NEW ATYPICAL ANTIDEPRESSANTS: AN EFFICIENT PROCESS FOR PREPARING CIS-1,3,4,6,7,11B-HEXAHYDRO-2-METHYL-7-ARYL-2H-PYRAZINO[2,1-a]ISOQUINOLINES.[1]

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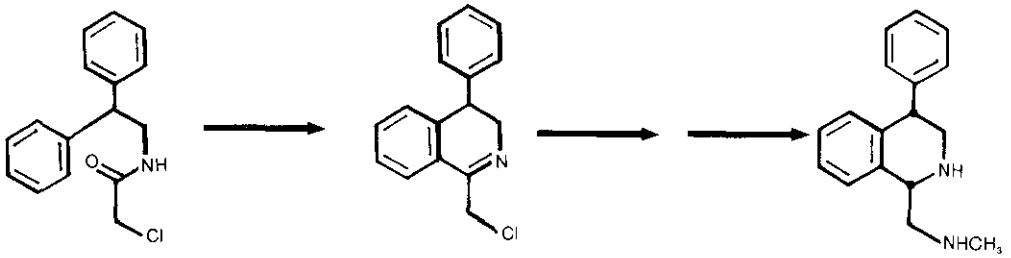
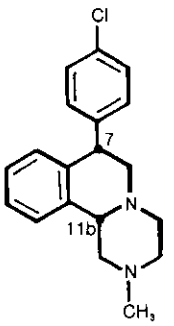
Abstract- Starting from 3-phenyl-2-piperazinone, cis-1,3,4,6,7,11b-hexahydro-2-methyl-7-(4-chlorophenyl)-2H-pyrazino[2,1-a] isoquinoline (1) was synthesized utilizing as the pivotal step of the sequence a highly stereocontrolled base-catalyzed equilibration of 3,4,6,7-tetrahydro-7-(4-chlorophenyl)-2H-pyrazino[2,1-a]isoquinolin-1(11bH)-ones (2).

A series of novel cis-1,3,4,6,7,11b-hexahydro-2-methyl-7-aryl-2H-pyrazino[2,1-a]isoquinolines have recently been synthesized and were found to possess an atypical antidepressant biological profile[3]. As shown in Scheme 1, the key steps of that synthesis were a Bischler-Napieralski cyclization of the symmetrical 2,2-diphenylethylamide, followed by a stereoselective catalytic hydrogenation of the resulting 3,4-dihydro-4-phenylisoquinoline to give a 10:1 ratio of cis/trans isomers.



Scheme 1

However, when employed to prepare other compounds in the series, particularly aryl substituted analogs, various shortcomings in the original synthetic process are encountered: ring-closure isomers are possible when using an unsymmetrical 2,2-diarylethylamide, while phenyl substitution in the latter stages of the synthesis employing classical procedures (e.g., nitration ➡ diazotization ➡ salt decomposition) gives ring positional isomers. We wish to describe in this report a novel and more versatile process for preparation of the title compounds by which a greater than 100:1 ratio of cis/trans isomers is possible and by which aryl substituted analogs are readily accessible. Also, by slightly modifying this new procedure a 19:1 ratio of trans/cis isomers can be generated. The following is an exemplary procedure.



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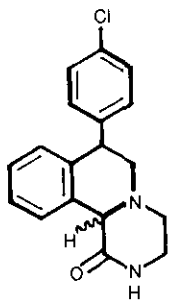
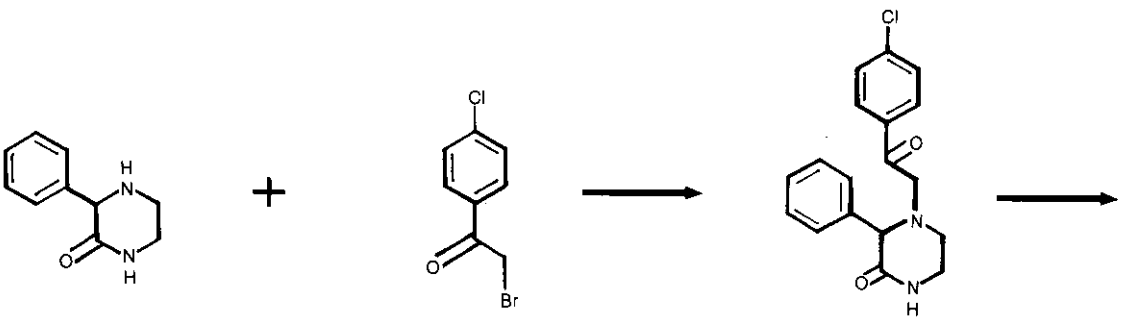


2

Alkylation of 3-phenyl-2-piperazinone[4] with 4-chlorophenacyl bromide in the presence of potassium carbonate gave the piperazinone (3) in 85% yield. Selective carbonyl reduction with sodium borohydride to give (4) followed by cyclization of the resulting mixture of alcohols in concentrated sulfuric acid at ambient temperature afforded a 98% overall yield of 3,4,6,7-tetrahydro-7-(4-chlorophenyl)-2H-pyrazino[2,1-a] isoquinolin-1(11bH)-ones (5) and (6) as a 4.5:1 trans/cis mixture of isomers respectively. Adjustment of the stereochemistry of this mixture is readily accomplished by subjecting it to a catalytic amount of sodium methoxide in methanol. The cis isomer preferentially crystallizes from the reaction mixture during the equilibration process and is then filtered and washed to give an 89% yield of the cis isomer contaminated by less than 1% of the trans isomer (determined by HPLC).



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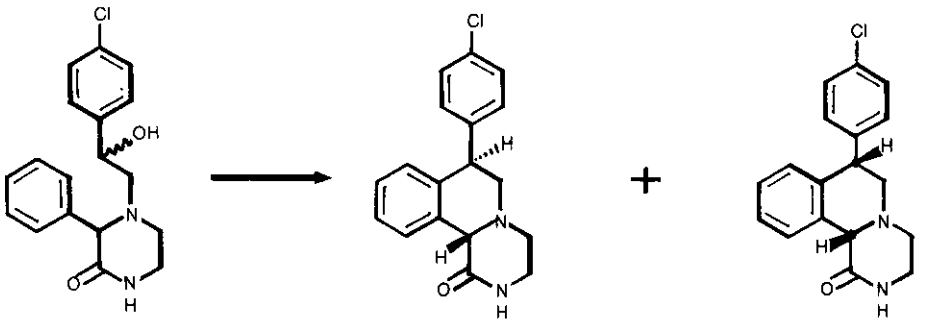

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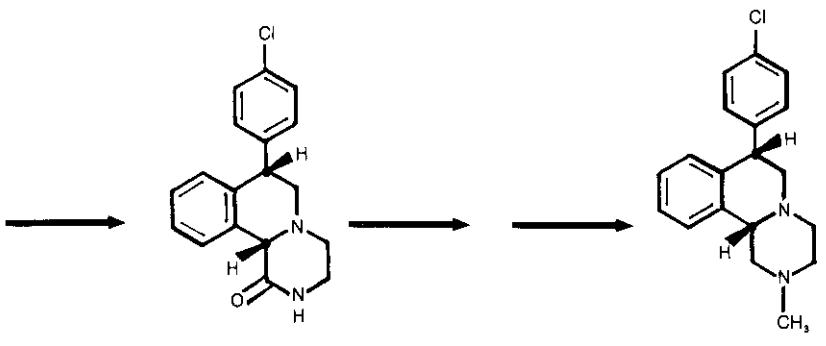

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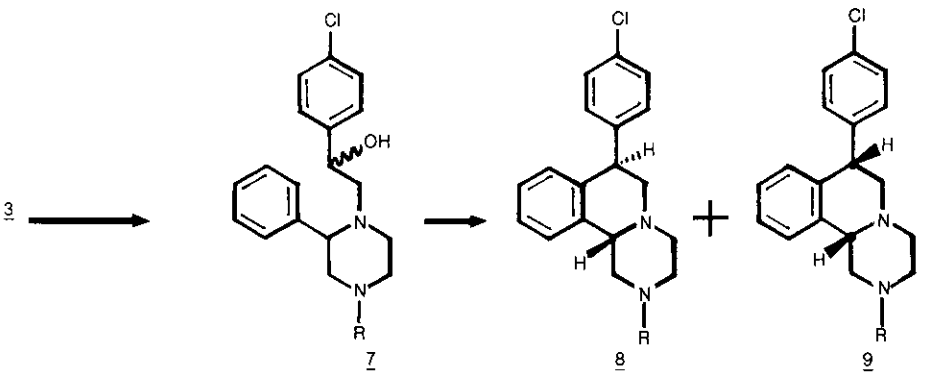
The success of this equilibration step can evidently be attributed to the solubility differential between the isomers[5], as an examination of the filtrate of aliquots at various times during the reaction revealed (by high field nmr or HPLC) an approximately 1:1 mixture of isomers. Both sodium ethoxide in ethanol and sodium isopropoxide in isopropanol were less effective in this reaction. Synthesis of compound (1) was completed by diborane reduction of the amide carbonyl[6] followed by N-methylation under Eschweiler-Clarke conditions.

The above process appears quite general in scope, the crucial base-catalyzed equilibration step being successful in the preparation of stereochemically pure analogues. By slightly modifying the synthetic sequence on the other hand, a much higher than 4.5:1 ratio of trans/cis isomers can be generated. Thus, reduction of (3) with diborane gives the piperazine (7, R = H). Cyclization of (7) under the aforementioned conditions gives (8) and (9) as a 19:1 ratio of trans/cis isomers. The same ratio could also be obtained from cyclization of (7) where R is methyl.



We were thus able to readily synthesize under stereocontrolled conditions a number of cis and/or trans-1,3,4,6,7,11b-hexahydro-2-methyl-7-aryl-2H-pyrazino[2,1-a]isoquinolines starting with 3-aryl substituted 2-piperazinones and/or substituted phenacyl halides.

EXPERIMENTAL

3-Phenyl-4-(4-chlorophenacyl)-2-piperazinone (3). A stirred mixture of 58.0 g (0.33 mol) of 3-phenyl-2-piperazinone, 85.0 g (0.62 mol) of blended potassium carbonate, and 76.9 g (0.33 mol) of 4-chlorophenacyl bromide in 400 ml of dichloromethane was heated at reflux for 12 h. The mixture was cooled to ambient temperature, filtered, and the solid washed thoroughly with dichloromethane. The filtrate was concentrated to dryness, isopropanol added and stirred, the solid collected by filtration, washed thoroughly with isopropanol and dried in a vacuum oven at 50 °C to give 92.5 g (85%) of (3). This material was used as such in the next step. [Pure material could be obtained by recrystallization from methanol to give a white solid (mp 157-158 °C dec.).]

3,4,6,7-Tetrahydro-7-(4-chlorophenyl)-2H-pyrazino[2,1-a]isoquinolin-1(11bH)-ones (5) & (6). To a stirred solution of 1066.9 g (3.245 mol) of 3-phenyl-4-(4-chlorophenacyl)-2-piperazinone (3) in 4.2 l of methanol was added in portions so as to maintain a reaction temperature at or below 50 °C, 62.5 g (1.65 mol) of sodium borohydride (30 min addition time). The resulting mixture was stirred for an additional 1 h and concentrated to give crude (4) as a yellow amorphous solid. To this solid was added in a rapid stream 4.3 l of concentrated sulfuric acid. The resulting mixture was stirred at ambient temperature overnight and then poured onto a mixture of 90 kg of ice and 11.2 l of 50% aqueous sodium hydroxide. The solid was collected by filtration, washed neutral with water, and dried in a vacuum oven at 50 °C to give 997.1 g (98%) of (5) & (6) as a pale yellow solid consisting of a 4.5:1 trans/cis mixture of isomers, respectively. For (5) hydrochloride; ^{1}H-nmr ($CDCl_3$/CF_3COOD): 7.80-6.80 (m,8H,Ar), 5.70 (s,1H,H-11b) 4.60 (dd, 1H, H-7, J = 11.0, 6.6 Hz) and 4.30-3.50 (m,6H,CH_2). Anal. Calcd for $C_{16}H_{16}Cl_2N_2O$: C, 61.90; H, 5.19; Cl, 20.30; N, 8.02. Found: C, 61.85; H, 5.29; Cl, 20.01; N, 7.91.

cis-3,4,6,7-Tetrahydro-7-(4-chlorophenyl)-2H-pyrazino[2,1-a]isoquinolin-1(11bH)-one (6). To 1905.0 g (6.09 mol) of 3,4,6,7-tetrahydro-7-(4-chlorophenyl)-2H-pyrazino[2,1-a]isoquinolin-1(11bH)-ones (5) & (6) in 4 l of methanol was added, while stirring at ambient temperature, a solution of 36.5 g (1.59 mol) of metallic sodium dissolved in 15 l of methanol. The resulting stirred suspension was heated at reflux for 24 h, allowed to cool to ambient temperature, and stirred for a further 12 h. The solid was collected by filtration, washed thoroughly with methanol, and dried in a vacuum oven at 60 °C to give 1692.g (89%) of (6) as a white solid (mp 239-244 °C dec.) contaminated by less than 1% of (5). For (6) hydrochloride; ^{1}H-nmr ($CDCl_3$/CF_3COOD): 7.60-7.30 (m,5H,Ar), 7.10 (AA'BB',2H,Ar,J = 8.3Hz), 7.0-6.80 (m,1H,Ar), 5.50 (s, 1H,H-11b), 4.80 (dd,1H,H-7,J = 12.3,5.5 Hz), 4.10-3.60 (m,5H,CH_2) and 3.40 (t,1H,CH_2,J = 12.3 Hz). Anal. Calcd for $C_{18}H_{18}Cl_2N_2O \cdot 1/2H_2O$:C, 60.35; H, 5.35; Cl, 19.79; N, 7.82. Found: C, 60.36; H, 5.40; Cl, 19.36; N, 7.74.

cis-1,3,4,6,7,11b-Hexahydro-2-methyl-7-(4-chlorophenyl)-2H-pyrazino[2,1-a]isoquinoline (1) dihydrochloride. To a stirred suspension of 1810.0 g (5.79 mol) of cis-3,4,6,7-tetrahydro-7-(4-chlorophenyl)-2H-pyrazino[2,1-a]isoquinolin-1(11bH)-one (6) in 5.7 l of tetrahydrofuran under nitrogen was added rapidly 28.6 l of a 1.0 M solution of borane in tetrahydrofuran. The mixture was heated at reflux for 15 h, cooled to ambient temperature, and treated cautiously with 4.2 l of 2.5 M aqueous hydrochloric acid. This resulting mixture was heated at reflux for 3.5 h and then allowed to cool to ambient temperature. The solid (contaminated with approximately 20% of boric acid) was collected by filtration and treated with 2.4 l of 88% formic acid, 3.92 l of 35-40% formaldehyde, and 805.0 g of sodium formate. The resulting mixture was heated at 80-85 °C for 1.2 h, cooled to ambient temperature, poured onto 44.0 kg of ice, and made basic (pH 10-11) by adding concentrated ammonium hydroxide. The solid was collected by filtration, washed neutral with water, and dried in a vacuum oven at 65 °C. A solution of this solid in 5.5 l of methanol was acidified to pH 1 with dry gaseous hydrochloric acid. The resulting solid was collected by filtration, washed with 4 l of a 1 to 1 mixture of diethyl ether and methanol followed by 1 l of diethyl ether, and dried in a vacuum oven at 60 °C for 24 h to give 1573.0 g (80% overall) of (1) dihydrochloride as a white solid (mp 274-276 °C), identical in all respects to material obtained by Griffith, et al[3].

trans-1,3,4,6,7,11b-Hexahydro-7-(4-chlorophenyl)-2H-pyrazino[2,1-a]isoquinoline (8, R = H) dihydrochloride. To a suspension of 8.22 g (25.0 mmol) of 3-phenyl-4-(4-chlorophenacyl)-2-piperazinone (3) in 25 ml of anhydrous tetrahydrofuran was added 150 ml of a 1.0 M solution of borane in tetrahydrofuran. The resulting mixture was heated at reflux for 18 h, cooled to ambient temperature, and treated with dropwise addition of 125 ml of 2.5 M aqueous hydrochloric acid. This mixture was heated at reflux for 3 h, cooled to ambient temperature, and stirred for 2 h. The resulting solid was collected by filtration, washed with 50 ml of tetrahydrofuran, and dried giving 10.9 g of the crude (7, R = H) as a white solid contaminated with boric acid. To 30 ml of concentrated sulfuric acid at 0 °C was added portionwise 8.50 g (26.8 mmol) of (7, R = H) over a period of 0.5 h. The resulting mixture was warmed to ambient temperature, stirred for 2 h, poured onto ice chips, and made basic with 50% aqueous sodium hydroxide. The resulting solid was collected, air dried, dissolved in 50 ml of absolute methanol, and made acidic with gaseous hydrochloric acid (pH 1). Addition of 50 ml of diethyl ether gave a white solid which was collected by filtration and washed with 50 ml of a 1:1 methanol/ether mixture to give 2.7 g (27%) of (8, R = H) as a white solid (mp 265-267 °C dec.) containing less than 1% of the responding cis isomer (9, R = H). For (8, R = H) dihydrochloride; ^{1}H-nmr ($CDCl_3$/CF_3COOD): 7.50-6.90 (m, 8H, Ar), 5.50 (d, 1H, H-11b, J = 11.0Hz), 4.80 (dd, 1H, H-7, J = 12.2, 5.5 Hz), 4.55 (d, 1H, CH_2, J = 13.7 Hz), 4.40-3.75 (m, 6H, CH_2) and 3.60 (t, 1H, CH_2, J = 12.3 Hz). Anal. Calcd for $C_{18}H_{20}Cl_3N_2 \cdot 1/2H_2O$: C, 56.78; H, 5.82; Cl, 27.93; N, 7.36. Found: C,56.16; H, 6.01; Cl, 27.07; N, 6.83.

trans-1,3,4,6,7,11b-Hexahydro-2-methyl-7-(4-chlorophenyl)-2H-pyrazino[2,1-a]isoquinoline (8, R = Me) dihydrochloride.

2-Phenylpiperazine. To an ice-cooled stirred suspension of 25.g (0.66 mol) of lithium aluminum hydride in 2.6 l of anhydrous diethyl ether was added in portions over 1.5 h 30 g (0.17 mol) of 3-phenyl-2-piperazinone. The resulting mixture was heated at reflux for 20 h and then cooled to 0 °C. Isolation of the product by standard methods gave 23 g (83%) of 2-phenylpiperazine as an off-white solid (mp 83-85 °C).

1-Methyl-3-phenylpiperazine. To an ice-cooled stirred solution of 5.45 g (0.033 mol) of 2-phenylpiperazine and 5.3 g (0.53 mol) of triethylamine in 580 ml of acetone was added dropwise over 20 min a solution of 4.8 g of methyl iodide in 20 ml of acetone. The resulting mixture was stirred at 0 °C for 1 h and then allowed to gradually warm to ambient temperature over 3 h. The residue obtained upon concentration of the reaction mixture was dissolved in 200 ml of diethyl ether and treated with a solution of methanol and ether saturated with gaseous hydrochloric acid to give 4.5 g (54%) of 1-methyl-3-phenylpiperazine dihydrochloride as a white solid.

1-Methyl-3-phenyl-4-(4-chlorophenacyl)piperazine. To a stirred mixture of 14.0 g (0.08 mol) of 1-methyl-3-phenylpiperazine and 20 g (0.2 mol) of triethylamine in 160 ml of tetrahydrofuran was added dropwise a solution of 18.2 g (0.08 mol) of 4-chlorophenacyl bromide in 55 ml of chloroform. The resulting mixture was stirred at ambient temperature for 3.5 h, poured into 50% aqueous sodium bicarbonate and extracted with chloroform. The organic extracts were combined, washed with water and saturated sodium chloride and dried over sodium sulfate. The filtrate was concentrated to dryness to give 25 g of crude 1-methyl-3-phenyl-4-(4-chlorophenacyl)piperazine. This material was used as such in the next step of the process.

1-Methyl-3-phenyl-4-[2-hydroxy-2-(4-chlorophenyl)ethyl]piperazine. To a stirred solution of 25 g (0.076 mol) of the 1-methyl-3-phenyl-4-(4-chlorophenacyl) piperazine in 450 ml of ethanol was added in portions 2.9 g (0.076 mol) of sodium borohydride. The resulting mixture was stirred at ambient temperature for 2 h, poured into 50% aqueous sodium chloride and extracted with ethyl acetate. The organic extracts were combined, washed with water and saturated sodium chloride and dried over sodium sulfate. The resulting crude product obtained from concentration of the filtrate was subjected to rapid liquid chromatography on a silica gel column eluting with a solution of 4% methanol in chloroform to give 16 g (60% overall) of an isomeric mixture of 1-methyl-3-phenyl-4-[2-hydroxy-2-(4-chlorophenyl)ethyl] piperazine (7, R = Me) as a white solid.

trans-1,3,4,6,7,11b-Hexahydro-2-methyl-7-(4-chlorophenyl)-2H-pyrazino[2,1-a]isoquinoline (8, R = Me) dihydrochloride. To 35 ml of concentrated sulfuric acid at 0 °C was added portionwise 9.1 g (27.5 mmol) of (7, R = Me) dihydrochloride over a period of 0.5 h. The resulting mixture was warmed to ambient temperature, stirred for 2 h, poured onto ice chips, and made basic with 50% aqueous sodium hydroxide. The resulting solid was collected, air dried, dissolved in 50 ml of absolute methanol, and made acidic with gaseous hydrochloric acid (pH 1). The resulting white solid which crystallized was collected by filtration, washed with cold methanol, and dried to give 7.5 g (78%) of (8, R = Me) (mp 313-315 °C dec.) containing less than 1% of the corresponding cis isomer (9, R = Me). For (8, R = CH_3) dihydrochloride; ^{1}H-nmr ($CDCl_3$/CF_3COOD): 7.40-6.90 (m, 8H, Ar), 5.50 (d, 1H, H-11b, J = 11.0 Hz), 4.90 (dd, 1H, H-7, J = 12.3, 5.5 Hz), 4.57 (d, 1H, CH_2, J = 13.7 Hz), 4.30-3.70 (m, 6H, CH_2), 3.60 (t, 1H, CH_2, J = 12.3 Hz) and 3.25 (s, 3H, CH_3). Anal. Calcd for $C_{19}H_{22}Cl_3N_2 \cdot .75\ H_2O$: C, 57.16; H, 6.19; Cl, 26.64; N, 7.02. Found: C, 57.57; H, 6.28; Cl, 25.94; N, 7.04.

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5. An interesting example of this solubility difference was evident when 3,4,6,7-tetrahydro-7-phenyl-2H-pyrazino[2,1-a]isoquinolin-1(11bH)-ones (des-chloro 5 and 6) were used as substrate. In this case, both the cis and trans isomers were soluble at reflux temperature, it thus being necessary to perform the equilibration process at ambient temperature to give an 84% isolated yield of pure cis isomer.
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