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SYNTHESIS OF RACEMIC 1,2,3,4-TETRAHYDROISOQUINOLINES AND THEIR RESOLUTION*

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1-Aniline-substituted 3,4-dihydroisoquinolines were obtained in various ways using the Bischler–Napieralski reaction. The effect of the protecting group at the aniline nitrogen atom on the course of the reaction has been studied and it was found that the N-phthalyl group was stable under the cyclization conditions. The dihydroisoquinolines were reduced to the racemic 1,2,3,4-tetrahydroisoquinolines which were resolved by crystallization of the diastereomeric tartrates. Two examples of 1,2,3,4-tetrahydroisoquinolines were obtained in optically pure form (> 99% ee).

Keywords: dihydroisoquinolines, 1,2,3,4-isoquinolines, resolution of isomeric tartrates.

The high interest in 1,2,3,4-tetrahydroisoquinolines is connected with the presence of this fragment in a number of natural alkaloids. In the last two decades enantioselective syntheses of many isoquinoline alkaloids have been carried out (e. g., laudanosine, reticuline, xilopinine, and salsalodine). The successful synthesis of isoquinoline alkaloids is graphically described in a review [1]. Some derivatives of this class of compounds are central nervous system depressants [2] and blockers of NMDA receptors [3].

Quite recently one representative of the chiral compounds of this class - 1-(2-methylamino-5-chloro)phenyl-1,2,3,4-tetrahydroisoquinoline (Aldrich) has been used successfully as an effective hydrogen donor in stoichiometric [4, 5] and catalytic amounts [6]. Although some interesting and original methods have been developed for the synthesis of derivatives of 1,2,3,4-tetrahydroisoquinolines [3, 7-10] the papers have given no general method for the synthesis of chiral substituted 1-(aminophenyl)-1,2,3,4-tetrahydroisoquinolines.

In the present paper the convenient methods we have developed for the synthesis of such racemic compounds and their resolution by crystallization of diastereomeric salts with chiral organic acids, e.g., tartrates, are described. The method is convenient and cheap because the chiral reagent can be reused after simple acid-base treatment.

The isoquinoline nucleus was obtained by various means, using one of the known methods: Bischler–Napieralski, Pictet–Spengler, Pomeranz–Fritsch, or Schlittler–Müller [1]. Formation of chiral tetrahydroisoquinolines by Bischler–Napieralski cyclization is the most attractive because it is possible to use available benzoic acids **1** to obtain the amides **2**. Cyclization of the later leads to the 3,4-dihydroisoquinolines **3**, which can be further converted to the 1,2,3,4-tetrahydroisoquinolines **4** by direct asymmetric reduction of the C=N double bond or by reduction with subsequent resolution of the racemate by crystallization of its diastereomeric salts. Asymmetric reduction is the subject of a separate paper, while the possibility of crystallization of diastereomeric salts is described in this paper.

* Dedicated to Professor M. A. Yurovskaya on her jubilee.

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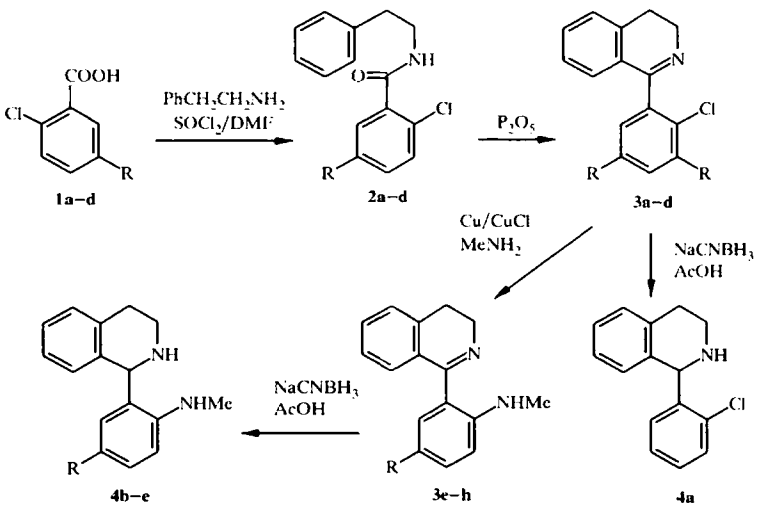
The Bischler–Napieralski cyclization has been thoroughly studied [9, 11, 12]. Since our objective was the synthesis of the different 1-(aminophenyl)derivatives **4a-h**, the choice of appropriate protective groups for the aniline nitrogen atom was a key problem. Under Bischler–Napieralski reaction conditions cyclization of mono-N-substituted aniline-β-phenylethylamides [2] was unsuccessful with N-acetyl- and N-tosyl-substituted substrates. Our choice of electron acceptor substituents in 1-aryltetrahydroisoquinolines was based on the idea that an increase in the polarization of the amide groups in the β-phenethylamides **2** might facilitate formation of the imidoyl chloride and the nitrilium salt. We proposed that the use of an N-benzyl protecting group (compound **2h**, Table 1) would lead to an increase in the electron deficient nature of the aniline substituent in the hydrochloride of **2h** and thus facilitate formation of the dihydroisoquinolines. However only the debenzylated compound **3e** (16% yield) was isolated in this case because of side reactions. Cyclization of the β-phenylethylamide of 2-(N-methyl-N-acetyl)aminobenzoic acid was also unsuccessful. An increase in the yield (30%) when the electron accepting tosyl group on the aniline nitrogen atom was used (amide **2f**) led to an attempt to use two protecting groups on the aniline nitrogen atom.

In principle, the phthalyl groups should be the most successful choice. The initial result under classical cyclization conditions was unsatisfactory (20% yield). On the basis of work on the mechanism of the Bischler–Napieralski reaction [11, 12] we changed the dehydrating agent (from P_2O_5 to PCl_5) and solvent (from xylene to chloroform) and also added a Lewis acid ($SnCl_4$) which led to the formation of the 3,4-dihydroisoquinoline **3j** in 73% yield. This is the first example in which the phthalyl unit was retained under Bischler–Napieralski conditions. After heating in chloroform for 30 min a yellow precipitate was formed, the color of which changed to brick red on addition of the Lewis acid ($SnCl_4$). The change in color indicated formation of the cyclic compound **3j** (3,4-dihydroisoquinolines have an intense red color in acid conditions). An increase of charge (to 85 g) did not affect the yield. The protecting group was carried out according to [13] which resulted in conversion of the dihydroisoquinoline **3j** into the unsubstituted aniline **3k** in 38% overall yield (two steps).

We found an alternative to the direct cyclization of amides **2e-i** in direct amination of the 1-(2-chlorophenyl)-3,4-dihydroisoquinolines **3a-d** (scheme 1) under conditions of the Ullmann exchange reaction [2]. The 3,4-dihydroisoquinolines **3e-g** were obtained in this way. Compound **3g** had not been described previously, **3h** was not isolated pure, but was characterized only after reduction to compound **4b**.

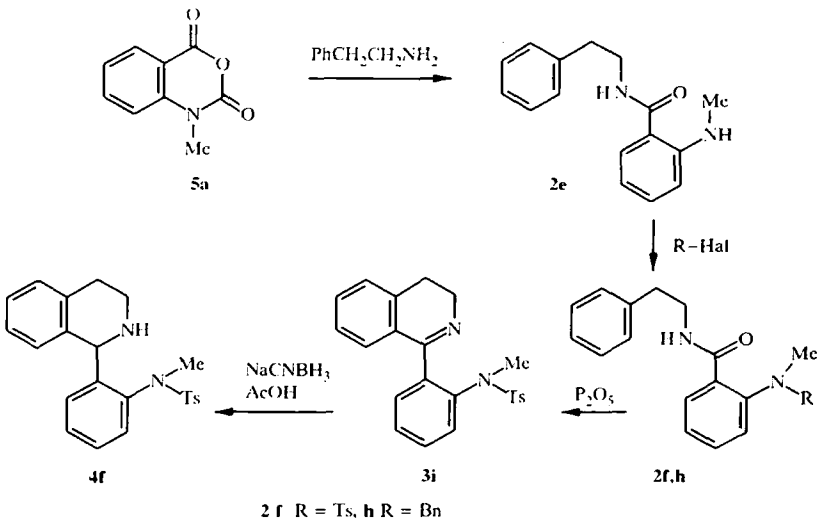
The starting imines **3a-e** were obtained from mono- and disubstituted benzoic acids **1** (scheme 1) or the isatoanhydrides **5a** and **5b** (schemes 2 and 3).

Scheme 1



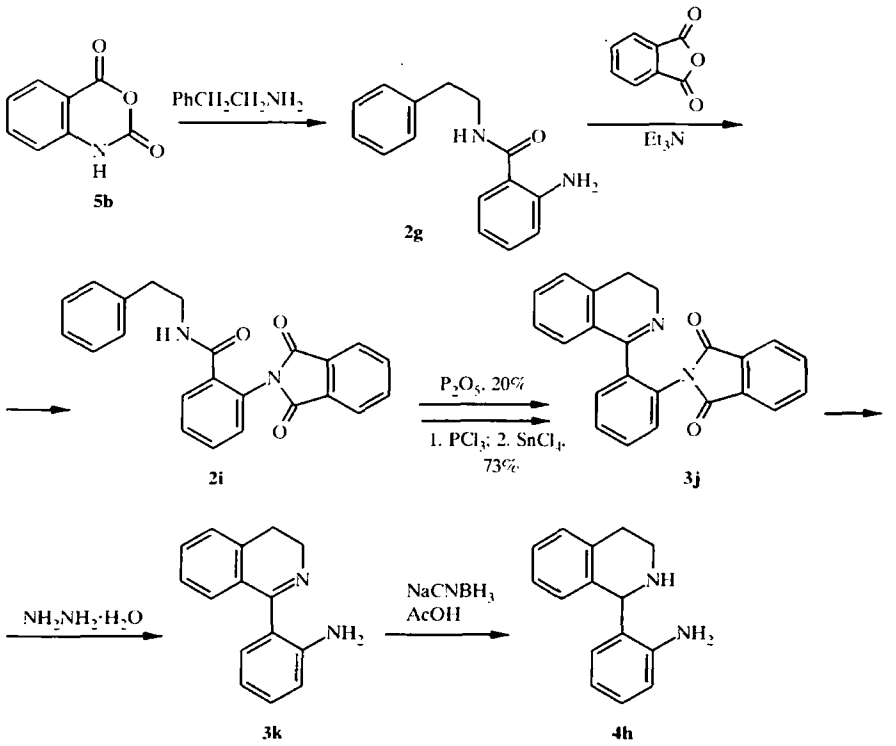
1–3 **a** R = H; **b** R = CF_3; **c** R = NO_2; **d** R = SO_2Me;
3 **e** R = H; **f** R = NO_2; **g** R = SO_2Me; **h** R = CF_3;
4 **b** R = CF_3; **c** R = NO_2; **d** R = SO_2Me; **e** R = H

Scheme 2

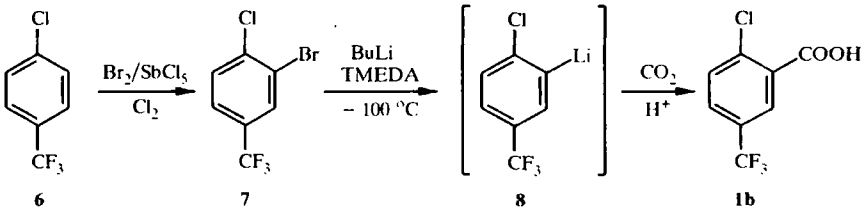


The benzoic acids **1a-c** are commercially available, but some of them are expensive (e.g., the trifluoromethyl derivative **1b**). We therefore developed a two step synthesis for the latter from 4-chlorotrifluoromethylbenzene (**6**) (scheme 4) by selective low temperature (-100°C) metallation of the corresponding *o*-bromochlorobenzene **7**.

Scheme 3



Scheme 4



6 7 8 1b

Monobromination of 4-chlorotrifluoromethylbenzene (**6**) was carried out as described earlier [14]. Metallation of the bromide **7** (scheme 4) at low temperature was important for two reasons: 1) selective substitution of the bromine atom in the presence of the chlorine atom [15] and 2) decrease in the quantity of side reactions, including dehydrobromination. At temperatures above -50°C the side reactions predominated giving rise to the unwanted dehydrobenzene. Additional stabilization of the carbanion **8** was observed when the bidentate ligand tetramethylethylenediamine was used, the role of which in organolithium chemistry is well known [16]. Treatment of the intermediate carbanion **8** with solid carbon dioxide gave the carboxylic acid **1b** in 52% overall yield (in three steps). Methylsulfonylbenzoic acid **1d** was obtained in three steps by a known method [17]. An alternative approach to the synthesis of compounds is connected to the choice of the nitro precursors of the anilines in which the nitro group is readily reduced to the amino group in the presence of the C=N double bond of 3,4-dihydroisoquinolines [18].

All of the 3,4-dihydroisoquinolines obtained were reduced to the tetrahydroisoquinolines **4a-h** with sodium cyanoborohydride in acetic acid [19]. The reduction occurred under mild conditions and gave greater yields in comparison with reduction with $NaBH_4$ in ethanol [2].

By analogy with the resolution of 1-(2-methylamino-5-chloro)phenyl-1,2,3,4-tetrahydroisoiquinoline [2] optically active tartaric acid was used for resolution of the tetrahydroisoquinlines [20]; resolution of the diastereomeric tartrates of the N-unsubstituted analog has been described [21].

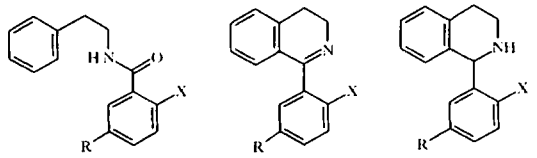
Resolution of the diastereomeric tartrates of two racemic tetrahydroisoquinolines **4b** and **4d** after two crystallizations from ethanol were very successful (scheme 5). Subsequent treatment of the tartrates with the OH^- form of the strongly basic ion exchanger Amberlite IRA-401 gave the free bases **4b** and **4d** with optical purities >99.5%.

However we have not had success in finding a suitable solvent for the poorly soluble tartrates of the racemic nitro compound **4c**. Resolution of the racemic methylsulfonyltetrahydroisoquinoline **4d** by crystallization of its tartrates or its salts with (+)-malic acid from various solvents was unsuccessful. Apparently the difference in solubility of the diastereomeric salts of **4d** is insufficient for selective crystallization. The process of crystallization of diastereomeric salts is strictly substrate specific which makes it considerably more difficult to develop general methods.

TABLE 1. Cyclization of β-Phenylethylamides **2**

Sub-strate	X	Dehydrating agent	Cyclization conditions	Reaction product	Yield, %
2g	$N(Me)CH_2Ph$ HCl salt	P_2O_5	6 h, xylene, reflux	**3e**	16
2f	N(Me)Tos	P_2O_5	20 h, xylene, reflux	**3i**	30
2i	N-Phthalyl	P_2O_5	24 h, xylene, reflux	**3j**	20
2i	N-Phthalyl	PCl_5	30 min, $CHCl_3$, reflux; $SnCl_4$, 8 h	**3j**	73
2a	Cl	P_2O_5	24 h, xylene, reflux	**3a**	70

TABLE 2. IR, ^1H, and ^{13}C NMR Spectra of the β-Phenylethylamides **2**, 3,4-Dihydroisoquinolines **3**, and 1,2,3,4-Tetrahydroisoquinolines **4**



2 3 4

Compound	R	X	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm	^{13}C NMR spectrum, δ, ppm
1	2	3	4	5	6
2a	H	Cl	3275 (N–H) 1642 (C=O)	7.63-7.58 (1H, m, H_{Ar}); 7.38-7.19 (8H, m, H_{Ar}); 6.20 (1H, br. s, CONH); 3.76 (2H, dt, J = 6.8; 6.0 Hz, CH_2N); 2.96 (2H, t, J = 6.8 Hz, $ArCH_2$)	166.4; 138.6; 135.1; 131.1; 130.5; 130.1; 129.9; 128.7; 128.6; 128.4; 128.3; 126.9; 126.6; 41.2; 35.4
2b	CF_3	Cl	3270 (N–H) 1650 (C=O)	7.85 (1H, d, J = 1.8 Hz, H_{Ar}); 7.58 (1H, dd, J = 8.4; 1.8 Hz, H_{Ar}); 7.49 (1H, d, J = 8.6 Hz, H_{Ar}); 7.38-7.20 (5H, m, H_{Ar}); 6.20 (1H, br. s, CONH); 3.77 (2H, dt, J = 6.8; 6.0 Hz, CH_2N); 2.97 (2H, t, J = 6.8 Hz, $ArCH_2$)	165.0; 138.6; 135.8; 134.4; 130.8; 129.3; 128.7; 128.5; 127.7; 127.2; 126.7; 126.4; 125.9; 120.5; 41.3; 35.3
2c	NO_2	Cl	3260 (N–H) 1650 (C=O)	8.44 (1H, d, J = 2.8 Hz, H_{Ar}); 8.19 (1H, dd, J = 8.8; 2.8 Hz, H_{Ar}); 7.56 (1H d, J = 8.8 Hz, H_{Ar}); 7.40-7.20 (5H, m, H_{Ar}); 6.14 (1H, br. s, CONH); 3.79 (2H, dt, J = 6.8; 5.8 Hz, CH_2N); 2.99 (2H, t, J = 6.8 Hz, $ArCH_2$)	164.1; 146.4; 138.2; 137.5; 136.4; 131.3; 128.8; 128.75; 128.5; 127.6; 126.8; 125.5; 125.1; 41.4; 35.3
2d	SO_2Me	Cl	3260 (N–H) 1645 (C=O)	8.10 (1H, d, J = 2.2 Hz, H_{Ar}); 7.89 (1H, dd, J = 8.4; 2.2 Hz, H_{Ar}); 7.58 (1H, d, J = 8.4 Hz, H_{Ar}); 7.39-7.21 (5H, m, H_{Ar}); 6.14 (1H, br. s, CONH) 3.77 (2H, dt, J = 7.0; 6.0 Hz, CH_2N); 3.06 (3H, s, SO_2CH_3); 2.97 (2H, t, J = 7.0 Hz, $ArCH_2$)	164.7; 139.4; 138.2; 136.74; 136.66; 131.3; 129.5; 128.8; 128.75; 128.70; 126.7; 44.4; 41.3; 35.3
2e	H	NHMe	3405 (N–H) 3318 (N–H) 1627 (C=O)	7.43 (1H, br. s, ArNH); 7.32-7.15 (7H, m, H_{Ar}); 6.61 (1H, d, J = 8.0 Hz, H_{Ar}); 6.54-6.45 (1H, m, H_{Ar}); 6.3-6.2 (1H, m , CONH); 3.62-3.53 (2H, m, CH_2N); 2.83 (2H, t, J = 7.0 Hz, $ArCH_2$); 2.78 (3H, s, NCH_3)	169.7; 150.2; 138.8; 132.6; 132.5; 128.6; 128.5; 127.0; 126.3; 115.1; 114.3; 110.8; 40.7; 35.5; 29.5

TABLE 2 (continued)

1	2	3	4	5	6
2f	H	NMeTs	3380 (N–H) 1655 (C=O)	7.73 (1H, dd, J = 7.4; 1.5 Hz, H_{Ar}); 7.60 (2H, d, J = 8.0 Hz, H_{Ar}); 7.41-7.00 (10H, m, H_{Ar}, CONH); 6.51 (1H, d, J = 8.0 Hz, H_{Ar}); 3.78 (2H, dt, J = 7.0; 6.0 Hz, CH_2N); 3.10 (3H, s, NCH_3); 3.02 (2H, t, J = 7.0 Hz, $ArCH_2$); 2.48 (3H, s, $ArCH_3$)	166.8; 144.2; 138.9; 138.1; 137.2; 133.9; 130.4; 130.3; 129.6; 128.8; 128.7; 128.4; 128.3; 128.1; 126.6; 126.2; 41.2; 39.7; 35.4; 21.5
2g	H	NH_2	3410 (N–H) 3290 (N–H) 1620 (C=O)	7.38-7.14 (7H, m, H_{Ar}); 6.66 (1H, d, J = 8.6 Hz, H_{Ar}); 6.60 (1H, ddd, J = 8.0, 8.0, 0.8 Hz, H_{Ar}); 6.03 (1H, br. s, CONH); 5.49 (2H, br. s, $ArNH_2$); 3.68 (2H, dt, J = 7.0; 6.0 Hz, CH_2N); 2.92 (2H, t, J = 7.0 Hz, $ArCH_2$)	169.2; 148.6; 138.9; 132.2; 128.8; 128.7; 126.9; 126.5; 117.2; 116.5; 116.1; 40.8; 35.7
2h	H	NMeBn	3325 (N–H) 1630 (C=O)	10.05-9.95 (1H, m, CONH); 8.23 (1H, dd, J = 7.6; 1.8 Hz, H_{Ar}); 7.38 (1H, ddd, J = 7.6; 7.6; 1.8 Hz, H_{Ar}); 7.31-6.99 (12H, m, H_{Ar}); 3.90 (2H, s, CH_2Ph); 3.80-3.71 (2H, m, CH_2N); 2.90 (2H, t, J = 7.0 Hz, $ArCH_2$); 2.37 (3H, s, NCH_3)	166.2; 151.4; 139.3; 136.5; 131.6; 131.4; 131.3; 129.1; 128.71; 128.67; 128.50; 128.48; 128.45; 128.42; 128.37; 127.6; 126.34; 126.31; 124.7; 61.2; 42.3; 40.5; 35.3
2i	H	NPhth	3255 (N–H) 1630 (C=O) 1720 (C=O)	7.93 (2H, dd, J = 5.6; 3.0 Hz, H_{Ar}); 7.77 (2H, dd, J = 5.6; 3.0 Hz); 7.62-7.19 (9H, m, H_{Ar}); 6.10 (1H, t, J = 5.8 Hz, CONH); 3.54 (2H, dt, J = 7.0; 6.2 Hz, CH_2N); 2.80 (2H, t, J = 7.0 Hz, $ArCH_2$)	167.4; 166.8; 138.8; 134.2; 132.0; 131.2; 130.0; 129.9; 129.0; 128.7; 128.6; 128.3; 127.8; 126.5; 123.8; 41.0; 35.5
3a	H	Cl	1615 (C=N)	7.46-7.16 (7H, m, H_{Ar}); 6.91 (1H, d, J = 7.4 Hz, H_{Ar}); 4.14-3.64 (2H, m, CH_2N); 2.88 (2H, m, $ArCH_2$)	166.0; 138.3; 137.1; 132.5; 130.8; 130.3; 129.7; 129.5; 128.8; 127.3; 126.80; 126.77; 126.71; 47.7; 25.8
3b	CF_3	Cl	1620 (C=N)	7.72-7.71 (1H, m, H_{Ar}); 7.64 (1H, dd, J = 8.4; 2.0 Hz, H_{Ar}); 7.55 (1H, d, J = 8.4 Hz, H_{Ar}); 7.40 (1H, ddd, J = 7.4; 7.4; 1.2 Hz, H_{Ar}); 7.29-7.17 (2H, m, H_{Ar}); 6.86 (1H, d, J = 7.6 Hz, H_{Ar}); 4.2-3.7 (2H, m, CH_2N); 2.93-2.86 (2H, m, $ArCH_2$)	165.1; 139.0; 137.1; 136.5; 131.3; 130.2; 128.3; 127.6; 127.5; 127.0; 126.6; 126.5; 97.2; 47.8; 25.7

TABLE 2 (continued)

1	2	3	4	5	6
3c	NO_2	Cl	1620 (C=N)	8.33 (1H, d, J =2.6 Hz, H_{Ar}); 8.24 (1H, dd, J = 8.6; 2.6 Hz, H_{Ar}); 7.61(1H, d, J = 8.6 Hz, H_{Ar}); 7.41 (1H, ddd, J = 7.6; 7.6; 1.2 Hz, H_{Ar}); 7.32-7.16 (2H, m, H_{Ar}); 6.85 (1H, d, J = 7.6 Hz, H_{Ar}); 4.2-3.7 (2H, m, CH_2N); 2.94-2.87 (2H, m, $ArCH_2$)	164.4; 146.6; 139.69; 139.65; 137.1; 131.4; 130.7; 129.5; 128.5; 128.0; 127.6; 127.0; 126.4; 47.9; 44.5; 25.6
3d	SO_2Me	Cl	1620 (C=N)	8.03 (1H, d, J = 2.4 Hz, H_{Ar}); 7.95 (1H, dd, J = 8.4; 2.4 Hz, H_{Ar}); 7.65 (1H, d, J = 8.4 Hz, H_{Ar}); 7.41 (1H, ddd, J = 7.6; 7.6; 1.2 Hz, H_{Ar}); 7.30-7.17 (2H, m, H_{Ar}); 6.82 (1H, d, J = 7.6 Hz, H_{Ar}); 4.2-3.6 (2H, m, CH_2N); 3.10 (3H, s, SO_2CH_3); 2.93-2.86 (2H, m, $ArCH_2$)	164.8; 139.7; 139.4; 138.8; 137.0; 131.4; 130.7; 129.5; 128.5; 128.0; 127.6; 127.0; 126.4; 47.9; 44.5; 25.7
3e	H	NHMe	3315 (N–H) 1610 (C=N)	7.42-7.21 (6H, m, H_{Ar}); 7.09 (1H, br. s, ArNH); 6.75 (1H, d, J = 8.4 Hz, H_{Ar}); 6.64 (1H, ddd, J = 7.4; 7.4; 1.0 Hz, H_{Ar}); 3.87-3.80 (2H, m, CH_2N); 2.88 (3H, d, J = 2.6 Hz, NCH_3); 2.80-2.73 (2H, m, $ArCH_2$)	167.8; 149.1; 139.0; 131.3; 130.3; 129.4; 128.4; 127.1; 126.3; 120.2; 114.4; 110.5; 94.2; 47.0; 30.0; 26.4
3f	NO_2	NHMe	3260 (N–H) 1610 (C=N)	8.82 (1H, br. s, ArNH); 8.27 (1H, d, J = 2.6 Hz, H_{Ar}); 8.18 (1H, dd, J = 9.2; 2.6 Hz, H_{Ar}); 7.47-7.25 (4H, m, H_{Ar}); 6.70 (1H, d, J = 9.2 Hz, H_{Ar}); 3.86-3.78 (2H, m, CH_2N); 3.00 (3H, d, J = 5.2 Hz, NCH_3); 2.79-2.72 (2H, m, $ArCH_2$)	166.9; 154.3; 139.1; 135.5; 131.0; 128.6; 128.5; 127.8; 127.5; 126.9; 126.8; 117.4; 109.5; 47.0; 29.8; 26.3
3g	SO_2Me	NHMe	3320 (N–H) 1610 (C=N)	8.19 (1H, br. s, ArNH); 7.83-7.76 (2H, m, H_{Ar}); 7.45-7.21 (4H, m, H_{Ar}); 6.78 (1H, d, J = 8.6 Hz, H_{Ar}); 3.87-3.79 (2H, m, CH_2N); 2.98 (3H, s, SO_2CH_3); 2.95 (3H, d, J = 5.0 Hz, NCH_3); 2.79-2.72 (2H, m, $ArCH_2$)	167.0; 153.0; 139.0; 131.3; 130.9; 129.7; 128.6; 127.7; 127.5; 126.9; 124.4; 118.6; 110.1; 47.1; 45.0; 29.7; 26.2
3i	H	NMeTs	1611 (C=N) 1350 (SO_2N)	7.49-7.14 (10H, m, H_{Ar}); 7.04-6.99 (2H, m, H_{Ar}); 3.91-3.77 (2H, m, CH_2N); 2.98 (3H, s, NCH_3); 2.82 (2H, t, J = 7.2 Hz, $ArCH_2$); 2.39 (3H, s, $ArCH_3$)	166.1; 143.2; 140.2; 140.0; 137.6; 130.6; 130.5; 129.7; 129.3; 129.2; 128.1; 127.96; 127.95; 127.8; 127.4; 127.1; 126.5; 47.6; 39.6; 25.9; 21.5

TABLE 2 (continued)

1	2	3	4	5	6
3j	H	NPhth	1780 (C=O) 1730 (C=O) 1610 (C=N)	7.74 (2H, dd, J = 5.8; 2.9 Hz, H_{Ar}); 7.67 (1H, dd, J = 7.9; 1.8 Hz, H_{Ar}); 7.64 (2H, dd, J = 5.8; 2.9 Hz, H_{Ar}); 7.59 (1H, ddd, J = 7.6; 7.6; 1.8 Hz, H_{Ar}); 7.53 (1H, ddd, J = 7.4; 7.4; 1.6 Hz, H_{Ar}); 7.42-7.40 (1H, m, H_{Ar}); 7.13-7.07 (3H, m, H_{Ar}); 7.00-6.97 (1H, m, H_{Ar}); 3.63-3.59 (2H, m, CH_2N); 2.66-2.62 (2H, m, $ArCH_2$)	166.88; 165.3; 138.1; 136.7; 133.86; 133.8; 131.61; 131.6; 130.4; 130.2; 129.6; 129.2; 128.7; 128.3; 126.81; 126.5; 123.13; 123.12; 47.5; 25.5
3k	H	NH_2	3419 (N–H); 3307 (N–H); 1610 (C=N)	7.39-7.12 (6H, m, H_{Ar}); 6.75 (1H, dd, J = 7.8; 1.0 Hz, H_{Ar}); 6.69 (1H, ddd, 7.4; 7.4; 1.2 Hz, H_{Ar}); 5.11 (2H, br. s, ArNH); 3.87-3.81 (2H, m, CH_2N); 2.79-2.73 (2H, m, $ArCH_2$)	167.4; 146.9; 138.8; 131.1; 130.4; 129.8; 129.1; 128.1; 127.2; 126.4; 121.4; 116.6; 116.5; 47.1; 26.2
4a	H	Cl	3320 (N–H) 3260 (N–H)	7.44-7.39 (1H, m, H_{Ar}); 7.26-6.97 (6H, m, H_{Ar}); 6.77 (1H, d, J = 7.6 Hz, H_{Ar}); 5.65 (1H, s, CH); 3.24-2.81 (4H, m, $ArCH_2CH_2N$); 2.02 (1H, br. s, NH)	142.0; 136.9; 135.8; 134.0; 131.0; 129.5; 129.1; 128.4; 128.0; 126.6; 126.4; 125.7; 57.5; 41.2; 29.6
4b	CF_3	NHMe	3330 (N–H)	7.45 (1H, dd, J = 8.8; 1.8 Hz, H_{Ar}); 7.21 (1H, d, J = 1.8 Hz, H_{Ar}); 7.17-7.00 (3H, m, H_{Ar}); 6.76 (1H, d, J = 7.8 Hz, H_{Ar}); 6.58 (1H, d, J = 8.8 Hz, H_{Ar}); 6.36 (1H, br. s, ArNH); 5.10 (1H, s, CH); 3.33-2.99 (3H, m, $ArCH_2CH_2N$); 2.88-2.76 (1H, m, $ArCH_2CH_2N$); 2.71 (3H, d, J = 2.6 Hz, NCH_3); 1.95 (1H, br. s, NH)	151.1; 136.5; 134.9; 129.0; 127.6; 126.7; 126.5; 126.1; 126.0; 125.6; 117.0; 116.6; 109.4; 62.3; 43.0; 29.9; 29.6
4c	NO_2	NHMe	3240 (N–H)	8.15 (1H, dd, J = 8.8; 2.6 Hz, H_{Ar}); 7.95 (1H, d, J = 2.6 Hz, H_{Ar}); 7.26-7.02 (4H, m, H_{Ar}, CONH); 6.78 (1H, d, J = 7.6 Hz, H_{Ar}); 6.51 (1H, d, J = 8.8 Hz, H_{Ar}); 5.14 (1H, s, CH); 3.33-3.22 (1H, m, $ArCH_2CH_2N$); 3.17-2.99 (2H, m, $ArCH_2CH_2N$); 2.91-2.78 (1H, m, $ArCH_2CH_2N$); 2.79 (3H, d, J = 5.0 Hz, NCH_3); 2.07 (1H, br. s, NH)	153.9; 136.4; 135.7; 134.8; 129.2; 127.0; 126.9; 126.3; 126.1; 126.0; 124.8; 108.6; 62.1; 42.8; 29.8; 29.4

TABLE 2 (continued)

1	2	3	4	5	6
4d	SO_2Me	NHMe	3320 (N–H)	7.75 (1H, dd, J = 8.4; 2.2 Hz, H_{Ar}); 7.55 (1H, d, J = 2.2 Hz, H_{Ar}); 7.17-6.99 (3H, m, H_{Ar}); 6.83-6.75 (1H, m, ArNH); 6.73 (1H, d, J = 7.8 Hz, H_{Ar}); 6.59 (1H, d, J = 8.8 Hz, H_{Ar}); 5.13 (1H, s, CH); 3.38-3.23 (1H, m, $ArCH_2CH_2N$); 3.16-3.00 (2H, m, $ArCH_2CH_2N$); 3.03 (3H, s, SO_2CH_3); 2.89-2.77 (1H, m, $ArCH_2CH_2N$); 2.74 (3H, d, J = 5.0 Hz, NCH_3); 2.04 (1H, br. s, NH)	152.7; 135.9; 134.9; 129.7; 129.1; 129.0; 126.8; 126.2; 125.9; 125.5; 125.2; 109.4; 62.4; 45.1; 43.1; 29.7; 29.5
4e	H	NHMe	3307 (N–H)	7.23-7.13 (4H, m, H_{Ar}); 6.93 (1H, dd, J = 7.8; 1.8 Hz, H_{Ar}); 6.85-6.79 (1H, m, H_{Ar}); 6.68-6.61 (1H, m, H_{Ar}); 6.62 (1H, d, J = 7.8 Hz, H_{Ar}); 6.2-5.2 (1H, br. s, NH); 5.10 (1H, s, CH); 3.31-2.96 (3H, m, $ArCH_2CH_2N$); 2.87-2.66 (1H, m, $ArCH_2CH_2N$); 2.71 (3H, s, NCH_3); 2.1-1.4 (1H, br. s, NH)	148.6; 137.5; 135.0; 130.7; 128.9; 128.6; 126.8; 126.5; 126.3; 125.7; 115.5; 110.5; 61.8; 42.7; 30.3; 29.6
4f	H	NMeTs	3321 (N–H) 1342 (SO_2N)	7.68-7.56 (2H, m, H_{Ar}); 7.35-6.92 (8H, m, H_{Ar}); 6.93 (0.2H, s, CH); 6.61-6.42 (2H, m, H_{Ar}); 5.74 (0.8H, s, CH); 3.37-2.74 (4H, m, $ArCH_2CH_2N$); 3.26 (3H, s, NCH_3); 2.47 (3H, s, $ArCH_3$); 1.85-1.50 (1H, br. s, NH)	145.8; 143.7; 140.2; 139.3; 136.0; 134.1; 131.7; 129.48; 129.47; 128.9; 128.8; 128.21; 128.20; 127.8; 127.5; 125.8; 125.7; 125.4; 56.1; 43.4; 40.0; 29.9; 21.6
4h	H	NH_2	3388 (N–H) 3323 (N–H) 3261 (N–H)	7.18-6.98 (5H, m, H_{Ar}); 6.81 (1H, d, J = 7.8 Hz, H_{Ar}); 6.69 (1H, ddd, J = 7.5; 7.5; 1.5 Hz, H_{Ar}); 6.62 (1H, dd, J = 8.1; 1.2 Hz, H_{Ar}); 5.09 (1H, s, CH); 4.49 (2H, br. s, $ArNH_2$); 3.31-3.22 (1H, m, $ArCH_2CH_2N$); 3.13-3.00 (2H, m, $ArCH_2CH_2N$); 2.84-2.75 (1H, m, $ArCH_2CH_2N$); 2.00 (1H, br. s, NH)	146.2; 137.5; 135.2; 131.2; 129.1; 128.6; 127.3; 127.0; 126.6; 126.0; 117.5; 116.9; 62.0; 43.1; 29.8

TABLE 3. Elemental Analysis and Melting Points of Compounds **2-4**

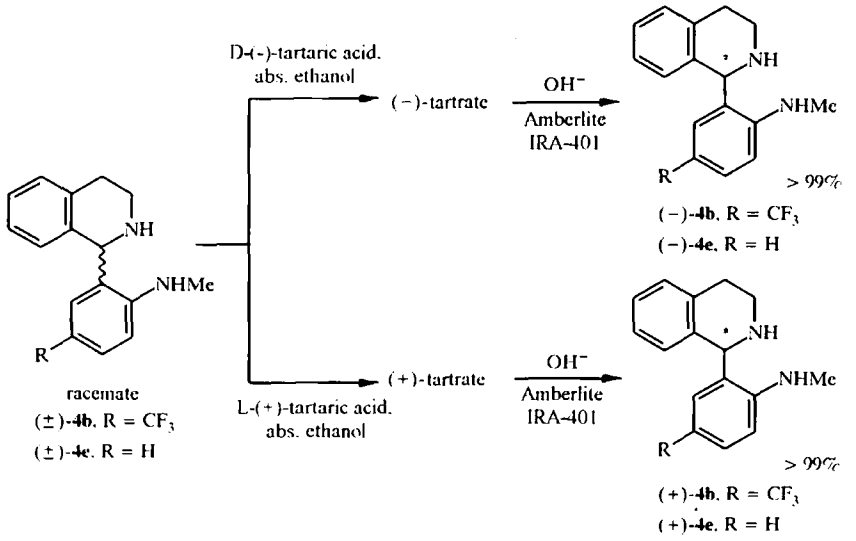
Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	mp, °C*[2]	Yield*[3], %
		C	H	N	S			
2a	$C_{15}H_{14}ClNO$	69.26 / 69.37	5.43 / 5.43	5.41 / 5.39	—	101-102 (A)		89
2b	$C_{16}H_{13}ClF_3NO$	58.67 / 58.64	3.99 / 4.00	4.27 / 4.27	—	99-100 (A)		80
2c	$C_{15}H_{13}ClN_2O_3$	59.13 / 59.12	4.21 / 4.30	9.18 / 9.19	—	159-160 (A)	155 (B)	44 (90)
2d	$C_{16}H_{16}ClNO_3S$	56.81 / 56.89	4.93 / 4.77	4.13 / 4.15	9.41 / 9.49	145-146 (A)		76
2e	$C_{16}H_{18}N_2O$	73.10 / 72.98	6.95 / 6.89	10.78 / 10.64	—	105-106 (A)	106-107 (C)	79 (76)
2f	$C_{23}H_{24}N_2O_3S$	67.40 / 67.62	6.11 / 5.92	6.85 / 6.86	7.75 / 7.85	89-90 (A)		62
2g	$C_{15}H_{16}N_2O$	74.87 / 74.97	6.75 / 6.71	11.63 / 11.66	—	89-90 (E)	90-91(D)	75 (83)
2h	$C_{23}H_{24}N_2O$	80.05 / 80.20	6.88 / 7.02	7.93 / 8.13	—	89-91 (A)		87
2i	$C_{23}H_{18}N_2O_3$	74.05 / 74.58	4.62 / 4.90	7.12 / 7.56	—	133-134 (E)		87
3A	$C_{15}H_{12}ClN$	74.31 / 74.53	4.92 / 5.00	5.78 / 5.79	—	79-80 (F)		72
3b	$C_{16}H_{11}ClF_3N$	61.87 / 62.05	3.54 / 3.58	4.45 / 4.52		213-214 (A)	212-214 (G)	86 (40)
3c	$C_{15}H_{11}ClN_2O_2$	73.84 / 74.53	4.87 / 5.00	5.77 / 5.79	—	151-153 (A)	150 (B)	84 (73)
3d	$C_{16}H_{14}ClNO_2S$	60.09 / 60.09	4.45 / 4.41	4.34 / 4.38	—	161-162 (H)		76
3e	$C_{16}H_{16}N_2$	81.33 / 81.32	6.84 / 6.82	11.81 / 11.85	—	75-76 (A)	Oil	87 (95)
3f	$C_{16}H_{15}N_3O_2$	67.05 / 68.31	5.36 / 5.37	14.55 / 14.94	—	149-150 (A)	148 (B)	66 (92)
3g	$C_{17}H_{18}N_2O_2S$	65.03 / 64.94	5.88 / 5.77	8.84 / 8.91	—	165-166 (H)		53
3i	$C_{23}H_{22}N_2O_2S$	70.65 / 70.74	5.59 / 5.68	7.16 / 7.17	8.23 / 8.21	139-140 (A)	138-140 (B)	30 (43)
3j	$C_{23}H_{16}N_2O_2$	78.37 / 78.39	4.53 / 4.58	7.92 / 7.95	—	189-190 (E)		20
3k	$C_{15}H_{14}N_2$	80.98 / 81.05	6.36 / 6.35	12.60 / 12.56	—	96-97 (A)	95-96 (C)	85 (94)
4A	$C_{15}H_{14}NCl$	74.50 / 73.92	5.94 / 5.79	6.05 / 5.75	—	Oil		
4b	$C_{17}H_{17}F_3N_2$	66.20 / 66.66	5.44 / 5.59	8.94 / 9.14	—	131-132 (F)	131-133 (D)	75 (40)
4c	$C_{16}H_{17}N_3O_2$	66.71 / 67.83	5.81 / 6.05	14.62 / 14.83	—	185-186 (E)	182 (B)	69 (76)
4d	$C_{17}H_{20}N_2O_2S$	64.66 / 64.53	6.44 / 6.37	8.80 / 8.85	10.0 / 10.13	163-164 (E)		76
4e	$C_{16}H_{18}N_2$	79.70 / 80.63	7.69 / 7.61	11.61 / 11.75	—	87-88 (I)	Oil	84 (98)
4f	$C_{23}H_{24}N_2O_2S$	70.31 / 70.38	6.24 / 6.16	7.10 / 7.14	8.20 / 8.17	154-156 (E)	72	
4h	$C_{15}H_{16}N_2$	80.09 / 80.32	7.37 / 7.19	12.43 / 12.49	—	109-110 (A)	108 (B)	(83)

* Solvent systems for crystallization: hexane–ethyl acetate (A), ether (B), ethanol (C), toluene–petroleum ether (D), ether–petroleum ether (E), hexane (F), acetone–ether (G), ethyl acetate (H), ethanol–water (I).

*[2] Ref. [2].

*[3] Yield data from [2] are given in brackets.

Scheme 5



EXPERIMENTAL

Melting points were determined with a Gallenkamp apparatus and were not corrected. ^{1}H and ^{13}C NMR spectra were recorded with Varian Mercury 200 machine using TMS as internal standard. IR spectra of Nujol mulls or KBr disks were recorded with a Perkin-Elmer 580B spectrometer. HPLC analysis was carried out with Knauer system using Hewlett-Packard HP 3396A integrator. Column chromatography used Acros silica gel (0.06-0.2 mm). Reactions were monitored by TLC on Merck Kieselgel 60_{254} plates. Optical rotation was determined with a Perkin-Elmer 141 polarimeter using the Na 589 line. Solvents were distilled over $CaCl_2$ or CaH_2 (hexane, ethyl acetate, acetonitrile, DMF, methylene chloride, and ether) or over Mg (methanol), or over $CaCl_2$ and Na-benzophenone (THF).

5-Trifluoromethyl-2-chlorobenzoic Acid (1b). A mixture of dry ether (distilled over Na-benzophenone) (120 ml), a solution of *n*-BuLi in hexane (50 ml, 1.6 mol/l, 80 mmol), and tetramethylethylenediamine (freshly distilled over sodium) (7.0 ml, 70.1 mmol) was cooled to -100°C under argon atmosphere. A solution of 2-bromo-4-trifluoromethylchlorobenzene (**7**) (prepared by a known method [14]) (18.1 g, 70 mmol) in dry ether (50 ml) was added over 5 min. The mixture was stirred for a further 20 min at the same temperature and then dry carbon dioxide was bubbled through. After 2 h the reaction mixture was warmed to room temperature, poured into water (250 ml), 1N hydrochloric acid added to a pH 4, and the organic layer was separated. The water layer was extracted with methylene chloride (3 × 40 ml). The combined extracts were evaporated in vacuum. The residue was dissolved in hexane (100 ml) and extracted with 1N NaOH (4 × 20 ml). The water layer was acidified to pH 4 with 1N hydrochloric acid, the precipitate was filtered off, washed with water and dried over Na_2SO_4 to give 5-trifluoromethyl-2-chlorobenzoic acid (13.8 g, 88%); mp 90-91°C (lit. data, mp 90-91°C [22]). ^{1}H NMR spectrum ($CDCl_3$): 7.51-7.74 (2H, m, aryl); 8.11 (1H, s, aryl); 9.7-10.2 ppm (1H, br. s, COOH).

General Method for the Preparation of N-β-Phenylethylamides of Disubstituted Benzoic Acids 2a-d. DMF (1 ml) was added to a solution of 90 mmol of the disubstituted benzoic acid **1a-d** in thionyl chloride (75 ml) and the mixture was boiled for 12 h. Excess thionyl chloride was distilled off and the acid chloride was crystallized with dry hexane, filtered and washed several times with hexane (5-nitro and 5-methylsulfonyl derivatives) or distilled in vacuum (5-unsubstituted and 5-trifluoromethyl derivatives). The obtained acid chlorides were dissolved in dry dioxane (100 ml) and added dropwise at 0°C to a suspension of phenylethylamine (10.9 g,

90 mmol) in 1N NaOH (100 ml). The precipitate obtained was filtered off, washed with 2N hydrochloric acid and water, and dried in the air. The NMR and IR spectra of the amides obtained are given in Table 2, the yields, melting points, and elemental analyses in Table 3.

N-β-Phenylethylamide of 2-Methylbenzoic Acid (2e) was obtained in 79% yield from N-methylisatoic anhydride (97.5 g, 620 mmol) by a known method [23].

N-β-Phenylethylamide of 2-[N-4-Methylphenylsulfonyl-N-methylamino]benzoic Acid (2f) was obtained in 60% yield from amide **2e** (48.8 g, 192 mmol) by method [2].

N-β-Phenylethylamide of 2-(N-Benzyl-N-methylamino)benzoic acid (2h). A solution of Na_2CO_3 (2.12 g, 20 mmol) in water (10 ml) and freshly distilled benzyl bromide (1.71 g, 10 mmol) were added to a solution of amide **2e** (2.54 g, 10 mmol) in methylene chloride (25 ml). The reaction mixture was boiled for 2 days, the aqueous layer was separated and extracted with methylene chloride (2 × 10 ml). The combined organic extracts were dried over Na_2SO_4 and the solvent removed. The residue was dissolved in dry ether and a stream of dry hydrogen chloride was passed through it. The colorless precipitate was filtered off, washed with ether, and dried to give amide **2h** (3.31 g, 87%).

N-β-Phenylethylamide of 2-Aminobenzoic Acid (2g) was obtained in 75% yield from isatoic anhydride (163.0 g, 1.0 mol) by method [2].

N-β-Phenylethylamide of 2-(N-Phthalimido)benzoic Acid (2i). Triethylamine (30.5 g, 300 mmol) was added to a solution of amide **2g** (24.0 g, 100 mmol) and phthalic anhydride (14.8 g, 100 mmol) in dry benzene (150 ml) and the mixture was boiled with a Dean–Stark head for 48 h. After the addition of more phthalic anhydride (3.0 g, 20 mmol) boiling was continued for 12 h. After cooling the precipitate was filtered off, washed with benzene, and dried over Na_2SO_4 to give colorless amide **2i** (20.1 g). The combined filtrates were washed with 4N HCl (5 × 40 ml) and then saturated $NaHCO_3$ solution (2 × 40 ml), and dried over Na_2SO_4. Evaporation of the solvent left an oil which crystallized on seeding. It was filtered and washed with benzene to give 12.0 g more of the product. Overall yield of amide **2i** 32.1 g (87%).

General Method for the Preparation of 3,4-Dihydroisoquinolines 3a-d,i,j. P_2O_5 (300 mmol) was added to a hot solution of amide **2** (60 mmol) in xylene (300 ml) and the mixture was boiled for 6-48 h. The reaction mixture was cooled, the xylene was poured off, and the residue was poured into ice water. After formation of a clear mixture the residual xylene was separated, the aqueous layer was acidified to pH 2 with 4N HCl, the resulting oil was extracted with ether or methylene chloride, dried over Na_2SO_4, and the solvent evaporated. The substance was triturated (sometimes after column chromatography) and recrystallized. The ^1H NMR and IR spectra of all the dihydroisoquinolines are given in Table 2, the melting points and elemental analyses in Table 3.

General Method for the Preparation of 3,4-Dihydroisoquinolines 3e-g. 1(2-Chlorophenyl)-3,4-dihydroisoquinolines **3a-d** (15.0 mmol), liquid methylamine (50 ml), copper filings (0.17 g), and CuCl (0.17 g) were placed in a glass ampoule which was sealed and heated at 60°C for 72 h. The ampoule was cooled to -20 to -30°C, opened carefully and left in the fume hood until the remaining methylamine had evaporated. Methylene chloride (100 ml) was added to the dark blue residue, the copper salt was filtered off and the filtrate was evaporated in vacuum. The product was recrystallized after chromatographic purification on silica gel.

1-(2-N-Phthalimido)phenyl-3,4-dihydroisoquinoline (3j). PCl_5 (100.0 g, 480 mmol) was added in one portion to a vigorously stirred solution of amide **2i** (88.7 g, 240 mmol) in dry chloroform (freshly distilled over P_2O_5) (1200 ml). The mixture was boiled for 1 h until a bright yellow precipitate was formed. The reaction mixture was cooled to -30°C and a solution of $SnCl_4$ (85.5 g, 330 mmol) in dry chloroform (480 ml) was added dropwise; the temperature of the reaction mixture rose to room temperature. The mixture, which had a brick red color, was boiled for another 8 h, cooled, and poured into alkaline ice water. The organic layer was separated and the aqueous layer was extracted with chloroform (4 × 150 ml). The chloroform extracts were washed with 2N KOH (3 × 100 ml) and water (3 × 100 ml), and dried over Na_2SO_4. The solvent was evaporated, the residue was crystallized from ether, and then recrystallized from a toluene-petroleum ether mixture to give 1-(2-N-phthalimido)phenyl-3,4-dihydroisoquinoline (61.7 g, 73%).

1-(2-Aminophenyl)-3,4-dihydroisoquinoline (3k). Hydrazine hydrate (4.44 g, 88.6 mmol) was added in one portion to a hot suspension of phthalimide **3j** (6.43 g, 18.2 mmol) in ethanol (60 ml). A precipitate formed in the clear solution after 5 min. After boiling the reaction mixture for 15 min, the precipitate was filtered off and

washed with ethanol, and the filtrate was evaporated. The residue was treated with ether, filtered, and the ether layer was extracted with 1N HCl (4 × 20 ml). The hydrochloric acid extracts were basified to pH 10 with 2N KOH, extracted with ether (4 × 20 ml), dried over Na_2SO_4 and filtered through silica gel. Light yellow crystals (2.0 g, 50%) were obtained after removal of the solvent in vacuum.

General Method for the Preparation of 1,2,3,4-Tetrahydroisoquinolines 4a-h. Reactions were carried out in an atmosphere of argon. $NaBH_3CN$ (7.0 mmol) was added in portions to a stirred solution of a 3,4-dihydroisoquinoline **3** (3.5 mmol) in glacial acetic acid (15 ml). The reaction mixture was kept at room temperature for 3 h, heated at 60°C for 1 h, and then stirred at room temperature for 10 h. The color of the mixture changed from red to yellow green which was a sign that the reaction was complete. The contents of the flask were cooled to 0°C, 50% NaOH solution (30 ml) was added, it was extracted with methylene chloride (4 × 20 ml), washed with saturated NaCl solution, and the solvent was evaporated. The residue was dissolved in methylene chloride and filtered through silica gel. After evaporation of the solvent solid substances were obtained by recrystallization.

Resolution of Racemic 1-(2-Methylamino-5-trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (4b). A hot solution of D-(-)-tartaric acid (75.0 mg, 0.5 mmol) in ethanol (1 ml) was added to a hot solution of the racemate **4b** (153.2 mg, 0.5 mmol) in ethanol (1 ml). Immediately after the addition crystallization began. The reaction mixture was cooled, the precipitate was filtered off, recrystallized twice from absolute ethanol, and dried to give the tartrate of **4b** (76.8 mg, 34%) with $[\alpha]_D^{20}$ -43.2 (*c* = 1.01, DMF) which was dissolved in water (0.5 ml), passed through a column of Amberlite IRA-401 (in the chloride form), and eluted with ethanol. Discharge of the free amine (-)-**4b** from the column was monitored with a 254 nm UV detector. The optically pure amine (-)-**4b** (51.1 mg, 98%) with $[\alpha]_D^{20}$ -48.8 (*c* = 0.67, $CHCl_3$) was obtained after evaporation of the eluant. This corresponds to >99% optical purity (HPLC on a Chiralcel OJ column, mobile phase 1% ethanol in hexane, rate of flow 1.0 ml/min, detector UV_{254}, retention time 11.4 min).

The (+)-tartrate of (+)-**4b** with $[\alpha]_D^{20}$ +41.1 (*c* = 1.05, DMF) and the optically pure amine (+)-**4b** with $[\alpha]_D^{20}$ + 48.7 (*c* = 0.67, $CHCl_3$) were obtained analogously. This corresponds to >99% optical purity (HPLC on a Chiralcel OJ column, mobile phase 1% ethanol in hexane, rate of flow 1.0 ml/min, detector UV_{254}, retention time 12.7 min).

Resolution of Racemic 1-(2-Methylamino)-1,2,3,4-tetrahydroisoquinoline (4e) was carried out analogously to the resolution of compound **4b**. The (-)-tartrate of **4e** (1.76 g, 36%) (from methanol) with $[\alpha]_D^{20}$ -37.3 (*c* = 1.04, DMF) and the optically pure amine (-)-**4e** with $[\alpha]_D^{20}$ -5.3 (*c* = 1.17, $CHCl_3$) were obtained from the reaction of the racemate of **4e** (3.0 g, 12.6 mmol) with (-)-tartaric acid. The amine was >99% optically pure (HPLC on a Chiralcel OD column, mobile phase 5% isopropanol in hexane, rate of flow 0.8 ml/min, detector UV_{254}, retention time 10.4 min).

The (+)-tartrate of compound **4e** (from methanol) with $[\alpha]_D^{20}$ +40.2 (*c* = 1.06, DMF) and the optically pure amine (+)-**4e** with $[\alpha]_D^{20}$ +5.2 (*c* = 1.17, $CHCl_3$) were obtained analogously. The amine was >99% optically pure (HPLC on a Chiralcel OD column, mobile phase 5% isopropanol in hexane, rate of flow 0.8 ml/min, detector UV_{254}, retention time 11.2 min).

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