

## 158. Mammalian Alkaloids: Configurations of Optically Active Salsoline- and 3',4'-Dideoxynorlaudanosoline-1-carboxylic Acids<sup>1)</sup>

by Maria Chrzanowska<sup>2)</sup>, Bernhard Schönenberger, and Arnold Brossi\*

Medicinal Chemistry Section, Laboratory of Analytical Chemistry, NIDDK, National Institutes of Health, Bethesda, Maryland 20892, USA

and Judith L. Flippen-Anderson

Naval Research Laboratory, Department of the Navy, Washington, D. C. 20375, USA

(29.VI.87)

Synthesis of the optical isomers of ( $\pm$ )-methyl 6,7-dimethyl-3',4'-dideoxynorlaudanosoline-1-carboxylate (( $\pm$ )-**2**) was accomplished by reaction of ( $\pm$ )-**2** with (+)-(*R*)-1-phenylethyl isocyanate, separation of the urea diastereoisomers (–)-**4A** and (+)-**4B**, and alcoholysis of the ureas in refluxing BuOH. Optically active isoquinoline-carboxylates **2A**, **B** and hydantoins **8A**, **B** isolated were characterized. The absolute configuration of the reaction products was established by X-ray analysis of the optically active hydantoin (+)-**8A**. Hydrolysis of the methyl isoquinolinecarboxylates **2A**, **B** with 48% HBr soln. at reflux afforded the desired optically active 3',4'-dideoxynorlaudanosoline-1-carboxylic acids **1A**, **B** required for enzyme-inhibition studies. Details of the X-ray diffraction analysis of (+)-methyl salsoline-1-carboxylate hydrobromide ((+)-**11A**·HBr) prepared earlier are included. CD spectra of (+)-(*S*)-methyl 6,7-dimethyl-3',4'-dideoxynorlaudanosoline-1-carboxylate hydrobromide ((+)-**2A**·HBr) and (–)-(*R*)-methyl salsoline-1-carboxylate hydrochloride ((–)-**11B**·HCl) confirmed the assignment of their (*S*)- and (*R*)-configurations, respectively.

**1. Introduction.** – Tetrahydroisoquinoline-1-carboxylic acids substituted at C(1) with a CH<sub>3</sub> group are biosynthetic precursors of isoquinoline cactus alkaloids [1] [2]. Some 1-benzyl-substituted analogs were detected in alcoholics [3], phenylketonurics [4], and L-dopa-treated *Parkinsonian* patients [5], and these compounds were, therefore, named 'mammalian alkaloids' and have been reviewed [6–8]. *Bobbitt et al.* [9] showed that phenolic tetrahydroisoquinoline-1-carboxylic acids are oxidatively decarboxylated by enzymes, and it seemed appropriate, therefore, to prepare the optical isomers of these compounds so far assayed as racemic mixtures [4] [10].

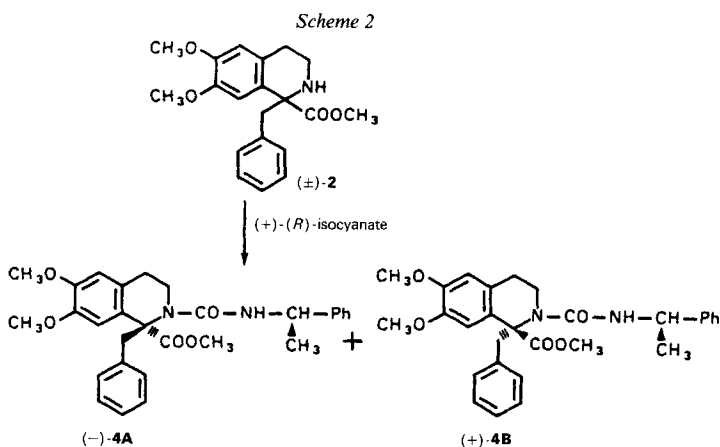
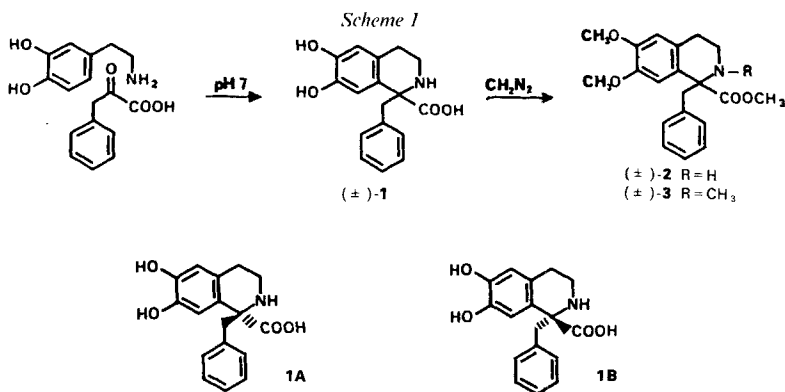
Study of the enantiospecific behavior of optically active tetrahydroisoquinoline-1-carboxylic acids in enzymatic reactions seemed particularly worth studying since optically active salsolinols, derived from 1-carboxy precursors by nonoxidative decarboxylation, showed considerable difference in behavioral effects when compared with optical isomers [11]. In this paper, we present the synthesis of the optically active 3',4'-dideoxynorlaudanosoline-1-carboxylic acids<sup>1)</sup> (**1A**, **B**) and the assignment of their

<sup>1)</sup> Salsoline and norlaudanosoline are well known alkaloids, and these names will be used in the *General Part* (for systematic names, see *Exper. Part*). The systematic name for salsoline is 1-methyl-7-methoxy-1,2,3,4-tetrahydroisoquinolin-6-ol and that for norlaudanosoline, also named tetrahydropapaveroline, is 1-(3',4'-dihydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol.

<sup>2)</sup> Visiting scientist from A. Mickiewicz University, Poznań, Poland.

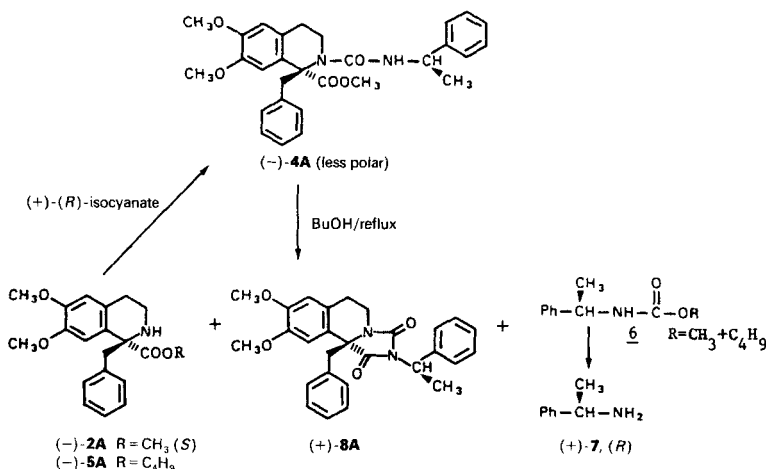
absolute configuration. Details of an X-ray analysis performed with hydantoin (+)-**8A**, obtained as a by-product, and with earlier prepared-(+)-(*S*)-methyl salsoline-1-carboxylate hydrobromide ((+)-**11A** · HBr) [12] will be presented.

**2. Results.** – 2.1. *Optically Active 3',4'-Dideoxynorlaudanosoline-1-carboxylic Acids 1A, B.* Acid ( $\pm$ )-**1** was prepared by the original procedure of *Hahn and Stiehl* [13], rather than by the recently published procedure [14] which afforded the desired product in lower yield and of insufficient purity. Methylation of ( $\pm$ )-**1** in MeOH with etheric diazomethane afforded a mixture of ( $\pm$ )-**2** and its known *N*-methyl derivative ( $\pm$ )-**3** in a ratio of 3:1 (*Scheme 1*), separated by crystallization from MeOH and chromatography of the mother liquors yielding first ( $\pm$ )-**3**, followed by ( $\pm$ )-**2**. The overall yield of ( $\pm$ )-**2** was 65%.



Reaction of ( $\pm$ )-**2** with (+)-(*R*)-1-phenylethyl isocyanate in CHCl<sub>3</sub> afforded ureas (-)-**4A** and (+)-**4B**, separated by flash chromatography on silica gel (*Scheme 2*). The less polar urea (-)-**4A** (hexane/AcOEt 3:2) was assigned the (1*S*)-configuration on the basis of data given below (products of the alcoholysis of the diastereoisomeric, more polar urea (+)-**4B**, not shown in the *Scheme 3*, have the (1*R*)-configuration).

Scheme 3



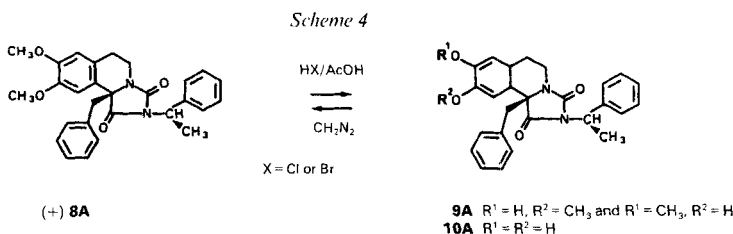
The products obtained by heating  $(-)-4\mathbf{A}$  in BuOH for 17 h were separated by extraction with 1N HCl and  $\text{Et}_2\text{O}$  (Scheme 3). The basic material obtained from the HCl solution after basification and extraction with  $\text{Et}_2\text{O}$  consisted of methyl ester  $(-)-2\mathbf{A}$  (80%) and butyl ester  $(-)-5\mathbf{A}$  (20%) on the basis of a HPLC analysis. The two esters could readily be separated by chromatography, and  $(-)-2\mathbf{A}$  obtained gave a crystalline hydrobromide salt  $(+)-2\mathbf{A} \cdot \text{HBr}$ . Refluxing  $(+)-2\mathbf{A} \cdot \text{HBr}$  in 48% HBr afforded carboxylic acid  $\mathbf{1A}$  which was precipitated from the reaction mixture with acetone, giving the crystalline ( $S$ )-enantiomer  $\mathbf{1A} \cdot \text{HBr}$  in the form of an acetone solvate. The optical rotation of  $\mathbf{1A} \cdot \text{HBr}$  measured in  $\text{H}_2\text{O}$  was positive, and a  $(-)$  sign resulted when 50% aqueous acetone was used as a solvent. Compounds  $(+)-2\mathbf{B}$ ,  $(-)-2\mathbf{B} \cdot \text{HBr}$ , and the ( $R$ )-enantiomer  $\mathbf{1B} \cdot \text{HBr}$  were similarly obtained from  $(+)-4\mathbf{B}$ . Compound  $\mathbf{1B} \cdot \text{HBr}$  showed optical rotations opposite in sign to the ones of  $\mathbf{1A} \cdot \text{HBr}$ , with a  $(-)$  sign in  $\text{H}_2\text{O}$  and a  $(+)$  sign in 50% aqueous acetone.

The optical purity of  $(-)-2\mathbf{A}$  and  $(+)-2\mathbf{B}$ , measured with analytical samples after reaction of these esters with  $(+)-(R)$ -1-phenylethyl isocyanate by HPLC, was  $> 95\%$ . The reconversion of optically active ester  $(-)-2\mathbf{A}$  with  $(+)-(R)$ -1-phenylethyl isocyanate into urea  $(-)-4\mathbf{A}$  which afforded quantitatively hydantoin  $(+)-8\mathbf{A}$  with NaOMe in MeOH further supports the configurational assignments made for these compounds as discussed below.

HPLC analysis of the neutral material obtained from  $(-)-4\mathbf{A}$ /BuOH after evaporation of the  $\text{Et}_2\text{O}$  extract indicated the presence of unreacted  $(-)-4\mathbf{A}$  besides hydantoin  $(+)-8\mathbf{A}$  and carbamates  $\mathbf{6}$  (Scheme 3). Refluxing  $(-)-4\mathbf{A}$  for a longer time did not increase the yield of esters  $(-)-2\mathbf{A}$  and  $(-)-5\mathbf{A}$ ; more transesterification to  $(-)-5\mathbf{A}$  occurred, but unreacted urea  $(-)-4\mathbf{A}$  and an increased amount of hydantoin  $(+)-8\mathbf{A}$  remained. Analysis of the reaction mixture obtained by the alcoholysis of urea  $(+)-4\mathbf{B}$  gave similar results. The neutral parts from these reactions were crystallized from  $(i\text{-Pr})_2\text{O}$  giving hydantoin  $(+)-8\mathbf{A}$  and  $(-)-8\mathbf{B}$ , respectively. The mother liquors enriched in carbamates  $\mathbf{6}$  were hydrolyzed with KOH in EtOH affording optically active ( $\alpha$ -methylbenzyl)amine  $((+)-7)$ .

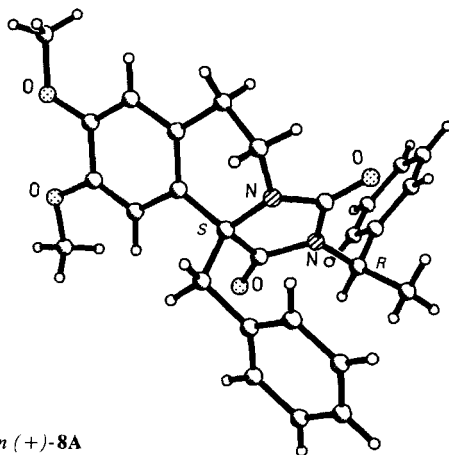
The  $[\alpha]_D$  of (+)-**7** was identical with that of commercially available (+)-(*R*)-( $\alpha$ -methylbenzyl)amine excluding that racemization had occurred during urea alcoholysis.

**2.2. Hydrolysis of Hydantoin 8A, B.** Hydantoin (+)-**8A** and (–)-**8B** obtained in 70 % yield without and quantitatively with addition of Na to an alcoholic solution of urea (–)-**4A** or (+)-**4B**, respectively, were found to be remarkably stable towards acid or base. The reaction of hydantoin (+)-**8A** (or (–)-**8B**) with HCl (conc. HCl/AcOH 1:1, reflux for 24 h) gave two isomeric monophenols **9A** (or **9B**; *Scheme 4*). Structures of monophenols **9A** (or **9B**) were confirmed by high resolution MS of the molecular ion, MS fragmentation, and the reddish color reaction with  $\text{FeCl}_3$  on TLC plates. Hydantoin **8A** when refluxed in 48 % HBr/AcOH for 2 h afforded diphenol **10A** (*Scheme 4*). The diphenol **10A**, showing a dark blue color with  $\text{FeCl}_3$ , had the correct mass and gave, with etheric diazomethane solution, starting material **8A**. Heating (+)-**8A** or (–)-**8B** with an alcoholic solution of NaOBu also did not alter the molecules.



**2.3. Absolute Configurations of the 3',4'-Dideoxynorlaudanosoline-1-carboxylic Acids 1A, B.** The absolute configuration of the isoquinolines in the 1-benzyl series was established by X-ray analysis of hydantoin (+)-**8A**. It established the (*S*)-configuration at C(1), as discussed below (*Fig. 1*). This together with the finding that benzylamine (+)-**7** was obtained from carbamates **6** in optically pure form excludes a racemization during urea alcoholysis and establishes the (1*S*)-configuration for methyl ester (+)-**2A**·HBr and the corresponding carboxylic acid **1A**·HBr.

*Fig. 1* shows the results of the X-ray study of (+)-**8A** drawn by using the experimentally determined coordinates with arbitrary thermal parameters. Tables of coordinates,

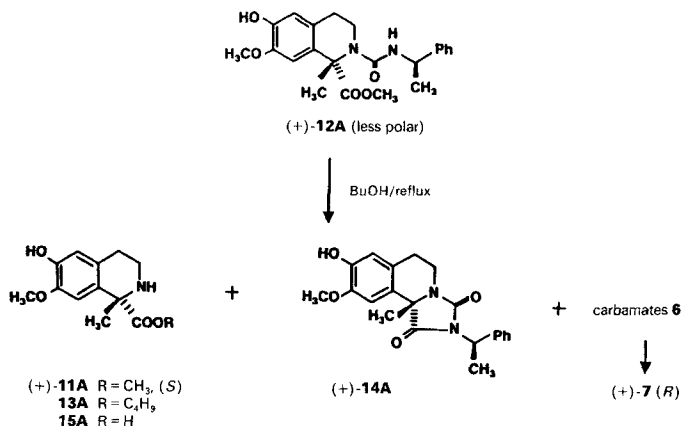


*Fig. 1. Conformation of hydantoin (+)-8A*

bond lengths and angles have been deposited with the *Cambridge Data Base* [15]. The configuration of the asymmetric C-atom substituted with the  $\text{CH}_3$  and the Ph group was determined to be *R* by spectroscopic means. This was also confirmed by further chemical transformation of the urea-alcoholysis products resulting in the isolation of (+)-**7** (see 2.1). The X-ray results then showed that the benzyl-substituted asymmetric C-atom has the (*S*)-configuration. In the fused ring system, the aromatic ring and the five-membered ring are planar and the central six-membered ring has a half-chair conformation. Of the two  $\text{CH}_3\text{O}$  groups on the fused aromatic ring, one is essentially coplanar with the ring while the other one (on the benzyl side of the molecule) is rotated by  $16.6^\circ$  out of the plane of the ring. Both of the other aromatic rings are 'gauche' to the fused-ring system.

2.4. *Absolute Configurations of Optically Active Methyl Salsoline-1-carboxylates 11A, B.* The optically active methyl salsoline-1-carboxylates **11A, B** were also prepared by (1-phenylethyl)urea alcoholysis [12] similar to the method used here for the 1-benzyl series. Configurational presentations of optically active ureas **12A, B** obtained from ( $\pm$ )-methyl salsoline-1-carboxylate **11** with (+)-(*R*)-1-phenylethyl isocyanate [12], were recently revised [16]. The correct absolute configuration of the less polar urea (+)-**12A** (hexane/AcOEt 1:1), affording methyl ester (+)-**11A**, butyl ester **13A**, and hydantoin (+)-**14A** by fragmentation in refluxing BuOH and carboxylic acid **15A** by acid hydrolysis of (+)-**11A**, are shown in *Scheme 5*. The X-ray analysis of (+)-methyl salsoline-1-carboxylate hydrobromide ((+)-**11A**·HBr) established the (*S*)-configuration at C(1). The derived carboxylic acid **15A**·HCl [12] also has the (*S*)-configuration at C(1).

Scheme 5



The result of the X-ray analysis of (+)-**11A**·HBr is shown in *Fig. 2*. Tables of coordinates, bond lengths, and angles have been deposited with the *Cambridge Data Base* [15]. The configuration at C(1) was determined to be *S* based on the anomalous scattering of the Br-atom by using *Friedel's* pairs as suggested by *Rogers* [17]. The aromatic ring system (the 6-membered ring plus the OH and  $\text{CH}_3\text{O}$  moieties) is planar, while the heterogeneous 6-membered ring has a half-chair conformation. Packing in this crystal is influenced by the presence of 3 H-bonds involving the Br-atom. Each Br-atom acts as the

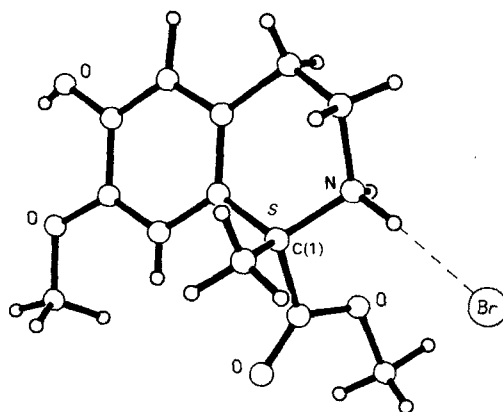


Fig. 2. Conformation of (+)-methyl salsoline-1-carboxylate hydrobromide ((+)-**11A**·HBr). One of the NH···Br H-bonds is indicated by the dashed line.

acceptor in a H-bond from 3 different (though symmetry-related) salsoline molecules. The two N···Br distances are 2.29 and 2.56 Å and the O···Br distance is 2.82 Å.

**2.5. CD Spectra of Methyl Tetrahydroisoquinoline-1-carboxylates.** Representatives of the 1-benzyl and 1-methyl series, namely (+)-**2A**·HBr and (–)-**11B**·HCl [12], were compared by CD analysis (Fig. 3). The CD curves are (within the experimental error)

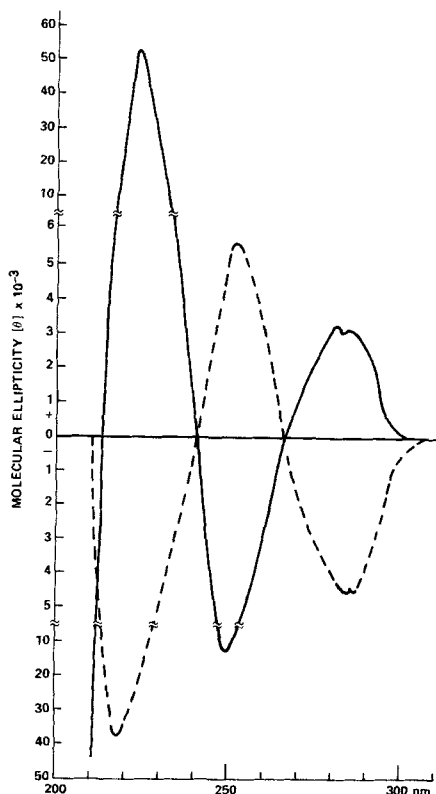


Fig. 3. CD spectra of (+)-(S)-methyl 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylate hydrobromide ((+)-**2A**·HBr; —) and (–)-(R)-methyl salsoline-1-carboxylate hydrochloride ((–)-**11B**·HCl; ---) in EtOH

mirror images. Minor shifts in the position and in intensities are caused by the different substitution pattern at C(1). The sign of long-wavelength *Cotton* effect (due to  $^1L_g$  transition) is in agreement with the assigned (*R*)- or (*S*)-configuration [18].

Generally, the first (at *ca.* 290–270 nm) and the second *Cotton* effect (at *ca.* 250–230 nm) of the simple 1-alkyl- or 1-benzyl-substituted tetrahydroisoquinolines have the same sign [19]. But in our case where the second 1-substituent is a COOMe group, the sign of the second *Cotton* effect at *ca.* 250 nm is opposite to that of the first one (at *ca.* 290–250 nm) and to the one in the 225–215 nm area. This is most presumably caused by the electric dipole/electric dipole or magnetic dipole/electric dipole coupling between the transition moments of the aromatic chromophore ( $^1L_a$  transition) and that of the COOMe substituent.

**3. Conclusions.** – It has to be assumed that mammalian alkaloids [6–8] originate from aromatic amino acids by processes which are largely controlled by enzymes. They are, therefore, most likely optically active entities. These products, originating from condensation of amines and ketocarboxylic acids, formed by decarboxylation, deamination or transamination of the parent amino acids, were found in patients having a variety of enzymic disorders, and their characterization may, therefore, be of diagnostic value. The optically active tetrahydroisoquinoline-1-carboxylic acids presented here and exemplified by **1A,B** and **15A,B** will now be tested for enantiospecific behavior in a variety of enzymically controlled reactions. They represent only a few of the many products which can be formed by a deviation of normal pathways in amino-acid metabolism, and an extension of this investigation including other amino acids, such as L-tryptophan and L-histidine, is contemplated.

Determination of the absolute configuration without using heavy atoms, by introducing a configurationally fixed component, is demonstrated here with the X-ray analysis of hydantoin (+)-**8A**, and this procedure will undoubtedly be useful.

### Experimental Part

*General.* (*R*)-1-Phenylethyl isocyanate was obtained from Aldrich Chemical Co. Phenylpyruvic acid and dopamine hydrochloride were purchased from Fluka AG. The  $\text{CHCl}_3$  used for reactions was freshly dried and purified through activated, neutral aluminium oxide. After extraction, all org. phases were dried ( $\text{Na}_2\text{SO}_4$ ). All crystalline compounds were dried under high vacuum at r.t. for 24 h. TLC: silica gel *GHLF* plates from *Analtech, Inc.* CC: silica gel 60 (*Merck*), 230–400 mesh, 60 Å (flash chromatography). Anal. HPLC:  $\mu$ -*Porasil* column (silica gel) from *Milipore*, AcOEt/hexane 3:2 or 3:1. M.p.: *Fisher-Johns* melting-point apparatus. Optical rotation: *Perkin Elmer 241 MC* polarimeter. CD spectra: in EtOH; *Jasco* model *J-20* recording spectropolarimeter. IR spectra: *Beckman IR 4230*.  $^1\text{H-NMR}$  spectra: *Varian XL 300* (300 MHz). MS: *Finingan 1015D* instrument (CI).

(*RS*)-Methyl 1-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-carboxylate (( $\pm$ )-**2**) and (*RS*)-Methyl 1-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline-1-carboxylate (( $\pm$ )-**3**). To the suspension of ( $\pm$ )-**1** (5.07 g, 17 mmol) [**13**] in 100 ml of MeOH, the soln. of diazomethane (8 mol-equiv.; freshly made from 42 g of *Diazald*<sup>®</sup>) in  $\text{Et}_2\text{O}$  was added dropwise at 0°. After the addition of  $\text{CH}_2\text{N}_2$  had been completed, the ice-water bath was removed and the mixture left at r.t. for 18 h and then evaporated. The residue was dissolved in 2N HCl and extracted with  $\text{Et}_2\text{O}$ . The acidic aq. phase was made alkaline with 20% NaOH soln. (pH 11) and the slightly yellow precipitate filtered, washed with  $\text{H}_2\text{O}$ , and dried. Two recrystallization from MeOH gave 3.1 g (54%) of pure ( $\pm$ )-**2**. M.p. 138–139°. IR (KBr): 3370 (NH), 1720 (C=O).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 7.27–7.22 (*m*, 4 arom. H); 7.14–7.11 (*m*, 2 arom. H); 6.55 (*s*, H–C(5)); 3.93 (*s*,  $\text{CH}_2\text{O}$ ); 3.86 (*s*,  $\text{CH}_2\text{O}$ ); 3.69 (*s*,  $\text{COOCH}_3$ ); 3.56 (*d*,  $J = 13.1$ , H–C( $\alpha$ )); 3.12 (*d*,  $J = 13.1$ , H'–C( $\alpha$ )); 3.08–3.04 (*m*, 2 H–C(3)); 2.72 (*ddd*,  $J_{\text{gem}} = 15.7$ ,  $J(3,4) = 6.4$ ,  $J(3',4') = 9.0$ , H–C(4)); 2.56 (*ddd*,  $J_{\text{gem}} = 15.7$ ,  $J(3,4') = J(3',4) = 3.9$ , H'–C(4)); 2.10 (*br. s*, 1 H, disappears on treatment with  $\text{D}_2\text{O}$ , NH).

CI-MS: 342 (100,  $M^+ + 1$ ), 282 (8), 250 (52), 190 (12). Anal. calc. for  $C_{20}H_{23}NO_4$  (341.41): C 70.36, H 6.79, N 4.10; found: C 70.29, H 6.85, N 4.09.

The combined mother liquors were evaporated, and the residue afforded, after CC (benzene/MeOH 100:1), 1.33 g (22%) of ( $\pm$ )-**3** followed by more polar ( $\pm$ )-**2** (0.64 g; overall yield 65%). Compound ( $\pm$ )-**3**, after recrystallization from MeOH, gave white crystals. M.p. 118–119° ([13]: m.p. 118°).  $^1H$ -NMR ( $CDCl_3$ ): 7.05–6.98 (*m*, 3 arom. H); 6.75–6.72 (*m*, 2 arom. H); 6.64 (*s*, 1 arom. H); 6.38 (*s*, 1 arom. H); 3.84 (*s*,  $CH_3O$ ); 3.81 (*s*,  $CH_3O$ ); 3.72 (*s*,  $COOCH_3$ ); 3.42 (*d*,  $J = 14.2$ ,  $H-C(\alpha)$ ); 3.25 (*d*,  $J = 14.2$ ,  $H'-C(\alpha)$ ); 3.11 (*ddd*,  $J_{gem} = J(3,4') = 11.5$ ,  $J(3,4) = 4.0$ ,  $H-C(3)$ ); 2.69 (*ddd*,  $J_{gem} = 11.5$ ,  $J(3',4) = 4.8$ ,  $J(3',4') = 3.0$ ,  $H'-C(3)$ ); 2.52 (*s*,  $CH_3N$ ); 2.35–2.23 (*m*, 2  $H-C(4)$ ). CI-MS: 356 (100,  $M^+ + 1$ ), 296 (24), 264 (89). Anal. calc. for  $C_{21}H_{25}NO_4$  (355.43): C 70.96, H 7.09, N 3.94; found: C 70.99, H 7.11, N 3.91.

When the methylation was carried out with ( $\pm$ )-**1**·HCl [14], ( $\pm$ )-**2** and ( $\pm$ )-**3** were obtained in a similar ratio, but the overall yield of ( $\pm$ )-**2** was only 44%.

*Methyl (1S)-1-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-[(R)-1-phenylethyl]carbamoyl]isoquinoline-1-carboxylate* ((-)-**4A**) and its (1R)-Diastereoisomer (+)-**4B**. To a stirred soln. of ( $\pm$ )-**2** (6.93 g, 20 mmol) in 65 ml of  $CHCl_3$  at 0°, 4.63 g (31 mmol) of (R)-1-phenylethyl isocyanate were added dropwise, refluxed for 7 h, and then left overnight at r.t. Evaporation and flash chromatography (hexane/AcOEt 2:1) gave 4.63 g (46%) of the less polar (-)-**4A**, 3.34 g (34%) of the more polar (+)-**4B** and 2.00 g (20%) of (-)-**4A**/(+)-**4B** 23:77 (by HPLC).

(-)-**4A**:  $[\alpha]_D = -85^\circ$  ( $c = 1.17$ ,  $CHCl_3$ ). IR (KBr): 3425 (NH), 1740 and 1725 (C=O).  $^1H$ -NMR ( $CDCl_3$ ): 7.38–6.97 (*m*, 9 arom. H); 6.66, 6.64 (2*s*, 2 arom. H); 6.40 (*s*, 1 arom. H); 5.11 (*qd*,  $J(PhCHCH_3, NH) = J(PhCHCH_3, CH_3) = 7.0$ ,  $PhCHCH_3$ ); 4.76 (*d*,  $J(PhCHCH_3, NH) = 7.1$ , NH); 4.17 (*d*,  $J = 13.4$ ,  $H-C(\alpha)$ ); 3.88 (*s*,  $CH_3O$ ); 3.84 (*s*,  $CH_3O$ ); 3.46 (*s*,  $COOCH_3$ ); 3.41 (*d*,  $J = 13.4$ ,  $H'-C(\alpha)$ ); 3.22 (*ddd*,  $J_{gem} = 11.0$ ,  $J(3,4') = 9.3$ ,  $J(3,4) = 4.2$ ,  $H-C(3)$ ); 2.86 (*ddd*,  $J_{gem} = 10.5$ ,  $J(3',4) = 5.4$ ,  $J(3',4') = 4.9$ ,  $H'-C(3)$ ); 2.39 (*ddd*,  $J_{gem} = 15.2$ ,  $J(3',4) = 5.4$ ,  $J(3,4) = 4.2$ ,  $H-C(4)$ ); 1.68–1.57 (*m*,  $H'-C(4)$ ); 1.59 (*d*,  $J(PhCHCH_3, CH_3) = 7.0$ ,  $PhCHCH_3$ ). CI-MS: 489 (7,  $M^+ + 1$ ), 457 (13), 365 (5), 342 (65), 282 (9), 261 (12), 250 (100), 190 (11), 105 (15). Anal. calc. for  $C_{29}H_{32}N_2O_5$  (488.58): C 71.29, H 6.60, N 5.73; found: C 71.22, H 6.62, N 5.72.

(+)-**4B**:  $[\alpha]_D = +43^\circ$  ( $c = 1.17$ ,  $CHCl_3$ ). IR ( $CHCl_3$ ): 3420 (NH), 1730 (br., C=O).  $^1H$ -NMR ( $CDCl_3$ ): 7.47–6.90 (*m*, 9 arom. H); 6.42–6.38 (*m*, 2 arom. H); 6.38 (*s*, 1 arom. H); 5.12 (*qd*,  $J(PhCHCH_3, NH) = J(PhCHCH_3, CH_3) = 7.1$ ,  $PhCHCH_3$ ); 4.73 (*d*,  $J(PhCHCH_3, NH) = 7.1$ , NH); 4.06 (*d*,  $J = 13.4$ ,  $H-C(\alpha)$ ); 3.89 (*s*,  $CH_3O$ ); 3.85 (*s*,  $CH_3O$ ); 3.71 (*s*,  $COOCH_3$ ); 3.36 (*d*,  $J = 13.4$ ,  $H'-C(\alpha)$ ); 3.24 (*ddd*,  $J_{gem} = 11.0$ ,  $J(3,4') = 8.3$ ,  $J(3,4) = 4.2$ ,  $H-C(3)$ ); 2.68 (*ddd*,  $J_{gem} = 11.0$ ,  $J(3',4) = 6.4$ ,  $J(3',4') = 4.4$ ,  $H'-C(3)$ ); 2.46 (*ddd*,  $J_{gem} = 15.1$ ,  $J(3',4) = 6.4$ ,  $J(3,4) = 4.2$ ,  $H-C(4)$ ); 1.66 (*ddd*,  $J_{gem} = 15.1$ ,  $J(3,4') = 8.3$ ,  $J(3',4') = 4.4$ ,  $H'-C(4)$ ); 1.52 (*d*,  $J(PhCHCH_3, CH_3) = 7.1$ ,  $PhCHCH_3$ ). CI-MS: 489 (8,  $M^+ + 1$ ), 475 (11), 365 (4), 342 (47), 282 (10), 261 (8), 250 (100), 190 (13), 105 (11). Anal. calc. for  $C_{29}H_{32}N_2O_5$  (488.58): C 71.29, H 6.60, N 5.73; found: C 71.30, H 6.61, N 5.69.

(-)-(*S*)-Methyl 1-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-carboxylate ((-)-**2A**) and (-)-(*S*)-Butyl 1-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-carboxylate ((-)-**5A**). A soln. of (-)-**4A** (4.9 g, 10 mmol) in 90 ml of BuOH was refluxed for 18 h, then evaporated, and the residue was dissolved in aq. 1N HCl/Et<sub>2</sub>O. The org. phase was extracted 2 times with 1N HCl. The combined aqueous phase was made alkaline (pH ca. 9) with 2N Na<sub>2</sub>CO<sub>3</sub> and extracted with Et<sub>2</sub>O. Evaporation afforded 0.97 g of a residue which, according to anal. HPLC, consisted of 80% of (-)-**2A** and 20% of (-)-**5A**. Separation by flash chromatography (hexane/AcOEt 10:1 to 5:1) gave 0.18 g (7%) of (-)-**5A** as an oil followed by 0.78 g (36%) of (-)-**2A**. Crystallization of the latter from acetone/5% HBr in MeOH gave (+)-**2A**·HBr. M.p. 273–275° (dec.).  $[\alpha]_D = +18^\circ$  ( $c = 1.0$ , MeOH);  $[\alpha]_{405} = +54^\circ$  ( $c = 1.0$ , MeOH). IR (KBr): 2750–2600 ( $R_2NH_2^+$ ), 1750 (C=O). Anal. calc. for  $C_{20}H_{24}BrNO_4$  (422.32): C 56.88, H 5.73, Br 18.92, N 3.32; found: C 56.95, H 5.74, Br 18.85, N 3.28.

(-)-**2A**:  $[\alpha]_D = -20^\circ$  ( $c = 1.01$ , MeOH);  $[\alpha]_{405} = -62^\circ$  ( $c = 1.01$ , MeOH).  $^1H$ -NMR and MS: identical with those of ( $\pm$ )-**2**.

(-)-**5A**:  $[\alpha]_D = -5^\circ$  ( $c = 1.2$ ,  $CHCl_3$ );  $[\alpha]_{405} = -25^\circ$  ( $c = 1.01$ ,  $CHCl_3$ ).  $^1H$ -NMR ( $CDCl_3$ ): 7.29–7.22 (*m*, 4 arom. H); 7.16–7.13 (*m*, 2 arom. H); 6.55 (*s*,  $H-C(5)$ ); 4.09 (*t*,  $J = 6.6$ ,  $COOCH_2CH_2CH_2CH_3$ ); 3.92 (*s*,  $CH_3O$ ); 3.87 (*s*,  $CH_3O$ ); 3.56 (*d*,  $J = 13$ ,  $H-C(\alpha)$ ); 3.10 (*d*,  $J = 13$ ,  $H'-C(\alpha)$ ); 3.09–3.03 (*m*, 2  $H-C(3)$ ); 2.75 (*ddd*,  $J_{gem} = 15.8$ ,  $J(3',4) = 9.3$ ,  $J(3,4) = 5.9$ ,  $H-C(4)$ ); 2.56 (*ddd*,  $J_{gem} = 15.8$ ,  $J(3,4') = J(3',4') = 3.8$ ,  $H'-C(4)$ ); 1.86 (br. *s*, disappears on treatment with D<sub>2</sub>O, NH); 1.59 (*m*,  $COOCH_2CH_2CH_2CH_3$ ); 1.32 (*m*,  $COOCH_2CH_2CH_2CH_3$ ); 0.89 (*t*,  $J = 7.3$ ,  $COO(CH_2)_3CH_3$ ). CI-MS: 383 (100,  $M^+ + 1$ ), 292 (19), 282 (22).

(10*S*)-10*b*-Benzyl-6,10*b*-dihydro-8,9-dimethoxy-2-[(R)-1-phenylethyl]imidazo[4,3-*a*]isoquinoline-1,3-(2*H*,5*H*)-dione ((+)-**8A**). The Et<sub>2</sub>O extract of the above acidified reaction mixture was evaporated. The residue (3.24 g, 66%) consisted of 59% of unreacted (-)-**4A**, 38% of (+)-**8A** and 3% of carbamates **6** (by anal. HPLC,



hexane/AcOEt 3:1). This residue, after dissolving in 0.25M NaOMe/MeOH at r.t., similar workup, and recrystallization from (i-Pr)<sub>2</sub>O, afforded pure (+)-**8A**. M.p. 133–134°. [ $\alpha$ ]<sub>D</sub> = +142° (c = 0.52, CHCl<sub>3</sub>). IR (KBr): 1765 (C=O), 1710 (br., C=O). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.44 (s, 1 arom. H); 7.26–7.11 (m, 8 arom. H); 7.03 (s, 1 arom. H); 7.00 (s, 1 arom. H); 6.59 (s, 1 arom. H); 5.07 (q, J = 7.3, PhCHCH<sub>3</sub>); 4.34 (ddd, J<sub>gem</sub> = 13.5, J(3',4) = 5.7, J(3',4') = 1, H'-C(3)); 3.97 (s, CH<sub>3</sub>O); 3.87 (s, CH<sub>3</sub>O); 3.39 (d, J = 13.7, H-C(α)); 3.25 (ddd, J<sub>gem</sub> = 13.5, J(3,4) = 12.0, J(3,4') = 4.0, H-C(3)); 3.12 (d, J = 13.7, H'-C(α)); 2.97 (ddd, J<sub>gem</sub> = 16.4, J(3,4) = 12, J(3',4) = 5.7, H-C(4)); 2.64 (ddd, J = 16.4, J(3,4') = 4.0, J(3',4') = 1.0, H'-C(4)); 1.42 (d, J = 7.3, PhCHCH<sub>3</sub>). CI-MS: 457 (100, M<sup>+</sup> + 1), 365 (37), 261 (43), 190 (5), 105 (7). Anal. calc. for C<sub>28</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub> (456.54): C 73.66, H 6.18, N 6.14; found: C 73.67, H 6.19, N 6.14.

Compound (+)-**8A** was also obtained quantitatively from pure (–)-**4A** with 0.25M NaOMe/MeOH (10 min, r.t.).

(+)-(R)-Methyl 1-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-carboxylate ((+)-**2B**) and (+)-(R)-Butyl 1-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-carboxylate ((+)-**5B**). Urea (+)-**4B** (3.0 g, 6.1 mmol) was treated in the same way as (–)-**4A** to yield 317 mg (18%) of (+)-**2B** and 92 mg (5%) of (+)-**5B** as oils. (–)-**2B**·HBr: M.p. 270–272° (dec.). [ $\alpha$ ]<sub>D</sub> = –18° (c = 1.01, MeOH); [ $\alpha$ ]<sub>405</sub> = –53° (c = 1.01, MeOH). IR (KBr): 2750–2600 (R<sub>2</sub>NH<sub>2</sub><sup>+</sup>), 1750 (C=O). Anal. calc. for C<sub>20</sub>H<sub>24</sub>BrNO<sub>4</sub> (422.32): C 56.88, H 5.73, Br 18.92, N 3.32; found: C 56.76, H 5.77, Br 18.84, N 3.30.

(+)-**2B**: [ $\alpha$ ]<sub>D</sub> = +20° (c = 0.91, MeOH); [ $\alpha$ ]<sub>405</sub> = +63° (c = 0.91, MeOH). <sup>1</sup>H-NMR and MS spectra: identical with those of (±)-**2**.

(+)-**5B**: [ $\alpha$ ]<sub>D</sub> = +4° (c = 1.15, CHCl<sub>3</sub>); [ $\alpha$ ]<sub>405</sub> = +25° (c = 1.15, CHCl<sub>3</sub>). <sup>1</sup>H-NMR and MS spectra: identical with those of (–)-**5A**.

(10bR)-10b-Benzyl-6,10b-dihydro-8,9-dimethoxy-2-[(R)-1-phenylethyl]-imidazo[4,3-a]isoquinoline-1,3-(2H,5H)-dione ((–)-**8B**). M.p. 111–113° ((i-Pr)<sub>2</sub>O/Et<sub>2</sub>O). [ $\alpha$ ]<sub>D</sub> = –106° (c = 1.04, CHCl<sub>3</sub>). IR (KBr): 1770 and 1710 (C=O). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.44 (s, 1 arom. H); 7.27–7.11 (m, 8 arom. H); 6.95–6.92 (m, 2 arom. H); 6.60 (s, 1 arom. H); 5.07 (q, J = 7.3, PhCHCH<sub>3</sub>); 4.35 (ddd, J<sub>gem</sub> = 13.4, J(3',4) = 6.6, J(3',4') = 1, H'-C(3)); 3.97 (s, CH<sub>3</sub>O); 3.87 (s, CH<sub>3</sub>O); 3.44 (d, J = 14, H-C(α)); 3.27 (ddd, J<sub>gem</sub> = 13.4, J(3,4) = 12.0, J(3,4') = 4.4, H-C(3)); 3.16 (d, J = 14, H'-C(α)); 2.99 (ddd, J<sub>gem</sub> = 16.1, J(3,4) = 12.0, J(3',4) = 6.6, H-C(4)); 2.65 (ddd, J<sub>gem</sub> = 16.1, J(3,4') = 4.4, J(3',4') = 1, H'-C(4)); 1.48 (d, J = 7.3, PhCHCH<sub>3</sub>). CI-MS: 457 (100, M<sup>+</sup> + 1), 365 (14), 261 (7). Anal. calc. for C<sub>28</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub> (456.43): C 73.66, H 6.18, N 6.14; found: C 73.74, H 6.22, N 6.10.

(+)-(R)-(1-Phenylethyl)amine ((+)-**7**). The neutral fraction from the reaction of the thermal decomposition of (+)-**4B** was crystallized from (i-Pr)<sub>2</sub>O/Et<sub>2</sub>O. The mother liquor was evaporated, and the residue (0.84 g) was refluxed in 13 ml of H<sub>2</sub>O/EtOH/KOH 2:8:1 for 40 h. Then, the mixture was acidified with 2N HCl and concentrated to remove EtOH. The resulting suspension was extracted with Et<sub>2</sub>O and afforded, after evaporation, 0.38 g of (–)-**8B**. The acid layer was made alkaline with 2N Na<sub>2</sub>CO<sub>3</sub> and extracted with Et<sub>2</sub>O and the combined extracts concentrated to ca. 5 ml. After addition of 3% HCl soln. in MeOH, ca. 0.21 g of (R)-**7**·HCl were isolated. From this, (+)-**7** was freed and distilled ('Kugelrohr' oven, 60°/0.5 Torr). [ $\alpha$ ]<sub>D</sub> = +33.2° (c = 2.28, CHCl<sub>3</sub>); reference sample (Aldrich): [ $\alpha$ ]<sub>D</sub> = +33.1° (c = 1.78, CHCl<sub>3</sub>).

(10bS)-10b-Benzyl-6,10b-dihydro-8(or 9)-hydroxy-9(or 8)-methoxy-2-[(R)-1-phenylethyl]imidazo[4,3-a]isoquinoline-1,3-(2H,5H)-dione (**9A**). Hydantoin (+)-**8A** (10 mg, 0.02 mmol) was refluxed in 2 ml of conc. HCl/AcOH 1:1 for 24 h. According to TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 50:1), 2 new compounds with R<sub>f</sub> 0.73 and 0.68 were present in the mixture beside (+)-**8A** (R<sub>f</sub> 0.82). Compounds with R<sub>f</sub> 0.73 and 0.68 gave the reddish color reaction with FeCl<sub>3</sub> (1% soln. in EtOH). The mixture was evaporated, the residue diluted with H<sub>2</sub>O and extracted with Et<sub>2</sub>O (pH ca. 1). Then, the pH of the aq. phase was adjusted to 6.5–7 with 20% NaOH soln. and AcOH and extracted with CHCl<sub>3</sub>. After evaporation, 5 mg of an oily residue were obtained. CI-MS: 457 (7, M<sup>+</sup>(**8A**) + 1), 443 (100, M<sup>+</sup>(**9A**) + 1), 351 (25, M<sup>+</sup>(**9A**) – CH<sub>2</sub>Ph), 247 (28, M<sup>+</sup>(**9A**) – CH(CH<sub>3</sub>)Ph), 105 (18). HR-MS: 422.1885 (M<sup>+</sup>, C<sub>27</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>, calc. 442.1892).

Diastereoisomer **9B**. The identical reaction with (–)-**8B** (10 mg, 0.02 mmol) afforded 4 mg of an oily residue. TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 50:1): R<sub>f</sub>(**8B**) 0.80; R<sub>f</sub> 0.70 and 0.65, reddish color reaction with FeCl<sub>3</sub>. CI-MS: 457 (3, M<sup>+</sup>(**8B**) + 1), 443 (100, M<sup>+</sup>(**9B**) + 1), 351 (24, M<sup>+</sup>(**9B**) – CH<sub>2</sub>Ph) 247 (12, M<sup>+</sup>(**9B**) – CH(CH<sub>3</sub>)Ph), 105 (11). HR-MS: 422.1889 (M<sup>+</sup>).

(10bS)-10b-Benzyl-6,10b-dihydro-8,9-dihydroxy-2-[(R)-1-phenylethyl]imidazo[4,3-a]isoquinoline-1,3-(2H,5H)-dione (**10A**). Hydantoin (+)-**8A** (52 mg, 0.11 mmol) was refluxed in 1 ml 48% HBr/AcOH 1:1 for 2 h. After evaporation, the residue was analyzed by TLC and MS. TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 50:1): R<sub>f</sub> 0.37, dark blue color reaction with FeCl<sub>3</sub>. CI-MS: 429 (100, M<sup>+</sup> + 1), 337 (19, M<sup>+</sup> – CH<sub>2</sub>Ph), 325 (9, M<sup>+</sup> – CH(CH<sub>3</sub>)Ph). EI-MS: 337 (42), 233 (62), 105 (100), 91 (28). HR-MS: 337.1180 (M<sup>+</sup>, C<sub>19</sub>H<sub>17</sub>N<sub>2</sub>O<sub>4</sub>, calc. 337.1188).

The above residue was dissolved in 2 ml of MeOH, and 8 ml of a  $\text{CH}_2\text{N}_2$  soln. in  $\text{Et}_2\text{O}$  were added at  $0^\circ$ . The mixture was left overnight at r.t. and then evaporated, the residue dissolved in 1N HCl and extracted with  $\text{Et}_2\text{O}$ . The  $\text{Et}_2\text{O}$  extract was evaporated and the residue crystallized from  $(i\text{-Pr})_2\text{O}$ : 40 mg of pure (+)-**8A**.  $[\alpha]_{\text{D}} = +140^\circ$  ( $c = 1.07$ ,  $\text{CHCl}_3$ ).

(S)-1-Benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (**1A**). For 2 h (+)-**2A**·HBr (304 mg, 0.8 mmol) was refluxed with 5 ml of 48% HBr soln. Then, the mixture was evaporated and the product precipitated with acetone to give 257 mg (85%) of **1A**·HBr as acetone solvate. M.p.  $209\text{--}214^\circ$ .  $[\alpha]_{405} = +21^\circ$  ( $c = 0.39$ ,  $\text{H}_2\text{O}$ );  $[\alpha]_{405} = -31^\circ$  ( $c = 0.30$ , 50% aq. acetone). IR (KBr): 3500–2750 (NH, OH,  $\text{R}_2\text{NH}_2^+$ ), 1740 and 1700 (C=O).  $^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ ): 7.40–7.36 (*m*, 4 arom. H); 7.29–7.24 (*m*, 2 arom. H); 6.73 (*s*, H–C(5)); 3.84 (*d*,  $J = 14.6$ , H–C( $\alpha$ )); 3.43–3.36 (*m*, 2 H–C(3)); 3.32 (*d*,  $J = 14.6$ , H'–C( $\alpha$ )); 2.97 (*ddd*,  $J_{\text{gem}} = 17.2$ ,  $J(3',4) = 9.5$ ,  $J(3,4) = 6.6$ , H–C(4)); 2.84 (*ddd*,  $J_{\text{gem}} = 17.2$ ,  $J(3,4) = J(3',4) = 5.0$ , H'–C(4)). CI-MS: 300 (100,  $M^+ + 1$ ), 282 (2), 254 (56), 208 (1), 164 (7). Anal. calc. for  $\text{C}_{17}\text{H}_{18}\text{BrNO}_4 \cdot \frac{1}{2}(\text{CH}_3)_2\text{CO}$  (409.28): C 54.29, H 5.17, Br 19.52, N 3.42; found: C 54.19, H 5.13, Br 19.43, N 3.53.

(R)-1-Benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (**1B**). As above, (–)-**2B**·HBr (182 mg, 0.38 mmol) afforded 160 mg (88%) of crystalline **1B**·HBr as acetone solvate. M.p.  $208\text{--}212^\circ$ .  $[\alpha]_{405} = -20^\circ$  ( $c = 0.7$ ,  $\text{H}_2\text{O}$ );  $[\alpha]_{405} = +30^\circ$  ( $c = 0.3$ , 50% aq. acetone). IR,  $^1\text{H-NMR}$ , and MS: identical with those of (±)-**1** and **1A**. Anal. calc. for  $\text{C}_{17}\text{H}_{18}\text{BrNO}_4 \cdot \frac{1}{2}(\text{CH}_3)_2\text{CO}$  (409.28): C 54.29, H 5.17, Br 19.52, N 3.42; found: C 54.18, H 5.39, Br 19.27, N 3.39.

*X-Ray Analysis of (+)-8A*.  $\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_4$ , mol.wt. 456.54, orthorhombic, space group  $P2_12_12_1$ ,  $a = 8.127(3)$ ,  $b = 8.619(3)$ ,  $c = 34.200(14)$  Å,  $V = 2395.6(3)$  Å<sup>3</sup>,  $Z = 4$ ,  $d_{\text{calc}} = 1.27$  gm/cm<sup>3</sup>,  $\mu = 0.8$  cm<sup>–1</sup>. Data were collected at  $-70^\circ$  with a Nicolet R3M automatic diffractometer using MoK $\alpha$  radiation ( $\lambda = 0.71069$  Å) with a graphite monochromator on the incident beam. Using the  $\theta$ – $2\theta$  scan technique with a variable scan rate out to a  $2\theta_{\text{max}} = 45^\circ$ , 1631 independent reflections were measured. Data were corrected for Lorentz and polarization effects but absorption effects were ignored. The structure was solved by direct methods and refined by full-matrix least-squares (non-H-atoms anisotropic, H-atoms riding on covalently bonded atoms with fixed thermal parameters) using the 1291 reflections for which  $|F_o| > 3\sigma|F_o|$  to a final  $R$  factor of 0.061,  $R_w = 0.052$ . The function minimized was  $\sum w(|F_o| - |F_c|)^2$  where  $w = 1/[\sigma^2(|F_o|) + g(F_o)^2]$  and  $g = 0.00023$ . The goodness of fit parameter was 1.40. All calculations were carried out using the MicroVAX versions of the SHELXTL system of programs [20].

*X-Ray Analysis of (+)-11A·HBr*.  $\text{C}_{13}\text{H}_{18}\text{BrNO}_4$ , mol.wt. 332.20, orthorhombic, space group  $P2_12_12_1$ ,  $a = 7.348(1)$ ,  $b = 8.260(1)$ ,  $c = 23.737(3)$  Å,  $V = 1440.6(3)$  Å<sup>3</sup>,  $Z = 4$ ,  $d_{\text{calc}} = 1.53$  gm/cm<sup>3</sup>,  $\mu = 40.04$  cm<sup>–1</sup>. Measurements were obtained with a Nicolet R3M automatic diffractometer using CuK $\alpha$  radiation ( $\lambda = 1.54178$  Å) with a graphite monochromator in the incident beam, 1972 independent reflections were measured (including Friedel equivalents for absolute-configuration calculations) at r.t. using the  $\theta$ – $2\theta$  scan technique with a variable scan rate out to a  $2\theta_{\text{max}} = 120^\circ$ . Data were corrected for Lorentz, polarization, and absorption effects (minimum and maximum transmission factors were 0.35 and 0.86, resp.). The structure was solved by direct methods and refined by full-matrix least-squares (non-H-atoms anisotropic) using the 1955 reflections for which  $|F_o| > 3\sigma|F_o|$  to a final  $R$  factor of 0.025,  $R_w = 0.034$ . The function minimized was  $\sum w(|F_o| - |F_c|)^2$  where  $w = 1/[\sigma^2(|F_o|) + g(F_o)^2]$  and  $g = 0.00025$ . The goodness of fit parameter was 1.68. All calculations were carried out with the SHELXTL system of programs [20].

We would like to thank Dr. Voldemar Toome, F. Hoffmann-La Roche, Inc., Nutley, N. J., for a CD analysis of representative compounds.

## REFERENCES

- [1] G. J. Kapadia, G. S. Rao, E. Leete, M. B. E. Fayeze, Y. N. Vaishnav, H. M. Fales, *Lloydia* **1969**, 32, 525.
- [2] G. J. Kapadia, G. S. Rao, E. Leete, M. B. E. Fayeze, Y. N. Vaishnav, H. M. Fales, *J. Am. Chem. Soc.* **1970**, 92, 6943.
- [3] M. A. Collins, W. P. Nijm, G. F. Borge, G. Teas, C. Goldfarb, *Science* **1979**, 206, 1184.
- [4] J. M. Lasala, C. J. Coscia, *Science* **1979**, 203, 283.
- [5] M. A. Collins, *Adv. Exp. Med. Biol.* **1980**, 126, 87.
- [6] M. A. Collins, 'The Alkaloids', Ed. A. Brossi, Academic Press, New York, 1983, Vol. 21, p. 329–358.
- [7] G. Bringmann, S. Schneider, A. Hille, *Nachr. Chem. Tech. Lab.* **1986**, 34, 222.

- [8] C. Melchior, M. A. Collins, *CRC Crit. Rev. Tox.* **1982**, 9, 313.
- [9] I. G. C. Coutts, M. R. Hamblin, E. J. Tinley, J. M. Bobitt, *J. Chem. Soc., Perkin Trans. I* **1979**, 2744.
- [10] R. Shen, R. V. Smith, P. J. Davis, A. Brubaker, C. W. Abell, *J. Biol. Chem.* **1982**, 257, 7294.
- [11] S. Teitel, J. O'Brien, W. Pool, A. Brossi, *J. Med. Chem.* **1974**, 17, 134.
- [12] B. Schönenberger, A. Brossi, *Helv. Chim. Acta* **1986**, 69, 1486.
- [13] G. Hahn, K. Stiehl, *Chem. Ber.* **1936**, 69, 2627.
- [14] T. Hudlicky, T. M. Kutchan, G. Shen, V. E. Sutliff, C. J. Coscia, *J. Org. Chem.* **1981**, 46, 1738.
- [15] *Crystallographic Data Centre*, Cambridge University, University Chemical Lab., Cambridge CB21EW, England.
- [16] B. Schönenberger, A. Brossi, *Helv. Chim. Acta* **1987**, 70, 271.
- [17] D. Rogers, *Acta Crystallogr., Sect. A* **1980**, 37, 734.
- [18] J. C. Craig, M. Martin-Smith, S. K. Roy, J. B. Stenlake, *Tetrahedron* **1966**, 22, 1335.
- [19] P. Crabbé, in 'Topics in Stereochemistry', Ed. N. L. Allinger and E. L. Eliel, Interscience, New York 1967, Vol. 1, pp. 94–198, and ref. cit. therein.
- [20] G. M. Sheldrick, 'SHELXTL, Minicomputer Programs for Structure Determination', University of Göttingen, 1980.