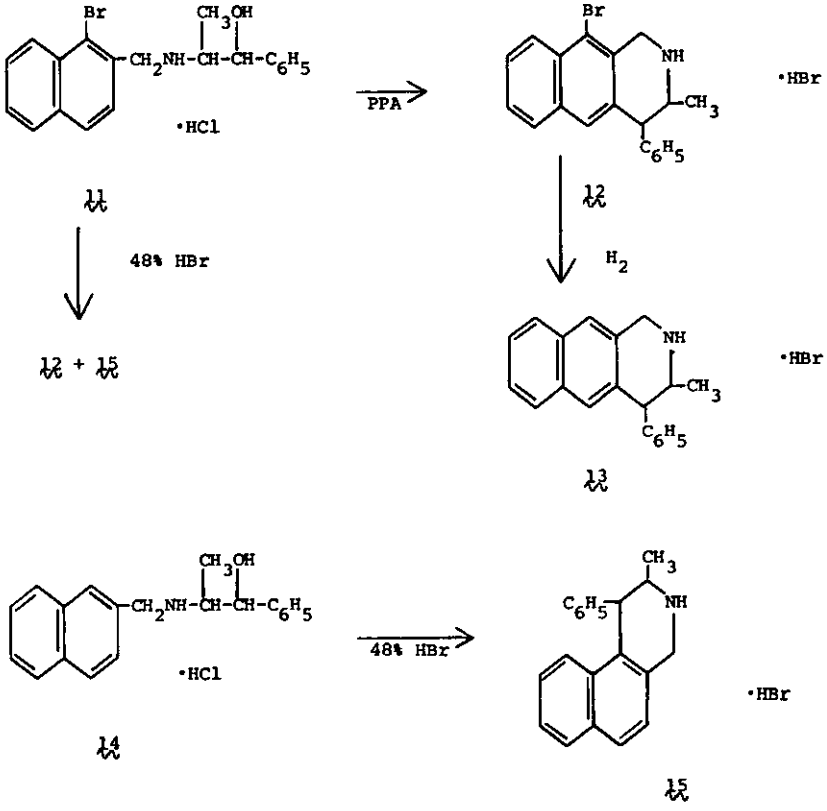
9 10

4. Benz[f]isoquinolines and benz[g]isoquinolines

Annelation of 11 in PPA at 90-95° gave an 88% yield of the benz[g]isoquinoline 12 which upon shaking with hydrogen in the presence of palladium-on-carbon gave 13, providing an unequivocal route to this product (7).

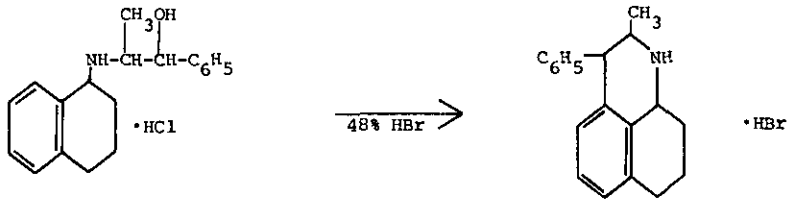
Cyclization of 14 in refluxing 48% HBr afforded an 81% yield at the benz[f]isoquinoline 15, the structure of which was indicated by non-identity with compound 13 (6).

Ring-closure of 11 in 48% HBr gave a mixture of 12 and 15 which was separable by fractional crystallization (6).



5. Benz[de]quinolines

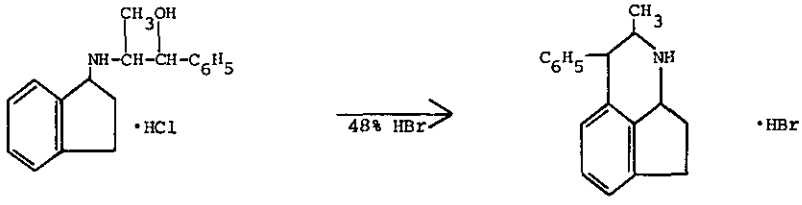
Reaction of the naphthylamine 16 with refluxing 48% HBr for 20 hours afforded the benz[de]-quinoline 17 in 49% yield (8).



16 17

6. Cyclopent[i,j]isoquinolines

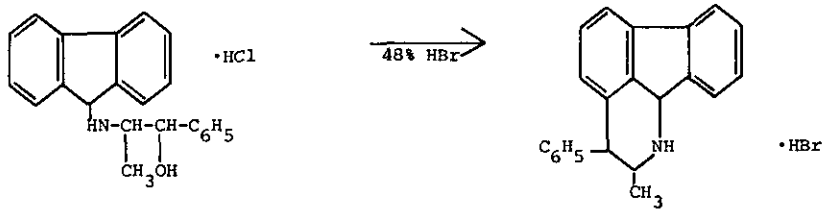
Annelation of the indanylamine 18 in refluxing 48% HBr gave the cyclopent[i,j]isoquinoline 19 in a yield of 40% (9).



18 19

7. Indeno[1,2,3-ij]isoquinolines

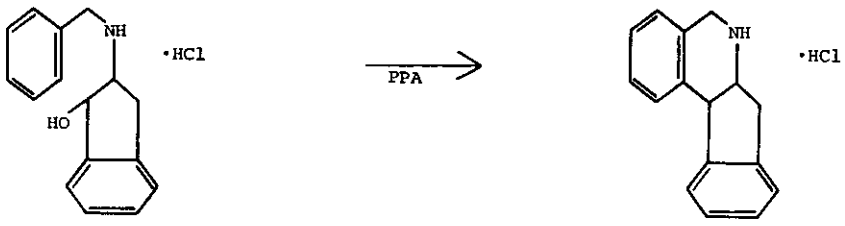
Treatment of the fluorenone derivative 20 with refluxing 48% HBr for 20 hours gave rise to a 14% yield of the cyclized product 21, an indeno[1,2,3-ij]isoquinoline (10).



20 21

8. Indeno[2,1-c]isoquinolines

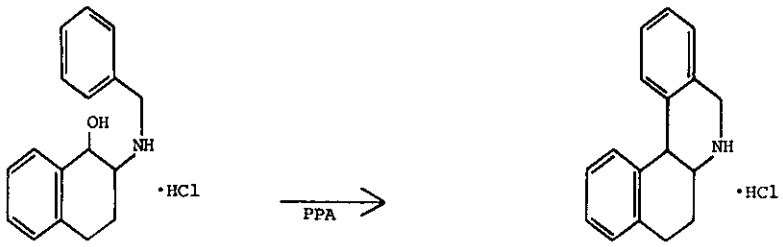
Cyclization of 2-benzylamino-1-indanol hydrochloride (22) in PPA at 95-100° for 18 hours gave the indeno[2,1-c]-isoquinoline 23 in 55% yield (11).



22 23

9. Benzo[a]phenanthridines

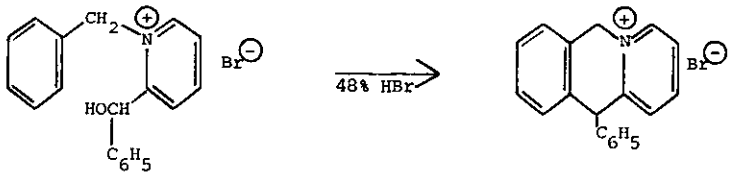
The carbinol 24 (12), when treated with PPA at 95-100°, gave the benzo[a]phenanthridine 25 in a 12% yield (13).



24 25

10. Dihydrobenzo[b]quinolizinium bromides

Reaction of the pyridinium compound 26 with refluxing 48% HBr gave a 53% yield of the benzo-[b]quinolizinium compound 27 (6) which was previously synthesized by another method (14).



26 27

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and those below 230° are corrected. IR spectra were determined as mineral oil mulls using a Perkin-Elmer 137B spectrophotometer. The NMR spectra were obtained on a Varian A-60A instrument and were compared with tetramethylsilane as an internal standard.

2-(5,8-Dichloro-1-naphthylmethylamino)-1-phenyl-1-propanol hydrochloride (7) and 2-(2-

methoxy-1-naphthylmethylamino)-1-phenyl-1-propanol hydrochloride (9) were reported previously (15).

3-Methyl-4-phenyl-1,2,3,4-tetrahydrobenz[h]isoquinoline hydrobromide (5) from 8

A mixture containing 2.12 g (0.005 mole) of 8, 3.0 g 5% Pd/C, and 150 ml of methanol was shaken with hydrogen on a Parr apparatus for 16 hr. The catalyst was filtered and the filtrate concentrated to dryness in vacuo. Treatment of a methanolic solution of the product with sodium methoxide, filtration, and reaction of the free base with 48% HBr gave 0.91 g (52%) of 5, the infrared spectrum of which was identical with that of the product derived from 4. A mixed melting point of the two products was not depressed.

10-Methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydronaphth[1,8-cd]azepine (10)

To 37.2 g (0.116 mole) of 9, free base, was added quickly 250 g PPA. The mixture was stirred and heated on a steam bath at 90-95° for 4 hr., cooled, and poured into 2 liters ice water. The water was decanted and the oily residue was dissolved in 600 ml hot CH_3OH. Sodium methoxide (20 g) was added, the mixture was diluted with 1,000 ml H_2O and extracted with 2 x 500 ml $CHCl_3$. The combined extracts were washed with 400 ml H_2O, dried ($MgSO_4$), and concentrated to dryness in vacuo to yield 30.5 g of an oil.

Treatment of an alcoholic solution of the oil with ethanolic hydrogen chloride gave in two crops 21.8 g (55%) of the hydrochloride which could not be purified.

An 11.35 g (0.0335 mole) portion of the hydrochloride was dissolved in 200 ml CH_3OH. The solution was diluted with 200 ml H_2O and made alkaline with solid K_2CO_3. The mixture was extracted with 2 x 150 ml $CHCl_3$, and the combined extracts were washed with 150 ml H_2O, dried ($MgSO_4$), decolorized, and concentrated to dryness in vacuo. Crystallization from heptane gave 6.60 g (61%) of the product, m.p. 101-104°.

An analytical sample, m.p. 102-104°, was obtained by recrystallization from heptane; nmr ($CDCl_3$) δ: 1.30 (d, J=6 Hz, 3, 3-CH_3); 1.85 (s, 1, exchanges in D_2O, N-H); 3.90 (s, 3, 10-OCH_3); 3.95-4.63 (m, 4, 1-CH_2, 3-CH, 4-CH); 6.87-7.80 (m, 10, aromatic C-H); ir μ: 2.97 (N-H); 6.18, 6.22 (C=C).

Anal. Calcd. for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62

Found: C, 83.36; H, 7.02; N, 4.62

2-(2-Naphthylmethylamino)-1-phenyl-1-propanol hydrochloride (14)

A mixture of 77.0 g (0.494 mole) of 2-naphthaldehyde, 50.5 g (0.50 mole) triethylamine, 92.4 g (0.494 mole) of 2-amino-1-phenyl-1-propanol hydrochloride, and 500 ml CH_3OH was stirred and refluxed for one hour, then cooled to 20-30° while 14.0 g (0.38 mole) of sodium borohydride was

added over 25 min. The reaction mixture was stirred at ambient temperature for 90 min. and diluted with 1000 ml H_2O. The mixture was extracted with 4 x 450 ml portions of $CHCl_3$. The combined extracts were dried ($MgSO_4$) and concentrated to dryness in vacuo to give 151 g (>100%) of the free base of the product. Treatment of a 31.0 g (0.106 mole) sample of the free base dissolved in ethanol with ethanolic hydrogen chloride gave 28.1 g (81%) of the product, m.p. 228-231°. An analytical sample, m.p. 226-229°, was obtained by drying the above sample at 100° in vacuo; ir μ: 3.05 (O-H); 6.20, 6.30 (C=C); 9.25, 9.80 (C-OH).

Anal. Calcd. for $C_{20}H_{21}NO \cdot HCl$: C, 73.27; H, 6.77; N, 4.27

Found: C, 73.12; H, 6.71; N, 4.12

2-Methyl-1-phenyl-1,2,3,4-tetrahydrobenz(f)isoquinoline hydrobromide (15)

To 64.0 g (0.191 mole) of 14 free base was added cautiously 250 ml 48% HBr. The mixture was stirred and refluxed for 20 hr, cooled, and filtered through a medium sintered glass funnel. The solid was air dried, washed with 4 x 125 ml ethyl acetate, air dried, and dried at 60° for one hour. The product weighed 63.5 g (81%) and melted at 300-307°. An analytical sample, m.p. 315-318°, was obtained by recrystallization from methanol; nmr (DMSO-d_6) δ: 1.50 (d, J=6 Hz, 3, 2-CH_3); 3.57-4.90 (m, 4, 1-CH, 2-CH, 4-CH_2) 7.72-8.05 (m, 11, aromatic C-H; 9.55 (broad s, 2, exchanges in D_2O, $\overset{\oplus}{N}H_2$); ir μ: 3.70-4.10 ($\overset{\oplus}{N}H_2$); 6.30 (C=C).

The infrared and nmr spectra of the product and that derived from 12 were not identical.

Anal. Calcd. for $C_{20}H_{19}N \cdot HBr$: C, 67.80; H, 5.69; N, 3.95

Found: C, 67.95; H, 5.76; N, 3.91

Treatment of 2-(1-bromo-2-naphthylmethylamino)-1-phenyl-1-propanol (11) free base with 48% HBr

A mixture of 54.0 g (0.146 mole) of 11 free base (6) and 250 ml 48% HBr was stirred and refluxed for 18 hr and cooled. The solid was filtered, washed with 4 x 75 ml of ethyl acetate, and air dried to give 35.8 g of the crude product.

A 4.0 g sample of the crude product was recrystallized from 50 ml of methanol to give 1.10 g of 12, the infrared spectrum of which was identical with that of the product obtained by cyclization of 11 with PPA (6).

Concentration of the methanolic filtrate to dryness and recrystallization of the residue from isopropanol gave 1.40 g of 15 which exhibited an infrared spectrum identical to that obtained from 14 and 48% HBr.

2-[(α-Phenyl)hydroxymethyl]pyridine

To a solution of 18.3 g (0.10 mole) of 2-benzoylpyridine in 130 ml CH_3OH was added over 10

min at 7-10° sodium borohydride (1.05 g, 0.0275 mole). The mixture was stirred at 10-20° for 1.5 hr, diluted with 250 ml H_2O, and extracted with 2 x 150 ml $CHCl_3$. The combined extracts were dried over $MgSO_4$ and concentrated to dryness in vacuo to give 18.0 g (97%) of an oil that was used directly in the next step.

1-Benzyl-2-[(α-phenyl)hydroxymethyl]pyridinium Bromide (26)

The above carbinol (18.0 g, 0.097 mole) and 17.1 g (0.10 mole) of benzyl bromide in 100 ml dioxane was stirred and refluxed for 4 hr and the mixture was allowed to stand at ambient temperature for 15 hr. The solid was filtered and washed with 3 x 10 ml of dioxane. The product, after drying at 110° for 5 hr, weighed 17.5 g (50%) and melted at 142-146°. An analytical sample, m.p. 151-155°, was obtained by recrystallization from acetonitrile; ir μ: 3.30 (O-H); 6.18, 6.32 (C=C and C=N).

Anal. Calcd. for $C_{19}H_{18}BrNO$: C, 64.05; H, 5.09; N, 3.93
Found: C, 63.93; H, 5.10; N, 3.97

11-Phenyl-6,11-dihydrobenzo[b]quinolizinium bromide (27)

A solution containing 23.4 g (0.0657 mole) of 26 and 210 ml 48% HBr was stirred and refluxed for 20 hr. The resulting mixture was concentrated to dryness in vacuo. To the residue was added 50 ml absolute ethanol and 25 ml toluene. The solution was concentrated to dryness in vacuo and the residue was dissolved in 75 ml acetonitrile.

There was obtained from the acetonitrile solution in three crops 12.43 g (53%) of the product, m.p. partially melts at about 150°; clean melt forms at 200°. An analytical sample, m.p. 206-209° (lit (14) m.p. of hydrate: 192-197°) was obtained by recrystallization from acetonitrile; ir μ: 6.12, 6.22, 6.31 (C=C and C=N).

Anal. Calcd. for $C_{19}H_{16}BrN$: C, 67.46; N, 4.14; H, 4.77
Found: C, 67.17; N, 4.21; H, 4.74

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