Synthetic Studies to the Octahydrobenzo[*f*]quinoline System

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Dedicated to the memory of professor Nicholas Alexandrou

An improved procedure to 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines is reported giving single intermediate products and higher total yields.

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Octahydrobenzoquinolines are molecules that have been long envisioned as biologically active compounds. These heterocyclic structures incorporate the phenethylamine moiety in a larger semi-rigid framework that allows for more accurate structure-activity relationship studies on neurotransmitter action systems, such as the dopamine receptors or the adrenoceptors. Although a host of benzoquinoline analogs has been already synthesized and studied for biological activity [1], there is still a need of a synthetic approach including intermediates which, under different reaction conditions, would furnish either the cis- or trans-fused B and C ring products.

An efficient route to the octahydrobenzo[*f*]quinoline system has been described by Cannon *et al.* [2,3]. This approach, as shown in Scheme 1, includes an aza-annulation of β-tetralone pyrrolidine enamines with acrylamide [4,5]. Catalytic hydrogenation of the resulting tetrahydrobenzo[*f*]quinolones provides the *cis*, whereas "ionic hydrogenation" [6] yields the *trans*-hexahydrobenzo[*f*]-quinolones. Finally, hydride reduction of the carbonyl group leads to the desired quinolines.

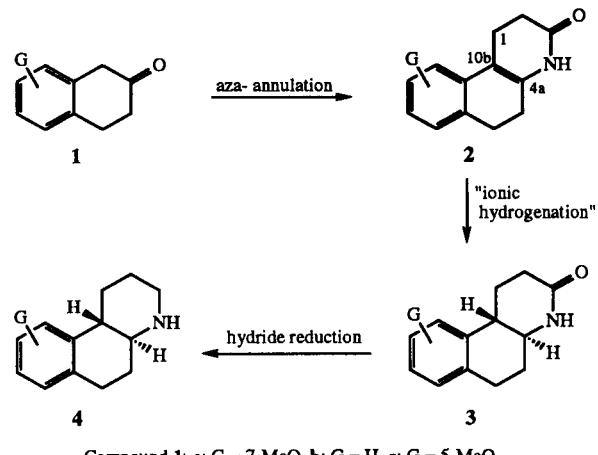
One of the major problems encountered on the application of this strategy was the formation of a significant percentage of the *cis* isomer during "ionic hydrogenation" [7]. Cannon rationalized these results in terms of the chemical nature of the starting material rather than the lack of stereospecificity of the reduction method. It was demonstrated [3] that under standard aza-annulation conditions 8-methoxy-2-tetralone (**1a**) yielded three isomeric products: compound **2a**, its $\Delta^{4a,5}$ enamide isomer, and a third component (identified as the $\Delta^{1,10b}$ isomer) which, upon "ionic hydrogenation" conditions, was the only one to give the *cis* hexahydrobenzo[*f*]quinolone. In a modified annulation procedure [3], only the desired enamide tetrahydrobenzo[*f*]quinolone isomers were obtained, however in only 30% overall yield.

In this communication we proposed a simple modification of the aza annulation procedure that results into only one enamide with the double bond positioned at the ring fusion. β-Tetralone pyrrolidine enamines are easily isolated and, subjected to aza-annulation conditions with neat acrylamide, give single products in 57-60% overall yields from the corresponding tetralones. In contrast to the reduced temperature annulation conditions suggested by Cannon *et al.* [3], reaction mixtures were heated up to 100°, thus increasing the product yield. Tlc (silica gel G, ether-petroleum ether 1:4) as well as gc-ms analysis verified the presence of only one product. The nmr spectra confirmed the absence of olefinic proton resonances as expected for type **2** structures.

Reduction of the enamide with triethyl silane-trifluoroacetic acid [6] furnished the desired amides in 75% yield and subsequent reduction with lithium aluminum hydride gave the final benzoquinolines. The *trans* disposition of the 4a and 10b hydrogens was verified by their coupling constants of 13.3 and 12.0 Hz on the nmr spectra of **3b** and **3c**, as well as the presence of "Bohlman bands" [8] at 2860 and 2873 cm^{-1} on the ir spectra of **4b** and **4c** respectively.

In respect to the difference of product distribution on the enamide preparations, it is likely that the two step synthesis that we propose, ensures cleaner annulation reaction conditions, vis a vis the one pot procedure. In the latter case the presence of unreacted material may lead to side products. Ninomiya *et al.* reported that β-tetralone reacts, under similar conditions with acrylamide to give the *N*-acryloylenamine. This thermally unstable intermediate undergoes cyclisation in poor yield when heated in the presence of *p*-toluenesulfonic acid [5].

Scheme 1



Compound **1**; **a**: G = 7-MeO, **b**: G = H, **c**: G = 5-MeO
Compounds **2-4**; **a**: G = 10-MeO, **b**: G = H, **c**: G = 7-MeO

Our results further verify the proposed mechanism of *trans* addition to double bonds during "ionic hydrogenation" in similar systems, although steric effects may reverse the geometry of addition. Ghosh *et al.* reported that reaction of 1-methyl-1,3,4,5-tetrahydro-benz[e]indol-2-ones with triethyl silane- trifluoroacetic acid yielded the *cis* rather than the *trans* fused product [9]. These results, supported by nmr and X-ray crystallography data, were attributed to the steric hindrance imposed by the 1-methyl group.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Ir spectra were taken on a Perkin-Elmer 1760X FT IR spectrometer. The ^{1}H nmr spectra were taken on a AC 250 Bruker FT-nmr spectrometer; proton chemical shifts are reported in ppm relative to tetramethylsilane. Mass spectra were taken on a Hewlett Packard Model 5890 Gas Chromatograph coupled with a Hewlett Packard 5971A Mass Selective Detector.

1,4,5,6-Tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (**2b**) [11,12].

To a flame dried 100 ml round bottomed flask were added β-tetralone pyrrolidine enamine [10] (0.7 g, 3.77 mmoles) and acrylamide (0.8 g, 11.3 mmoles). The mixture was heated at 100° for 30 minutes at which point the reaction was completed. The temperature was raised to 130° for 15 minutes to polymerize the excess acrylamide and the system was cooled to room temperature. Water (10 ml), and a drop of acetic acid was then added to the mixture which was stirred for 30 minutes. The system was diluted by the addition of ethyl acetate (50 ml), washed twice with brine, and the organic layer was filtered to remove the polymer and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was recrystallized from ethyl acetate to yield 0.55 g (73%) of **2b**, mp 172-175° (lit [11] 176-177°, lit [12] 179-180°); ^{1}H nmr (deuteriochloroform): δ 8.03 (s, 1H), 7.21 (dd, J_1 = 6 Hz, J_2 = 7.9 Hz, 1H), 7.07 (dd, J_1 = 3.8 Hz, J_2 = 6 Hz, 1H), 7.06 (d, J = 3.8 Hz, 1H), 7.03 (d, J = 7.9 Hz, 1H), 2.88 (t, J = 7.9 Hz, 2H), 2.72-2.60 (m, 4H), 2.36 (t, J = 8.1 Hz, 2H); ir (sodium chloride): ν 3402, 1681, 1656, 1490, 1383, 1248, 1213, 1046, 738 cm^{-1}.

Trans - 1,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-3(2*H*)-one (**3b**) [13].

To a flame dried 250 ml round bottomed flask were added dry methylene chloride (60 ml), **2b** (1.7 g, 8.54 mmoles) and triethylsilane (10 ml, 62.8 mmoles). The solution was cooled to 0°, trifluoroacetic acid (20 ml, 260.0 mmoles) was added dropwise and the system was stirred at room temperature for 20 hours. The solution was diluted by the addition of methylene chloride (20 ml) and subsequently washed with sodium bicarbonate saturated solution (3 x 20 ml), and brine (3 x 20 ml). The organic phase was dried over anhydrous sodium sulfate and the solvent was removed to yield the crude product which was recrystallized from ethyl acetate to give 1.3 g (75%) of **3b** mp 202-203° (lit [13] 191-192°); ^{1}H nmr (deuteriochloroform): δ 7.33 (s, 1H), 7.30-7.10 (m, 4H), 3.35 (dt, J_1 = 3.2 Hz, J_2 = 13.3 Hz, 1H), 2.95 (t, J = 4.6 Hz, 2H) 2.75-2.55 (m, 4H), 2.15-2.05 (m, 1H), 1.96-1.60 (m, 2H); ir (sodium chloride): ν 3284, 3058, 2937, 2878, 1656, 1452, 1371, 1248, 1211, 1045, 742 cm^{-1}; ms: m/z 201 (M$^+$).

Trans -1,2,3,4,4a,5,6,10b-octahydrobezo[*f*]quinoline (**4b**) [14]

To a solution of **3b**, (0.18 g, 0.90 mmoles) in dry ether (60 ml) , was added lithium aluminum hydride (0.32 g, 8.42 mmoles) and the mixture was heated under reflux for 4 hours. The system was then cooled to room temperature and consequently treated with water (0.3 ml) 15% sodium hydroxide solution (0.3 ml) and water (1 ml). The mixture was then filtered, washed twice with brine (20 ml) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give 0.14 g (84%) of **4b** mp 94° (lit [14] 88-90°); ^{1}H nmr (deuteriochloroform): δ 7.27-7.05 (m, 4H), 3.16 (br d, J = 10.8 Hz, 1H), 3.19-2.84 (m, 4H), 2.72 (dt, J_1 = 12.0 Hz, J_2 = 3.5 Hz, 1H), 2.60-2.45 (m, 2H), 1.90-1.65 (m, 2H), 1.80 (dd, J_1 = 8.5 Hz, J_2 = 3.5 Hz, 1H) 1.74 (dd, J_1 = 12.0 Hz, J_2 = 5.0 Hz, 1H), 1.3 (dd, J_1 = 10.8 Hz, J_2 = 3.8 Hz, 1H); ir (sodium chloride): ν 3400, 2932, 2860, 2839, 1489, 1436, 737; ms: m/z 187 (M$^+$).

7-Methoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3-(2*H*)-one (**2c**) [12].

To a flame dried 100 ml round bottomed flask were added 5-methoxy-β-tetralone pyrrolidine enamine [15] (1.6 g, 7.0 mmoles) and acrylamide (1.49 g, 21.0 mmoles). The mixture was heated at 100° for 30 minutes at which point the reaction was completed. The temperature was raised to 130° for 15 minutes to polymerize the excess acrylamide and the system was cooled to room temperature. Water (10 ml), and a drop of acetic acid was then added to the mixture which was stirred for 30 minutes. The system was diluted by the addition of ethyl acetate (70 ml), washed three times with saturated solution of sodium bicarbonate, twice with brine and the organic layer was filtered to remove the polymer and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was recrystallized from ethyl acetate to yield 1.1 g (69%) of **2c**, mp 244-245° (lit [12] 247.6°); ^{1}H nmr (deuteriochloroform): δ 8.19 (s, 1H), 7,14 (dd, J_1 = 8.2 Hz, J_2 = 7.8 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.7 (d, J = 8.2 Hz, 1H), 3.81 (s, 3H), 2.88 (t, J = 7.9 Hz, 2H), 2.65-2.58 (m, 4H), 2.33 (t, J = 8.4 Hz, 2H); ir (sodium chloride): ν 3214, 1683, 1657, 1495, 1374, 1340, 1257,1202, 738 cm^{-1}.

Trans-7-methoxy-1,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-3(2*H*)-one (**3c**) [2].

To a flame dried 250 ml round bottomed flask were added dry methylene chloride (50 ml), **2c** (1.3 g, 5.68 mmoles) and triethylsilane (6 ml, 37.7 mmoles). The solution was cooled to 0°, trifluoroacetic acid (13 ml, 170.4 mmoles) was added dropwise and the system was stirred at room temperature for 20 hours. The solution was diluted by the addition of methylene chloride (20 ml) and subsequently washed with sodium bicarbonate saturated solution (4 x 20 ml) and brine (4 x 20 ml). The organic phase was dried over anhydrous sodium sulfate and the solvent was removed to yield the crude product which was recrystallized from ethyl acetate to give 1.0 g (76%) of **3c** mp 294-295° (lit [2] 279-280° (dec); ^{1}H nmr (deuteriochloroform): δ 7.27 (dd, J_1 = 8.1 Hz, J_2 = 7.8 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 3.86 (s, 3H), 3.40 (dt, J_1 = 2.6 Hz, J_2 = 12.0 Hz, 1H), 3.05-2.97 (m, 1H), 2.76-2.55 (m,5H), 2.12-1.90 (m, 1H), 1.85-1.68 (m, 2H); ir (sodium chloride) ν: 3414, 2947,2836, 1651, 1577, 1474, 1437, 1261, 1085 cm^{-1}.

Trans -5-methoxy-1,2,3,4,4a,5,6,10b-octahydrobezo[*f*]quinoline (**4c**) [16].

To a solution of **3c**, (1.0 g, 4.33 mmoles) in dry ether (100 ml), lithium aluminum hydride (1.0 g, 26.3 mmoles) was added and the mixture was heated under reflux for 4 hours. The system was then cooled to room temperature and consequently treated with water (1 ml) 15% sodium hydroxide solution (1 ml) and water (3 ml). The mixture was then filtered, washed twice with brine (30 ml) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give 0.9 g (96%) of **4c**, mp of hydrochloride salt 300-301°(d) (lit [16] 300-301°); ^{1}H nmr (deuteriochloroform): δ 7.14 (t, J = 8.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 3.79 (s, 3H), 3.12 (br d, J = 12 Hz, 1H), 2.98-2.88 (m, 1H), 2.70 (dt, J_1 = 3 Hz, J_2 = 12 Hz, 1H), 2.51-2.36 (m, 3H), 1.93-1.60 (m, 6H), 1.31-1.22 (m, 1H); ir (sodium chloride): ν 3390, 2936, 2873, 2837, 1581, 1463, 1437, 1260, 1085, 734 cm^{-1}; ms: m/z 217 (M^+).

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