Conformational Analysis of 1,2,3,4-Tetrahydroisoquinolines

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Ring and nitrogen inversion account for the conformational equilibria of 3-phenyl-1,2,3,4-tetrahydroisoquinolines. In order to quantitate the relative contribution of each conformer to the equilibrium, we undertook a molecular mechanics study on several substituted 3-phenyl-1,2,3,4-tetrahydroisoquinolines. Predictions from calculations were checked against cmr chemical shift data. No boat conformation contributed significantly to the equilibrium. A general result of our calculations is that in all cases the 3-phenyl group in the equatorial position is strongly favored (by at least 2.50 kcal/mole). For 3-phenyl-1,2,3,4-tetrahydroisoquinolines without substitution at nitrogen, N-H in equatorial position is preferred over the axial conformer, although the energy difference between both is always small (0.30-1.10 kcal/mole). For the *cis*-1,3-disubstituted compounds the 1e'3e conformers are the only species present (at least 99.8%). The calculated energy differences between the 1a'3a conformer and the 1e'3e conformer are always large (3.80-6.10 kcal/mole for the NHe conformers and 3.60-3.80 kcal/mole for the NHa conformers). The lack of a γ_{1a} upfield shift at C3 also points to the preference for the pseudoequatorial-equatorial conformer. For *N*-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline a preference for the NMe group in the equatorial position is predicted (0.60-2.00 kcal/mole). The small downfield shift at C4 (γ_{Na} = 0.5 ppm) is consistent with the equatorial NMe preference. For the *cis*-1,2,3-trisubstituted compounds no significant γ_{1a} effect at C3 (γ_{1a} = -0.2 and 1.0 ppm) or γ_{Na} effect at C4 (γ_{Na} = 0.1 and 0.4 ppm) is observed. For these compounds, deformations due to steric congestion are evidenced by the deviation from the values of the C4a-C8a-C1-N and C4a-C4-C3-N torsional angles, as compared to less crowded 3-phenyl-1,2,3,4-tetrahydroisoquinolines. Here the heterocyclic ring adopts a distorted half-chair conformation.

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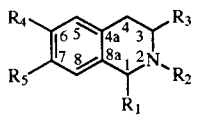
Introduction.

The structural framework of 1,2,3,4-tetrahydroisoquinolines (Scheme 1) is the common motif of several compounds with pharmacological activity [1,2]. Recently, molecular modeling of 1,2,3,4-tetrahydroisoquinoline agonists of the dopamine (D1) receptor served to probe structural features of the binding pocket, namely, substituted benzyl-1,2,3,4-tetrahydroisoquinolines were employed to probe the volume available for the ligand at the binding site [3]. On the other hand, 3-phenyl-1,2,3,4-tetrahydroisoquinoline is known to compete with the potent anesthetic drug phencyclidine for the binding site to its receptor. Here the presence of substituents at C6 and C7 is believed to influence such biological activity [4]. In order to assess the conformational preferences of 1,2,3,4-tetrahydroisoquinolines, we undertook a molecular mechanics study on several substituted 3-phenyl-1,2,3,4-tetrahydroisoquinolines. Predictions from calculations were correlated with cmr chemical shift data.

Scheme 1



Results and Discussion.

A pictorial description of the molecular species dominating the conformational equilibria of 1,2,3,4-tetrahydroisoquinolines is given in Figure 1. Inversions at the tetrahydropyridine ring and at the nitrogen center give rise to the main conformers in equilibrium. In order to quantitate the relative contribution of each conformer to the equilibrium at room temperature, we undertook a molecular mechanics study of several substituted 1,2,3,4-tetrahydroisoquinolines described in Table 1.

Starting geometries for this analysis were generated by building the tetrahydropyridine ring as either a boat or a half chair. Aryl substituents at C1 and C3 were located at their minimal energy positions by exhaustively searching on one (in the case of the phenyl group) or two (in the case of the benzyl or homoveratryl groups) dihedral angles across the bonds connecting them to the tetrahydropyridine ring. To complete the starting set of structures we also included conformers arising from *N*-inversion, and C-OMe rotation at C6 and C7 (compounds **1** and **3-7**). Energy minimization of each starting structure led to one of the four conformers depicted in Figure 1. As expected, no boat conformation contributed significantly to the equilibrium. In agreement with these results, neither Olefirowicz [6], for a series of mono-, di- and trimethyl substituted 1,2,3,4-tetrahydroisoquinolines (at

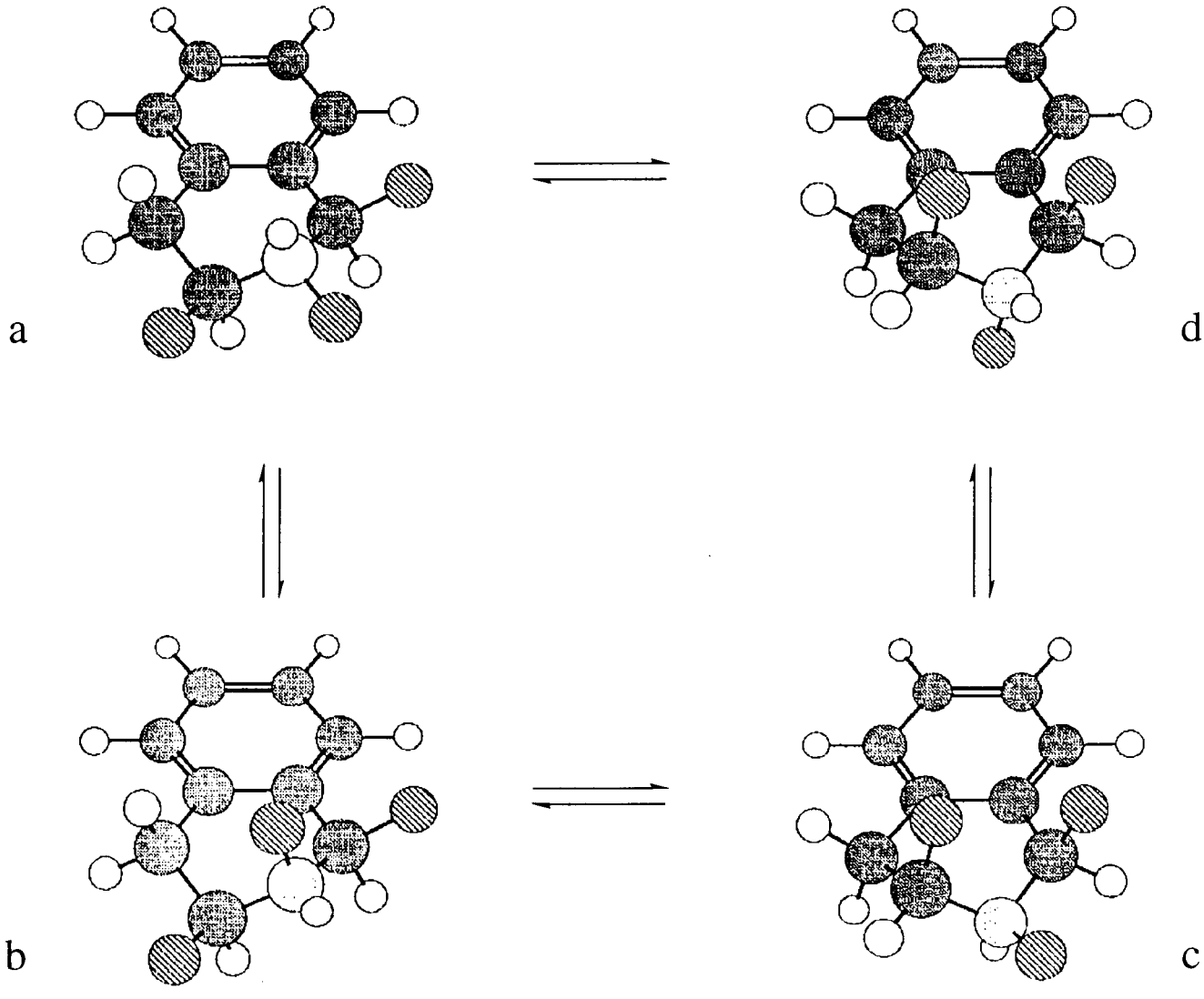


Figure 1. Conformational equilibria of 1,2,3,4-tetrahydroisoquinolines. Dashed circles stand for substituents R1, R2 and R3. Substituents R4 and R5 are not drawn.

positions 1, 2, 3 and 4), nor Charifson and coworkers [3] found any boat conformation to be significantly populated at equilibrium.

In the 1,2,3,4-tetrahydroisoquinoline heterocyclic system, C1 and C3 *syn*-axial interactions are comparatively less important than in cyclohexane, because of the presence of the unsaturation (replacement of an axial H atom by the π system). However, these interactions are more important than in tetralines due to the smaller CN bond distance [7].

A general result of our calculations is that in all cases the 3-phenyl group in the equatorial position is strongly favored, *i.e.* an energy difference of at least 2.50 kcal/mole exists between the axial (3a) and the equatorial (3e) conformers (Table 2). The absence of any significant γ_a upfield shift substantiates this prediction (Table 1), *e.g.* a very small change was observed in the C1 chemical shift of compounds **1** and **2** as compared to the parent compound **9**.

For those 3-phenyl-1,2,3,4-tetrahydroisoquinolines without substitution at nitrogen (**1-4** and **8**), NH in equatorial position (NHe3e) is preferred over the axial conformer (NHa3e), the energy difference between both being always small (0.30-1.10 kcal/mole). In practice, it is not possible to freeze one or the other NH conformational states. By contrast, when the nitrogen bears a methyl substituent (**5-7**), the conformers could, in principle, be distinguished in low temperature nmr experiments. In this regard, Olefirowicz characterized each NMe conformer in a series of methyl substituted 1,2,3,4-tetrahydroisoquinolines at -130° [6]. For the simplest *N*-substituted 3-phenyl-1,2,3,4-tetrahydroisoquinoline (compound **5**) a

Table 1

CMR Data of Substituted 1,2,3,4-Tetrahydroisoquinolines

Compound [a]	Substituents					Chemical Shifts [b] (ppm)			
	R1	R2	R3	R4	R5	C1	C3	C4	NMe
1	H	H	Ph	OMe	OMe	48.5	58.3	36.8	
2	H	H	Ph	OCH_2O		48.8	58.3	37.3	
3	Me	H	Ph	OMe	OMe	52.8	58.5	38.0	
4	Ver [c]	H	Ph	OMe	OMe	57.8	58.0	38.5	
5	H	Me	Ph	OMe	OMe	57.8	66.0	37.3	42.8
6	Me	Me	Ph	OMe	OMe	60.7	65.8	38.1	40.5
7	Ver [c]	Me	Ph	OMe	OMe	66.0	67.0	38.9	42.3
8	Bz [d]	H	Ph	OCH_2O		58.0	58.3	39.4	
9	H	H	H	H	H	48.7	44.3	29.6	
10	H	Me	H	H	H	58.3	53.3	29.7	46.3

[a] Compounds **1-7** were synthesized as described before [5]. The synthesis of compound **8** is described in the Experimental section. Only the *cis* isomers were obtained for compounds **3**, **4**, **6**, **7** and **8**, due to the stereochemistry of the reduction with sodium borohydride or platinic oxide/hydrogen of the respective 3,4-dihydroisoquinolines [5]. [b] All compounds were dissolved in deuteriochloroform and chemical shifts were referenced to TMS. The cmr data for compounds **9** and **10** were taken from Olefirowicz [6]. [c] 3,4-Dimethoxyphenylmethyl- (homoveratryl). [d] Benzyl-.

clear preference for the NMe in the equatorial position is predicted. The equatorial NMe conformers **5a** and **5c** are lower in energy by 2.00 and 0.60 kcal/mole than their corresponding axial conformers **5b** and **5d** (Table 2). The small downfield shift at C4 (γ_{Na} = 0.5 ppm, by comparing compounds **1** and **5**, Table 1) is consistent with the equatorial NMe preference. The preferred conformer (**5a**) explains the upfield shift observed at the NMe carbon ($\Delta\delta$ = 3.5 ppm, by comparing compounds **5** and **10**), which is further evidence for the presence of a gauche interaction between equatorial groups.

Not unexpectedly, for the *cis*-1,3-disubstituted compounds **3**, **4** and **8**, the 1e'3e conformers (NHe1e'3e and NHa1e'3e) are the only species present (at least 99.8%). The calculated energy differences between the 1a'3a conformer and the 1e'3e conformer are always large (3.80-6.10 kcal/mole for the NHe conformers and 3.60-3.80 kcal/mole for the NHa conformers), clearly showing the preference of the substituents at C1 and C3 for the pseudoequatorial and equatorial positions, respectively. The lack of a γ_{1a} upfield shift at C3 (by comparing compounds **3**, **4** and **8** with compound **1**, Table 1) also points to the pseudoequatorial-equatorial conformer as the highly preferred species. Because of the counter play of α_1 and γ_{3a} effects at C1 in these compounds, it is not clear how to accurately estimate each contribution independently. This arises from the lack of an appropriate reference compound, where the phenyl group at C3 could be unambiguously fixed in either the axial or equatorial positions. In addition, an interesting structural difference between compounds **4** and **8** arises from the nature of the aryl substituent at C1. The benzyl group in conformer **8a** folds over the heterocyclic ring plane, while in conformer **4a** the homoveratryl group turns away from it. This might bear significance in connection with the oxidative coupling leading to morphinane or to aporphine alkaloids [8].

Table 2

Conformational Analysis of Substituted 1,2,3,4-Tetrahydroisoquinolines

Compound [a]	Energy [b] (kcal/mol)	Abundance [c] (%)	Dihedral angles (°) C4a-C8a-C1-N	C4a-C4-C3-N
1a NHe3e	0.00	65.1	17.1	-50.3
1b NHa3e	0.40	33.2	18.3	-49.4
1c NHe3a	2.50	1.0	18.0	-46.8
1d NHa3a	2.70	0.7	18.5	-47.0
2a NHe3e	0.00	65.2	0.4	-56.2
2b NHa3e	0.40	33.2	18.7	-49.6
2c NHe3a	2.50	1.0	18.3	-47.1
2d NHa3a	2.80	0.6	18.8	-47.3
3a NHe1e'3e	0.00	62.3	8.6	-53.6
3b NHa1e'3e	0.30	37.5	10.2	-52.2
3c NHe1a'3a	3.80	0.1	12.5	-50.8
3d NHa1a'3a	3.90	0.1	13.1	-50.6
4a NHe1e'3e	0.00	76.5	3.8	-54.8
4b NHa1e'3e	0.70	23.5	9.6	-52.0
4c NHe1a'3a	6.10	0.0	22.4	-48.5
4d NHa1a'3a	4.50	0.0	22.9	-48.3
5a Ne3e	0.00	95.3	19.8	-49.3
5b Na3e	2.00	3.3	21.1	-47.0
5c Ne3a	2.70	1.0	20.7	-43.8
5d Na3a	3.30	0.4	22.5	-42.4
6a Ne1e'3e	0.00	92.2	-4.2	-58.5
6b Na1e'3e	1.50	7.4	18.0	-47.6
6c Ne1a'3a	4.50	0.0	15.3	-47.4
6d Na1a'3a	3.30	0.4	18.6	-46.1
7a Ne1e'3e	0.00	99.2	-11.5	-54.8
7b Na1e'3e	6.70	0.0	-41.0	-52.0
7c Ne1a'3a	4.20	0.1	24.6	-48.5
7d Na1a'3a	2.90	0.7	27.2	-48.3
8a NHe1e'3e	0.00	86.5	0.4	-56.2
8b NHa1e'3e	1.10	13.5	4.4	-54.2
8c NHe1a'3a	5.10	0.0	20.9	-49.0
8d NHa1a'3a	4.90	0.0	21.0	-48.8
9a NHe	0.00	52.5	17.7	-50.1
9b NHa	0.06	47.5	19.0	-49.0

[a] The "e" and "a" notation stands for equatorial or axial, respectively. Substituents at C1 are either pseudoequatorial (denoted by e') or pseudoaxial (denoted by a'). [b] The energy minimization protocol employs the block diagonal Newton Raphson method [9] on the MM2 force field [10] as implemented in Macromodel v. 3.0 (1990) [11]. Convergence to a local minimum is achieved when the energy gradient is less than 0.5 kJ/Å. [c] Calculated for the equilibria at 25°, as described in the Experimental.

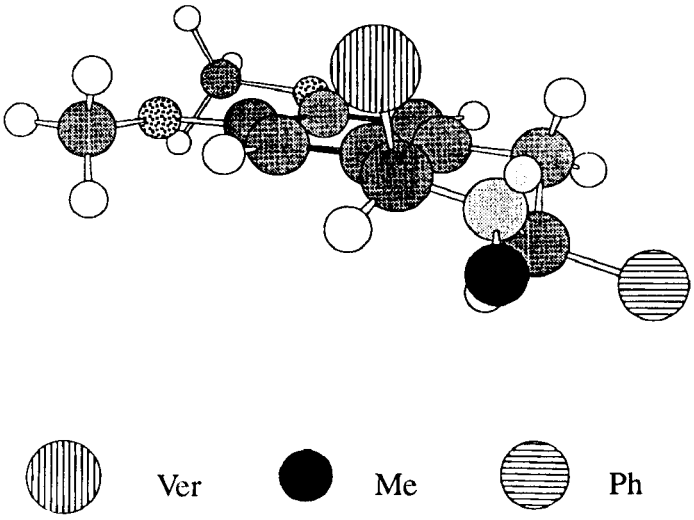


Figure 2. Least-energy conformation of *cis*-1,2,3-trisubstituted 1,2,3,4-tetrahydroisoquinolines (*e.g.* **7a** in Table 2). Substituents R1, R2 and R3 are represented as circles to allow for the view of the tetrahydropyridine ring.

In principle, for *cis*-1,2,3-trisubstituted 1,2,3,4-tetrahydroisoquinolines, the two *C*-equatorial substituents might force the *N*-substituent to adopt an axial position, as suggested by Olefirowicz for 1,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline [6]. By contrast, in our case, no experimental evidence for this exists, since for compounds **6** and **7** there is no significant γ_{1a} effect at C3 (γ_{1a} = -0.2 and 1.0 ppm, by comparing compounds **6** and **7** with compound **5**) or γ_{Na} effect at C4 (γ_{Na} = 0.1 and 0.4 ppm by comparing compounds **6** and **7** with compounds **3** and **4**, respectively). Ring deformations due to steric congestion are evidenced by the deviation from the values of the torsional angles C4a-C8a-C1-N and C4a-C4-C3-N calculated for compounds **6** and **7**, as compared to other less crowded 3-phenyl-1,2,3,4,-tetrahydroisoquinolines (Table 2). The heterocyclic ring in the most stable conformers (**6a** and **7a**) is a distorted half-chair (an envelope conformation) as shown in Figure 2.

In summary, the molecular mechanics calculations of various 3-phenyl-1,2,3,4-tetrahydroisoquinolines presented in this paper served to establish the preferred conformations in equilibrium. The predicted geometries are consistent with cmr chemical shift data. From the lack of γ effects arising from substituents in axial positions we inferred that the favored conformer at equilibrium should be the all equatorial form **a**. For most compounds, the half chair conformer prevails, except where the bulkiness of substituents at C1 and C3 and *N*-substitution force the heterocycle to adopt a distorted envelope conformation.

EXPERIMENTAL

Calculations.

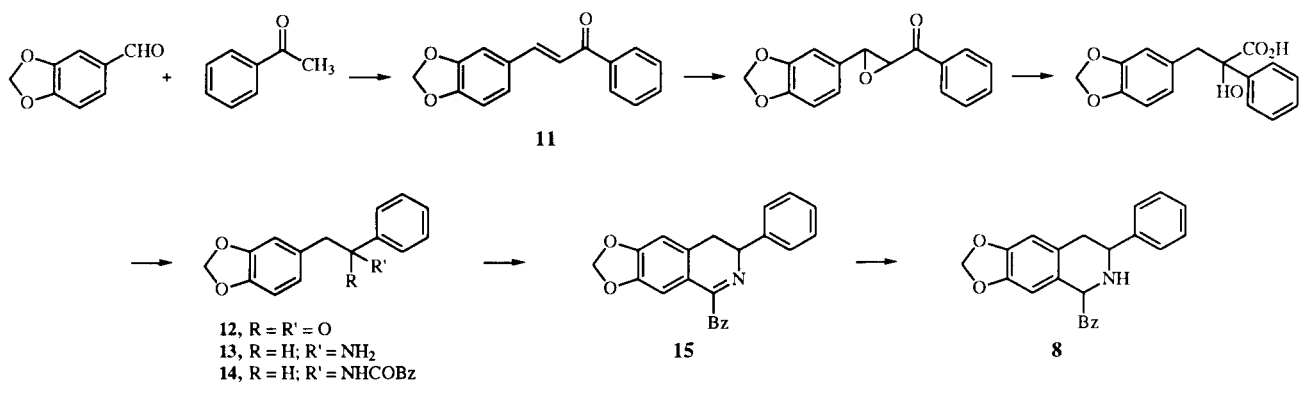
Macromodel v. 3.0 (W.C. Still, Columbia University, 1990) was implemented on a DEC MicroVAX 2000, using the graphics interface provided by a Macintosh II computer equipped with a RGB high resolution color monitor, *via* a Tektronix 4105 emulation (VersaTermPRO v. 5.0.1, Abelbeck Software, 1993).

The relative abundance of each species in equilibrium (see Figure 2) is calculated from the minimum energy associated with each conformer employing the relationships: (a) $\Delta G = -RT \ln K$, where ΔG stands for the standard energy difference between two given species; R is the molar gas constant expressed in units of kcal mole^{-1} °K^{-1}; T is the absolute temperature in °K and K is the corresponding equilibrium constant; and (b) a + b + c + d = 100, where a, b, c and d represent the percentage molar ratio of each conformer in equilibrium. A program that performs these calculations is available from the authors (submitted as supplementary material).

General Experimental Procedures.

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. The cmr spectra were recorded on a Varian FT 80A or on a Bruker WO SYFT. Chemical shifts are given in ppm (δ) relative to tetramethylsilane (TMS). Infrared spectra were performed on a Jasco A200 as Nujol mulls. Mass spectra were recorded on a

Scheme 2



Shimadzu GCQP1000 spectrometer or a GC-MS Shimadzu QP-5000 spectrometer.

Synthesis and Characterization of Compounds.

Synthesis and experimental data of substituted 1,2,3,4-tetrahydroisoquinolines were described before [5]. A more efficient synthetic pathway for this class of compounds is depicted in Scheme 2. The synthesis of compound **8** illustrates this procedure, which differs from that previously reported [12].

3-(3,4-Methylenedioxyphenyl)-1-phenylpropenone (**11**) [13].

To a stirred solution of 3,4-methylenedioxybenzaldehyde (2.25 g, 15 mmoles, from Aldrich) and methylphenylketone (1.92 g, 16 mmoles, from Aldrich) in 15 ml of anhydrous ethanol at 0°, sodium methoxide dissolved in 2 ml of methanol (prepared by the addition of 200 mg of sodium) was added. The mixture was stirred for 6 hours at 0° and then allowed to stand overnight without stirring at 4°. The precipitate formed was then filtered and this material was crystallized from ethanol to yield 3.16 g (83%) of **11**; mp 109-110°; pmr (deuteriochloroform, 80 MHz): δ 6.05 (s, 2H, OCH_2O), 6.85 (dd, 1H, J = 8.5 Hz, J = 1.5 Hz, Ar), 7.30 (d, 1H, J = 17.5 Hz, CH=CH), 7.75 (d, 1H, J = 17.5 Hz, CH=CH), 7.10-8.10 ppm (m, 7H, Ar); ir (mull): ν 1675, 1620 cm^{-1}.

2-(3,4-Methylenedioxyphenyl)-1-phenylethanone (**12**) [14].

This compound was prepared from compound **11** according to a published procedure [15]. Crystallization of the product from ethanol yields 1.39 g (58%) of **12**; mp 69-79°; pmr (deuteriochloroform, 80 MHz): δ 4.20 (s, 2H, CH_2), 5.95 (s, 2H, OCH_2O), 6.70 (s, 3H, Ar), 7.40 (m, 3H, Ar), 7.85 ppm (d, 2H, J = 8 Hz, Ar); ir (mull): ν 1695, 1240 cm^{-1}.

2-(3,4-Methylenedioxyphenyl)-1-phenylethanamine (**13**) [12].

To 1.56 g (6.5 mmoles) of **12** dissolved in 30 ml of ethanol were added 1.75 g of hydroxylamine hydrochloride and 6 ml of 30% aqueous sodium hydroxide. The solution was refluxed with stirring for 2 hours and then diluted with 15 ml of water. Subsequently, 2.5 g of Raney nickel alloy was carefully added and the mixture was stirred for 1 hour. After filtration through a fritted glass filter containing a 0.5 cm high bed of Celite, the filtrate was extracted with diethyl ether. The organic layer was dried with sodium sulfate and evaporated to yield an oil (1.1 g of **13**, 70% yield): pmr (deuteriochloroform, 80 MHz): δ 1.70 (s, 2H, NH_2), 2.75 (m, 2H, CH_2), 4.20 (m, 1H, CH), 6.05 (s, 2H, OCH_2O), 6.30 (m, 3H, Ar), 7.25 ppm (m, 5H, Ar); ir (mull): ν 3450, 1230 cm^{-1}; ms: (ei, 70 eV) m/z (relative intensity) 241 (1.1, M^+), 135 (7.6), 111.2 (9.3), 107 (10.6), 106 (100).

N-Benzoyl-2-(3,4-methylenedioxyphenyl)-1-phenylethanamine (**14**) [12].

To 1.0 g (3.6 mmoles) of **13** (hydrochloride form) dissolved in 10 ml of dichloromethane were added 1.0 ml of triethylamine and 0.7 ml of phenylacetyl chloride. The solution was stirred for 1 hour at room temperature and then allowed to stand overnight without stirring. In the end, the solvent was evaporated, the residue was re-suspended in water and chloroform was added. The organic layer was separated and washed twice with 50% ammonium hydroxide and then twice with water. The organic layer was dried with sodium sulfate and evaporated. The product was crystallized from ethanol to yield 830 mg (64%) of **14**, mp 179-180°; pmr (deuteriochloroform, 80 MHz): δ 2.85 (m, 2H, CH_2), 3.45 (s, 2H, CH_2), 5.20 (m, 1H, CH), 6.05 (s, 2H, OCH_2O), 6.25 (m, 3H, Ar), 7.25 ppm (m, 10H, Ar); ir (mull): ν 3330, 1650, 1235 cm^{-1}.

1-Benzyl-6,7-methylenedioxy-3-phenyl-3,4-dihydroisoquinoline (**15**) [12].

Ethyl polyphosphate (5.28 g) in chloroform solution [16] and 800 mg of **14** were heated at 80° for 8 hours. The solvent was then evaporated and the residue poured over 30 ml of water. The aqueous solution was then extracted with dichloromethane and alkalinized with ammonium hydroxide, and the reaction mixture was extracted again with diethyl ether. The organic layer was dried with sodium sulfate and evaporated. Crude compound **15** was reduced next without any previous purification.

1-Benzyl-6,7-methylenedioxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**8**).

Compound **15** was dissolved in 20 ml of methanol and 400 mg of sodium borohydride were added. After stirring for 30 minutes at room temperature, the solvent was evaporated and the residue extracted with diethyl ether. The combined extracts were dried with sodium sulfate and the solvent was removed under reduced pressure. Compound **8** was chromatographed on a silica gel column (20 g, 2 x 20 cm) employing chloroform: methanol (95:5, v/v) as the running solvent. Product **8** is an oil, (480 mg, 63% of theory): pmr (deuteriochloroform, 80 MHz): δ 2.15 (s, 1H, NH), 2.80 (m, 2H, CH_2), 3.50 (m, 1H, CH), 3.90 (m, 1H, CH), 4.10 (q, 1H, CH), 4.40 (m, 1H, CH), 5.95 (s, 2H, OCH_2O), 6.55 (s, 1H, Ar), 6.90 (s, 1H, Ar), 7.30 ppm (m, 10H, Ar); cmr (deuteriochloroform, 20 MHz): δ 39.4, 42.9, 58.0, 58.3, 100.5, 108.1, 108.4, 126.2, 127.0, 127.6, 127.7, 128.2, 128.7, 129.2, 130.8, 138.4, 144.2, 145.7, 145.9 ppm; ms: (ei, 70 eV) m/z (relative intensity) 343 (19, M^+), 268 (3), 267 (3), 266 (6), 265 (24), 250 (4), 222 (5), 165 (17), 164 (100), 151 (4), 149 (13), 121 (6).

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