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HYDANTOINS AND THIOHYDANTOINS DERIVED FROM 1,2,3,4-TETRAHYDROISOQUINOLINE-3-CARBOXYLIC ACID

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Abstract – The reaction of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate with isocyanates (phenyl, naphthalen-1-yl, cyclohexyl, (*S*)-1-methylbenzyl) in ether has been used to prepare *N*-substituted methyl (3*S*)-2-aminocarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylates. These compounds were cyclised by action of CF_3COOH to give the corresponding 2-substituted (10a*S*)-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-diones (hydantoins Tic-H). Hydantoins Tic-H were also prepared by the reaction of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate with isocyanates (methyl, (1*S*)-1-methylbenzyl, 4-methylphenyl, 3-methylphenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 4-methoxyphenyl, 5-chloro-2-methoxyphenyl, 3-chloro-4-ethoxyphenyl) and triethylamine in CH_2Cl_2. 2-Substituted (10a*S*)-3-thioxo-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinolin-1-ones (thiohydantoins Tic-TH) were prepared analogously by the reaction of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate with isothiocyanates (methyl,

ethyl, allyl, phenyl). The optical purity of selected substances was determined chromatographically.

INTRODUCTION

The derivatives of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic acid), which is chiral α-amino acids not occurring in nature, are interesting thanks to their very varied biological activities. They act as inhibitors of various enzymatic processes.[1-8] Tic acid can be considered a derivative of phenylalanine containing a methylene bridge between amino group and benzene ring, which restricts its conformational freedom, and this allows preparation of peptides with defined tertiary structures.[2,9-12] Some macrocyclic peptides containing Tic acid can block the biosynthesis of peptides.[13,14] Also the hydantoin derivatives exhibit a wide range of biological activity. They act as antiarrhythmics, anticonvulsant, antitumor, anxiolytic, antiinflammatory, analgetics, antiepileptics, antihypertensive agents).[15-17] One of the challenges of medicinal chemistry is the enhancement of the affinity of a given ligand for its target by decreasing its degrees of freedom and thereby reducing the entropy cost.[16,17] A possible way to this goal in the case of hydantoins consists in their combination with the conformationally little flexible 1,2,3,4-tetrahydroisoquinoline skeleton. The combination of hydantoin with tetrahydroisoquinoline skeleton introduces into the molecule the chirality derived from easily available, optically pure L-phenylalanine. The biological activity of these hydantoins has already been confirmed in literature.[3] Literature gives several cases of preparation of these tetrahydroisoquinoline-hydantoins (Tic-H) and thiohydantoins[18] (Tic-TH) as well as their subsequent substitution at nitrogen atom *N*-2. However, in none of the cases the products prepared were studied from the viewpoint of their optical purity.

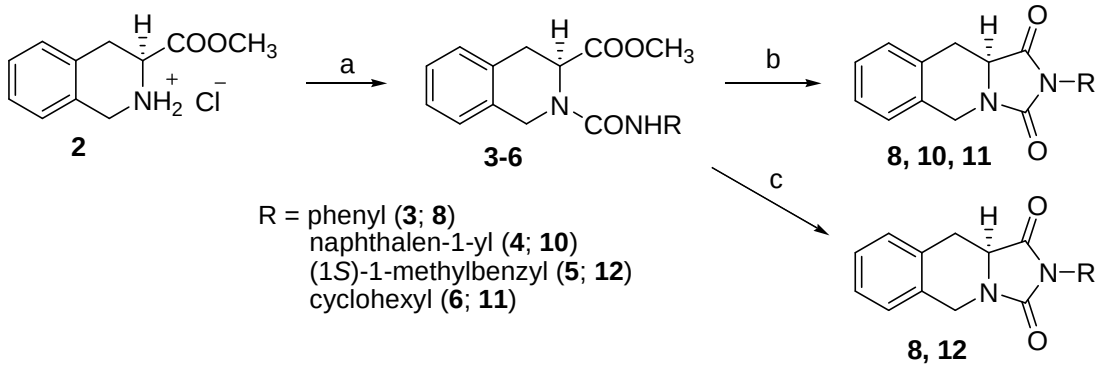
In our previous paper[19] we published preparation of some derivatives of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid both in optically pure *S*-forms and as racemates. The aim of this present work is to prepare 2-substituted (10a*S*)-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-diones (Tic-H) and their 3-thioxo derivatives (Tic-TH), at the same time using stereoslectivity control of the reactions leading to these substances. If the compound was prepared as both optically pure and racemate, the former is denoted “a” and the latter “b”.

RESULTS AND DISCUSSION

The preparation of tricyclic hydantoins derived from 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic-H) has already been described in literature because of their expected biological activity.[3,16,17,20-24] Although some syntheses[16,17] start from optically pure Tic acid, nothing is known about the optical purity of Tic-H. All the preparation methods are multistep procedures and, in addition, there is a danger of racemisation.

Niopas[18] prepared (10a±)-2-substituted-Tic-TH by reactions of racemic ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate with isothiocyanates.

Our preparation procedures of hydantoins Tic-H start from the optically pure hydrochloride of methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2a**) (ref.[19]) in analogy with the earlier described way of preparation of hydantoins.[25] We adopted two procedures: a two-step procedure involving preparation of carbamoyl derivatives in the first step, their isolation and subsequent ring closure, and a one-step procedure in which the carbamoyl derivatives primarily formed are, without isolation, cyclised to hydantoins.



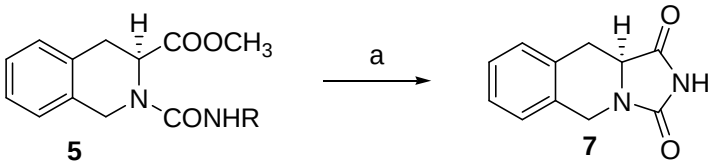
Scheme 1**.** (a) (i) NEt_3, Et_2O; (ii) RNCO, 79-91%; (b) CF_3COOH, 96-100%; (c) NEt_3, MeOH or Et_2O, 93%.

Carbamoyl derivatives (**3**-**6**) were prepared by reaction of the base of methyl ester (**2a**) with isocyanates (Scheme 1). The base of methyl ester (**2a**) was set free *in situ* by a reaction of its hydrochloride with triethylamine in dry ether. The reaction of ester (**2a**) with (*S*)-1-methylbenzyl isocyanate and triethylamine in dry ether was used to prepare methyl (3*S*)-*N*-[(1*S*)-1-methylbenzyl]carbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**5**) having diastereoisomeric purity of 100 % (according to the ^{1}H NMR). The yields of carbamoyl derivatives were above 80 %.

The subsequent ring closure of carbamoyl derivatives is catalysed with triethylamine (Scheme 1). The ring closures of methyl (3*S*)-*N*-phenylcarbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**3**) and methyl (3*S*)-*N*-[(1*S*)-1-methylbenzyl]carbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**5**) in methanol with triethylamine catalysis were accompanied by partial racemisation. No racemisation was observed in the ring closure reaction of compound (**5**) with catalytic amount of triethylamine in ether.

The carbamoyl derivatives can also undergo ring closure (Scheme 1) with acid catalysis (in CF_3COOH). The optical purity of hydantoins is practically the same, whether they have been prepared with acid catalysis or with base catalysis. A ring closure experiment with methyl (3*S*)-*N*-[(1*S*)-1-methylbenzyl] carbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**5**) in CF_3COOH at r.t. gave (10a*S*)-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**7a**) in a yield of 84 % (Scheme 2). Obviously, the 1-methylbenzyl group is split off after protonation of the carbonyl oxygen atom in the form of carbenium

ion by the $A_{Al}1$ mechanism, in the same way as the *tert*-butyl group from the *tert*-butyl esters or the protecting Boc group from *tert*-butyloxycarbonyl derivatives.[26,27]



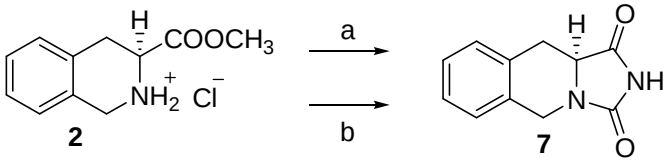
R = (1*S*)-1-methylbenzyl

Scheme 2. (a) CF_3COOH, 84%.

In the case of reaction of base of ester (**2a**) with methyl isocyanate in the presence of triethylamine, we isolated a mixture of hydantoin (**9**) and the corresponding carbamoyl derivative; the ring closure was finished by reaction in CF_3COOH.

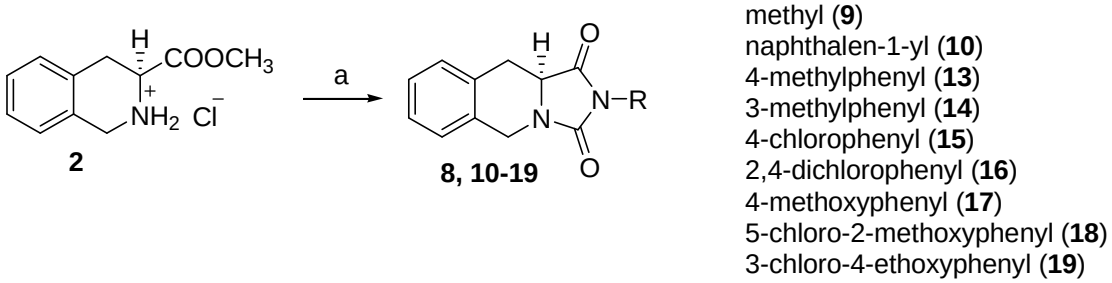
(10a*S*)-2-Cyclohexyl-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**11**) was prepared from methyl (3*S*)-*N*-cyclohexylcarbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**6**) by reaction in CF_3COOH in a practically quantitative yield, whereas the reaction of the base of ester (**2a**) with cyclohexyl isocyanate in CH_2Cl_2 only gave methyl (3*S*)-*N*-cyclohexylcarbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**6**) (Scheme 1).

(10a*S*)-10,10a-Dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**7a**) was prepared in a very good yield by a reaction of the hydrochloride of methyl ester (**2a**) with excess KOCN in water at r.t. (Scheme 3). We verified the possibility of preparation of compound (**7a**) by a reaction of the base of methyl ester (**2a**) with nitrourea in boiling water (Scheme 3). The yield of the substance thus prepared (**7a**) is good, but the optical purity is somewhat lower than in the preparation described before. Literature[3,17] describes two ways of preparation of this compound from 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid and KOCN in boiling water; experiments only gave the yields of 53 % and 25 %, respectively, the optical purity being unknown.



Scheme 3. (a) KNCO, H_2O, 92%; (b) $NH_2CONHNO_2$, H_2O, 90%.

In two cases (**7b**, **8b**) we also prepared racemic hydantoins from racemic ester (**2b**) for the purposes of chromatographic determination of optical purity. Substances (**9**), (**10**), (**13**)-(**19**) were prepared by one-step synthesis from methyl-(*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate and the respective isocyanate in dichloromethane (Scheme 4).



Scheme 4. (a) (i) NEt_3, CH_2Cl_2; (ii) RNCO, 85-98%.

In both ^1H and ^{13}C NMR spectra of hydantoins Tic-H substituted at 2-position by a 2-substituted phenyl group (2-(2,4-dichlorophenyl), 2-(5-chloro-2-methoxyphenyl) and also 2-(naphthalen-1-yl)) we observed doubling of signals, which we ascribe to formation of atropoisomers due to hindered rotation around N(2)—C(Ar) bond. The proportion of the atropoisomers is not in the ratio of 1:1, due to the presence of stereogenic centre at C10a. The situation is obvious from the ORTEP[28] diagram of (10a*S*)-2-(5-chloro-2-methoxyphenyl)-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**18**).

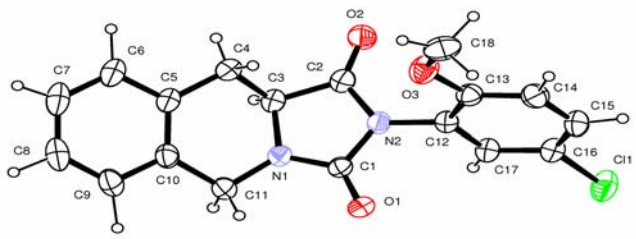


Figure 1. ORTEP view of compound (**18**) displaying the thermal ellipsoids at 30% probability.

Because this compound crystallizes in the non-centrosymmetric space group $P2_1$, the crystal contains only molecules of one diastereoisomer. The correct absolute configuration, *S*, of the carbon C3 (numbering after Figure 1) has been confirmed by the value of the Flack parameter of –0.03(6), obtained after the last cycle of refinement.[29] For the inverted absolute structure the value of the Flack parameter is 0.98(6). An ORTEP view of compound (**18**) is shown in Figure 1. The six membered ring C3-C4-C5 C10-C11-N1 exhibits an envelope conformation ^1E with puckering parameters[30] of: Q_T = 0.403(2) Å, φ_2 = 0.3(4)°, θ_2 = 49.1(3)°. The other rings are essentially planar. The C12-C17 phenyl group is rotated with respect to the hydantoin ring by an angle of 75.47(7)°. The molecules in the crystal are connected by C-H···O weak hydrogen bonds[31] which involve both O1 and O2 oxygens of hydantoin:

C15-H15···O1(1-x,1/2+y,1-z), H15···O1 = 2.42(3) Å; C18-H183···O1(-x,1/2+y,1-z), H183···O1 = 2.55(4) Å; C3-H3···O2(-x,y-1/2,-z), H3···O2 = 2.66(4) Å; C18-H182···O2(-x, 1/2+y,-z), H182···O2 = 2.31(4) Å. The crystal packing is shown in Figure 2.

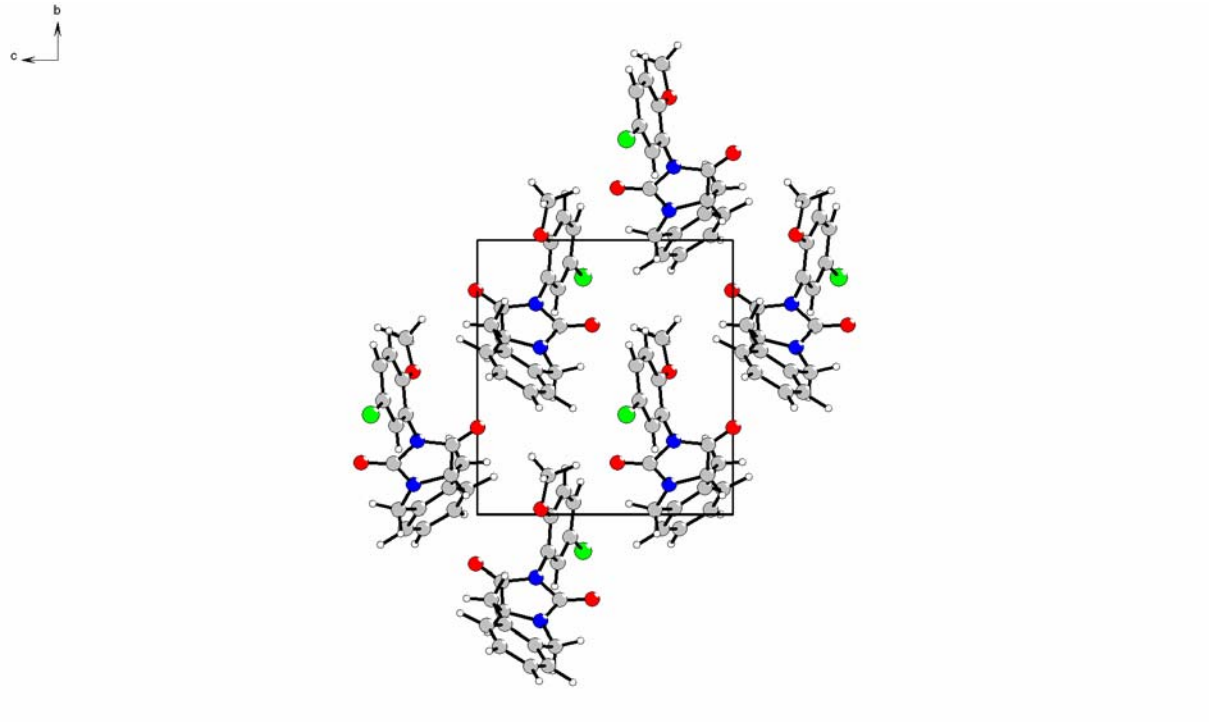
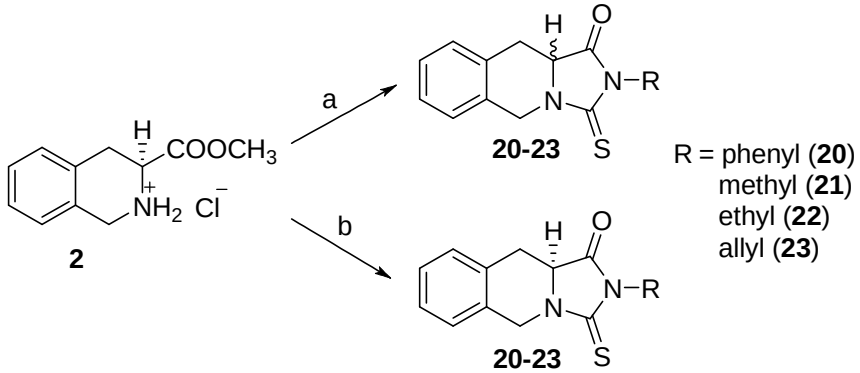


Figure 2. The crystal packing of (**18**) viewed down the crystallographic *a* axis.

2-Substituted 3-thioxo-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]-isoquinoline-1-ones (Tic-TH) were prepared by reactions of the hydrochloride of ester (**2a**) with the respective isothiocyanates in dry ether in the presence of triethylamine as catalyst. The substances show strong inclination to racemisation (Scheme 5).



Scheme 5. (a) (i)1.20 eq NEt_3, CH_2Cl_2; (ii) RNCS, 85-92%; (b) (i) 0.99 eq NEt_3, Et_2O; (ii) RNCS, 82-91%.

In the presence of excess triethylamine, as it is given in procedure 2 for the preparation of (10a*S*)-2-phenyl-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**8a**), we only obtained racemates (substances (**20b**), (**21b**), (**22b**) and (**23b**)) from the optically pure ester (**2a**). Therefore, we used

less than equimolar amount of triethylamine (99 % mol.) as compared with the hydrochloride of ester (Scheme 5). In spite of that, we never observed formation of the thiocarbamoyl derivative, an intermediate in the formation of thiohydantoin, but only thiohydantoin (Scheme 4), which means that the ring closure itself must be very fast in comparison with the formation of thiocarbamoyl derivative, being substantially faster than the ring closure reactions of the corresponding oxygen derivatives (which is usual).[32] Thiohydantoins Tic-TH were obtained by the above-described procedure in high yields (82-91%) and high optical purity (determined HPLC in the case of compound (**22a**)).

CONCLUSION

A method has been developed for preparing *N*-substituted methyl (3*S*)-2-aminocarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylates (**3**) – (**6**) from methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate and isocyanates (phenyl, naphthalen-1-yl, cyclohexyl, (*S*)-1-methylbenzyl) by reactions in ether. The yields of the aminocarbonyl derivatives (**3**) – (**6**) are in the range of 82-91%. The ring closure of aminocarbonyl derivatives giving 2-substituted (10a*S*)-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-diones (Tic-H) was carried out either in CF_3COOH, or in methanol with triethylamine catalyst. The base catalysed ring closure is accompanied by partial racemisation as a consequence of the presence of acidic proton at the α-carbon atom in the vicinity of methoxycarbonyl group. The racemisation can be prevented by using a catalytic amount of triethylamine, and ether as solvent. Tic-H can also be prepared by one-step reaction of hydrochloride of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2a**) with isocyanates and triethylamine in CH_2Cl_2. The yields of Tic-H are above 85 %, and the optical purity is high. (10a*S*)-10,10a-Dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**7a**) was prepared by reaction of hydrochloride of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2a**) with KOCN in water at r.t. in the yield of 92 % and optical purity of 99.7 %.

The preparation of (10a*S*)-2-substituted 3-thioxo-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinolin-1-ones (Tic-TH) by a reaction of hydrochlorides of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2a**) with isothiocyanates and triethylamine in dry ether has been described. This reaction is accompanied by easy racemisation, hence even the reaction of optically pure ester gives racemic Tic-TH. The fast racemisation of Tic-TH in excess base is obviously caused by higher acidity of thioamides as compared with analogous amides (e.g. the pK_a values of *N*,*N*-dimethylphenylacetamide and *N*,*N*-dimethylphenylthioacetamide in DMSO are 26.6 and 21.3, respectively; ref.[33]). Of course, in the case of Tic-TH, the C=S group is not adjacent to the acidic C–H group. Another reason of the fast racemisation may lie in the unwillingness of sulphur to form double bonds. Optically pure Tic-TH were prepared with application of less than equimolar amount of triethylamine, the yields being 85 % and above.

EXPERIMENTAL

The NMR spectra were measured at 298 K with Bruker AVANCE 500 spectrometer equipped with 5 mm broadband probe at the frequencies of 500.13 MHz (^{1}H) and 125.77 MHz (^{13}C) and with a Bruker AMX 360 spectrometer at the frequencies 360.14 MHz (^{1}H) and 90.57 MHz (^{13}C) in $CDCl_3$. The ^{1}H NMR spectra were calibrated on hexamethyldisiloxane (δ 0.05). *J* values are given in hertz. The ^{13}C NMR spectra were calibrated on the central signal of the solvent multiplet (δ 77.0 for $CDCl_3$). The carbon NMR spectra were measured in standard way and by means of the APT pulse sequence.

Melting points were determined with a Kofler hot stage microscope and were not corrected. The microanalyses were performed on a FISONS EA 1108 CHNS automatic analyser. Optical rotations were measured on PERKIN ELMER 341 Polarimeter at λ 589.3 nm and 298 K, concentration *c* is given in g/100 mL.

Optical purities were determined by chiral HPLC. HPLC system consisted of a Spectra Series P200 gradient pump (Fremont, CA, USA), a HP 1100 Series autosampler, a HP 1100 Series thermostated column compartment from Hewlett Packard (Waldbronn, Germany), and a SPD-10A_{VP} UV-Vis detector from Shimadzu (Prague, Czech Republic). The enantiomers were measured at 240, 243, and 212 nm for compounds (**8a**), (**22a**), and (**7a**), respectively. Data from chromatographic runs were processed using a chromatography station for Windows CSW (version 1.7) software from DataApex (Prague, Czech Republic). Separation of the respective enantiomers was performed using a 250 × 4.6 mm OD-R Chiralcel column from Daicel Chemical Industries (Tokyo, Japan). The mobile phase was prepared by mixing buffer (0.3 M sodium perchlorate, pH 3.0 set by $HClO_4$) with acetonitrile 40/60 (v/v) for (**8a**) and (**22a**), and 50/50 (v/v) for (**7a**). HPLC separation was performed at 25°C with a flow rate of 0.8 mL/min.

X-Ray diffraction data for compound (**18**) were collected at room temperature, 295 K, on a Nonius Kappa CCD diffractometer with graphite monochromated Mo Kα radiation (λ = 0.7107 Å). The structure was solved by direct methods (SIR97)[34] and refined (SHELXL-97)[35] by full matrix least squares with anisotropic non-hydrogen atoms and isotropic hydrogens.

Crystal data: (**18**), $C_{18}H_{15}ClN_2O_3$; monoclinic, space group $P2_1$, a = 8.2611(2), b = 10.2672(3), c = 9.9850(3) Å, β = 106.406(1)°, V = 812.43(4) Å^3, Z = 2, Dc = 1.401 g cm^{-3}. Intensity data collected with θ ≤ 30°; 4193 independent reflections measured; 3590 observed [I >2σ(I)]. Final R index = 0.0421 (observed reflections), Rw = 0.1158 (all reflections), S (goodness of fit) = 1.038.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 296411. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html or on application to CCDC, Union Road, Cambridge CB2 1EZ, UK [fax: (+44)1223-336033, e-mail: deposit@ccdc.cam.ac.uk

The starting **(*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid** (**1a**) (CMS Chemicals LTD), mp 331 °C, decomp, the content of 99.1% according to titration with $HClO_4$, and $[\alpha]_D^{20}$ –175.8° (*c* 1.1N NaOH, aq) (ref.[35]: $[\alpha]_D^{20}$ –177.4° (*c* 1.1N NaOH, aq)).

(±)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (**1b**) was prepared according to ref. [19], yield 91%.

Hydrochloride of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2a**) was prepared[19] from (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**1a**) and $SOCl_2$ in dry MeOH by a known procedure[36,37] with quantitative yield. mp 248-250°C (decomp.) (MeOH-Et_2O). Ref.[36] gives mp 250-255°C, (decomp.) (MeOH-Et_2O). The product recrystallised from a mixture of $CHCl_3$-Et_2O ether melts at 261-263°C (decomp.), $[\alpha]_D^{20}$ –155.1° (*c* 1, $CHCl_3$), $[\alpha]_D^{20}$ –128.2° (*c* 1, CH_3OH) (ref.[36]: $[\alpha]_D^{20}$ –104.1° (*c* 1, CH_3OH)).

Hydrochloride of methyl (±)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2b**) was prepared from (±)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**1b**) in the same way and in quantitative yield.[19] Its mp is 250-252°C (decomp.) (MeOH-Et_2O), ref.[37] gives mp 302-303°C (decomp.) (MeOH-Et_2O), and ref.[38] gives mp 278°C ($CHCl_3$-Et_2O). The ^1H and ^{13}C NMR spectra of compounds (**1**) and (**2**) are given in ref.[19]

Methyl (3*S*)-*N*-phenylcarbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**3**): A suspension obtained from dry Et_2O (20 mL) and hydrochloride of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2a**) (1.00 g, 4.40 mmol) was vigorously stirred, cooled, and treated with dry Et_3N (0.44 g, 4.36 mmol). Then, phenyl isocyanate (0.52 g, 4.35 mmol) in dry CH_2Cl_2 (2 mL) was quickly added. Vigorous stirring was continued for another 3 h, whereupon the separated solid was collected by suction and washed with Et_2O (5 mL) and H_2O (10 mL). The crude product was purified by flash chromatography (silica gel 60 μm, CH_2Cl_2). Yield 1.10 g (82%), white solid, mp 132–134°C, $[\alpha]_D^{20}$ +36.6° (*c* 1, $CHCl_3$). *Anal*. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.91; H, 6.02; N, 9.19.

^1H NMR (δ/ppm, $CDCl_3$): 7.53-7.10 (9H, m, arom.), 6.84 (1H, bs, NH), 4.78 (1H, d, H(1a), ^2J=15.1), 4.77 (1H, d, H(1b), ^2J=15.1), 5.44 (1H, dd, H(3), ^3J=3.1, ^3J=6.1), 3.37 (1H, dd, H(4a), ^2J=16.0, ^3J=3.1), 3.24 (1H, dd, H(4b), ^2J=16.0, ^3J=6.1), 3.65 (3H, s, OCH_3), 3H. ^{13}C NMR (δ/ppm $CDCl_3$): 172.05 (COO), 155.30 (NCON), 138.65 (C_q, phenyl, arom.), 131.87 131.48 (2xC_q, arom.), 128.82, 128.49, 127.06, 126.89, 126.20, 123.37, 120.28 (9xCH, arom.), 52.33 (OCH_3), 52.18 (**C**HCO), 44.85 (Ar**C**H_2N), 31.31 (Ar**C**H_2C).

Methyl (3*S*)-*N*-(naphthtalen-1-yl)carbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**4**): Prepared from (**2a**) and naphthalen-1-yl isocyanate in the same way as (**3**). After recrystallisation from a cyclohexane-hexane mixture, yield 82 % white solid, mp 140-142°C, $[\alpha]_D^{20}$ +39.6° (*c* 1, $CHCl_3$). *Anal.* Calcd for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.20; H, 5.72; N, 7.68.

^{1}H NMR (δ/ppm, $CDCl_3$): 8.01-7.92 (2H, m, arom., naphthyl), 7.82-7.74 (2H, m, arom., naphthyl), 7.61-7.50 (3H, m, arom., naphthyl), 7.35-7.21 (4H, m, arom.), 6.97 (1H, bs, NH), 4.94 (1H, d, H(1a), ^2J=15.3), 4.90 (1H, d, H(1b), ^2J=15.3), 5.48 (1H, dd, H(3), ^3J=3.2, ^3J=5.8), 3.41 (1H, dd, H(4a), ^2J=15.8, ^3J=3.2), 3.32 (1H, dd. H(4b), ^2J=15.8, ^3J=5.8), 3.70 (3H, s, OCH_3). ^{13}C NMR (δ/ppm, $CDCl_3$): 172.01 (COO), 156.28 (NCON), 134.23, 133.46, 128.19 (3xC_q, naphthyl), 132.02, 131.60 (2xC_q, arom.), 128.67, 128.61, 127.18, 126.97, 126.35, 126.25, 125.91, 125.78, 125.571, 121.43, 121.18 (11xCH arom.), 52.62 (**C**HCO), 52.47 (OCH_3), 45.15 (Ar**C**H_2N), 31.39 (Ar**C**H_2C).

Methyl (3*S*)-*N*-[(1*S*)-1-methylbenzyl]carbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**5**): Prepared from **2a** and (*S*)-1-methylbenzyl isocyanate in the same way as **3**. After recrystallisation from a cyclohexane-hexane mixture yield 87 %, white solid, mp 137-139°C, $[\alpha]_D^{20}$ +88.9° (*c* 1, $CHCl_3$). According to the NMR spectra the product was isolated in 100 % diastereoisomeric purity. *Anal*. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 71.13; H, 6.75; N, 8.44.

^{1}H NMR (δ/ppm, $CDCl_3$): 7.36-7.08 (9H, m, arom.), 4.61 (1H, d, H(1a) ^2J=14.2), 4.52 (1H, d, H(1b), ^2J=14.2), 5.34 (1H, dd, H(3), ^3J=3.0, ^3J=6.0), 3.57 (3H, s, OCH_3), 3.24 (1H, dd, H(4a), ^2J=15.8, ^3J=3.0), 3.12 (1H, dd, H(4b), ^2J=15.8, ^3J=6.0), 5.08 (1H, m, NCH, ^3J=7.0), 4.93 (1H, d, NH, ^3J=7.0), 1.55 (3H, d, CCH_3, ^3J=7.0). ^{13}C NMR (δ/ppm, $CDCl_3$): 172.28 (COO), 156.94 (NCON), 144.25 (C_q, phenyl, arom.), 131.89, 131.55 (2xC_q, arom.), 128.56, 128.56, 127.11, 126.88, 126.76, 126.19, 126.07 (9xCH, arom.), 52.17 (OCH_3), 51.86 (**C**HCO), 50.24 (Ar**C**HNH), 44.44 (Ar**C**H_2N), 31.30 (Ar**C**H_2C), 22.59 (CH**C**H_3).

Methyl (3*S*)-*N*-cyclohexylcarbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**6**): Prepared from **2a** and cyclohexyl isocyanate in the same way as **3**. After recrystallisation from a cyclohexane-hexane mixture yield 91 %, white solid mp 101-105°C, $[\alpha]_D^{20}$ +47.2° (*c* 1, $CHCl_3$). *Anal*. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.38; H, 7.69; N, 8.94.

^{1}H NMR (δ/ppm, $CDCl_3$): 7.23-7.17 (4H, m, arom.), 4.57 (1H, bs, NH), 4.62 (1H, d, H(1a), ^2J=14.4), 4.54 (1H, d, H(1b), ^2J=14.4), 5.40 (1H, dd, H(3), ^3J=2.9, ^3J=5.9), 3.31 (1H, dd, H(4a), ^2J=15.8, ^3J=2.9), 3.20 (1H, dd, H(4b), ^2J=15.8, ^3J=5.9), 3.63 (3H, s, OCH_3), 3.83-3.73 (1H, m, CHN, cyclohexyl), 2.08-2.03 (2H, m, cyclohexyl), 1.80-1.66 (4H, m, cyclohexyl), 1.46-1.41 (2H, m, cyclohexyl), 1.26-1.19 (2H, m, cyclohexyl). ^{13}C NMR (δ/ppm, $CDCl_3$): 172.38 (COO), 157.03 (NCON), 131.98, 131.43 (2xC_q, arom.), 128.53, 126.82, 126.71, 126.17 (4xCH, arom.), 52.12 (OCH_3), 51.82 (**C**HCO), 49.59 (CHN, cyclohexyl), 44.41 (Ar**C**H_2N), 31.37 (Ar**C**H_2C), 33.92, 33.90, 25.63, 25.03, 25.00 (5xCH_2, cyclohexyl).

(10a*S*)-10,10a-Dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**7a**):

Procedure 1: A saturated aqueous solution of KOCN (0.81 g, 10 mmol) was added to hydrochloride of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2a**) (1.14 g, 5 mmol) with stirring. After 12 h stirring separated white crystals, which were collected by suction and washed with H_2O (2 × 30 mL).

Yield 0.93 g (92%), white solid, $[\alpha]_D^{20}$ –353.4° (*c* 1, $CHCl_3$), mp 229-231°C (ref.[3]: mp 227-230°C). *R*-Enantiomer content (HPLC): 0.3 % (Figure 3).

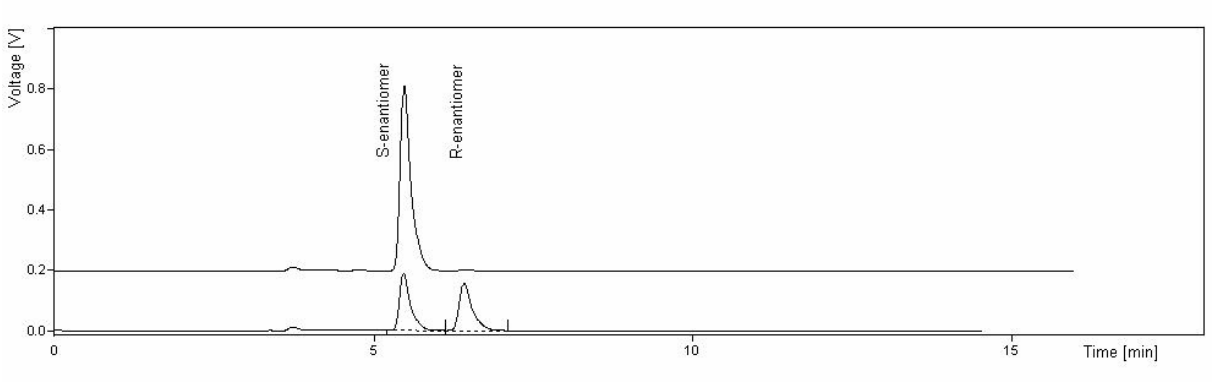


Figure 3. Chiral HPLC separation of 10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**7**) enantiomers. Lower chromatogram represents separation of racemic mixture and upper chromatogram represents the enantiomeric impurity in (10a*S*)-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**7a**). HPLC conditions are described in Experimental section.

Procedure 2: A solution of nitrourea (0.58 g, 5.52 mmol) and NEt_3 (0.64 mL, 4.57 mmol) in H_2O (20 mL) was added to hydrochloride of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline- 3-carboxylate (**2a**) (0.5 g, 2.2 mmol) with stirring, whereupon the reaction mixture was heated to boil for 10 h. The product gradually separated during the heating. Yield 0.4 g (90 %) white crystalline solid, $[\alpha]_D^{20}$ –348.9° (*c* 1, $CHCl_3$), mp 228-230°C. *Anal*. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.52; H, 5.10; N, 13.76. ^{1}H NMR (δ/ppm, $CDCl_3$) (For numbering of atoms in NMR spectra of compounds (**7**)-(**23**), carbon C(10a) is denoted as C(11) and the corresponding hydrogen as H(11). H(10a) and H(10b) are diastereotopic protons at carbon C(10).): 8.41 (1H, bs, NH), 7.29-7.14 4H, m, arom.), 5.02 (1H, d, H(5a), ^2J=16.7), 4.41 (1H, d, H(5b), ^2J=16.7), 4.15 (1H, dd, H(11), ^3J=4.7, ^3J=11.9), 3.27 (1H, dd, H(10a), ^2J=15.7, ^3J=4.7), 2.94 (1H, dd, H(10b), ^2J=15.7, ^3J=11.9). ^{13}C NMR (δ/ppm, $CDCl_3$): 173.17 (C**C**ON), 154.88 (NCON), 130.85 130.66 (2xC_q, arom.), 129.48, 127.42, 127.26, 126.67 (4xCH, arom.), 55.96 (**C**HCO), 41.45 (Ar**C**H_2N), 30.70 (Ar**C**H_2C).

(10a±)-10,10a-Dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**7b**): Prepared from racemic ester (**2b**) by Procedure 1. Yield 95%, mp 218-220°C. The ^{1}H and ^{13}C NMR spectra were identical with those of compound (**7a**).

A solution of methyl (3*S*)-*N*-[(1*S*)-1-methylbenzyl]carbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**5**) (0.1 g, 0.30 mmol) in CF_3COOH (10 mL) was stirred at rt for 4 h, whereupon the acid was removed in vacuum without heating. Yield 0.05 g (84 %), (10a*S*)-10,10a-dihydroimidazo[1,5-*b*] isoquinoline-1,3(2*H*,5*H*)-dione (**7a**), $[\alpha]_D^{20}$ –350.5° (*c* 1, $CHCl_3$), mp 228-230°C (ref.[3]: mp 227-230°C).

(10a*S*)-2-Phenyl-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**8a**):

Procedure 1: A solution of methyl (3*S*)-*N*-phenylcarbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**3**) (0.3 g, 0.97 mmol) in CF_3COOH (10 mL) was stirred at rt for 4 h, whereupon all of the liquid was removed in vacuum without heating. The evaporation residue was washed with H_2O (2 × 10 mL) and dried to give 0.26 g (96 %) white solid, mp 170-171°C, $[\alpha]_D^{20}$ –228.1 (*c* 1, $CHCl_3$).

Procedure 2: A suspension of hydrochloride of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2a**) (2 g, 8.8 mmol) in dry CH_2Cl_2 (70 mL) was vigorously stirred, cooled, and treated with dry NEt_3 (2.55 mL, 18.3 mmol) followed by phenyl isocyanate (2.39 mL, 22 mmol) added at once. The stirring at rt was continued 14 h, whereupon the reaction mixture was concentrated to a volume of 5 ml. The precipitate formed after addition of Et_2O (60 mL) was collected by suction on a sintered glass filter and subsequently washed with H_2O (2 × 20 mL), 5 % aqueous hydrochloric acid (2 × 20 mL), and H_2O (2 × 20 mL). The residue was recrystallised from a benzene-cyclohexane mixture to give 2.33 g (95%) white solid, mp 171-172°C, $[\alpha]_D^{20}$ –229.5 (*c* 1, $CHCl_3$). *R*-Enantiomer content (HPLC): 3.5 %.

Procedure 3: A solution of methyl (3*S*)-*N*-phenylcarbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**3**) (0.3 g, 0.97 mmol) and dry NEt_3 (0.02 mL, 0.14 mmol) in CH_3OH (10 mL) was stirred at rt for 14 h, whereupon the solvent was evaporated, and the evaporation residue was washed with 5 % aqueous hydrochloric acid (10 mL) and H_2O (10 mL). After recrystallisation from a benzene-cyclohexane mixture, yield 0.25 g (93%) white solid, mp 165-169°C, $[\alpha]_D^{20}$ –104.8 (*c* 1, $CHCl_3$). *Anal*. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.65; H, 5.21; N, 10.13.

^{1}H NMR (δ/ppm, $CDCl_3$): 7.47-7.34 (5H, m, arom., phenyl), 7.28-7.16 (4H, m, isoquin., arom.), 5.12 (1H, d, H(5a), ^2J=16.7), 4.51 (1H, d, H(5b), ^2J=16.7), 4.27 (1H, dd, H(11), ^3J=4.7, ^3J=11.9), 3.38 (1H, dd, H(10a), ^2J=15.5, ^3J=4.7), 3.01 (1H, dd, H(10b), ^2J=15.5, ^3J=11.9). ^{13}C NMR (δ/ppm $CDCl_3$): 171.65 (C**C**ON), 154.29 (NCON), 131.55 (C_q, phenyl, arom.), 130.95, 130.77 (2xC_q, isoquin.), 129.05, 125.98 (2x2xCH-phenyl, arom.), 129.44, 128.11, 127.40, 127.24, 126.64 (5xCH, arom.), 54.59 (**C**HCO), 41.83 (Ar**C**H_2N), 30.97 (Ar**C**H_2C).

(10a±)-2-Phenyl-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**8b**): Prepared from **2b** and phenyl isocyanate in the same way as **8a** by Procedure 2. Yield 95%, mp 157-159°C. The ^{1}H and ^{13}C NMR spectra ($CDCl_3$) were identical with those of compound (**8a**).

(10a*S*)-2-Methyl-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**9**):

A suspension of hydrochloride of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline- 3-carboxylate (**2a**) (0.5 g, 2.20 mmol) in dry CH_2Cl_2 (50 mL) was vigorously stirred, cooled, and treated with dry NEt_3 (0.64 mL, 4.57 mmol) followed by fast addition of methyl isocyanate (0.31 g, 5.50 mmol). After 14 h stirring at rt, the reaction mixture was concentrated to a volume of 5 mL. The triethylammonium chloride separated by addition of Et_2O (50 mL) was collected by suction, and the ethereal filtrate was extracted with H_2O (20 mL), 5% aqueous hydrochloric acid (20 mL), and H_2O (20 mL). Et_2O was distilled off to leave an oily

residue, which according to ^{1}H NMR contained 37 % (10a*S*)-2-methyl-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**9**) and 63 % methyl (3*S*)-*N*-methylcarbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate. This mixture was dissolved in CF_3COOH (10 mL), and the solution was stirred at rt for 4 h, whereupon the acid was distilled off in vacuum without heating. The evaporation residue was washed with H_2O (2 × 10 mL) and recrystallised from a cyclohexane-hexane mixture. Yield 0.42 g (89%), white solid, mp 136-138°C, $[\alpha]_D^{20}$ –325.1° (*c* 1, $CHCl_3$). *Anal*. Calcd: $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.59; H, 5.75; N, 12.71.

^{1}H NMR (δ/ppm, $CDCl_3$): 7.27-7.18 (4H, m, arom.), 5.02 (1H, d, H(5a), ^2J=16.7), 4.43 (1H, d, H(5b), ^2J=16.7), 4.09 (1H, dd, H(11), ^3J=4.5, ^3J=11.5), 3.27 (1H, dd, H(10a), ^2J=15.6, ^3J=4.5), 2.84 (1H, dd, H(10b), ^2J=15.6, ^3J=11.5), 3.08 (3H, s, NCH_3). ^{13}C NMR (δ/ppm, $CDCl_3$): 172.92 (C**C**ON), 155.56 (NCON), 130.99, 130.78 (2xC_q, arom.), 129.32, 127.25, 127.11, 126.55 (4xCH, arom.), 54.74 (**C**HCO), 41.61 (Ar**C**H_2N), 30.70 (Ar**C**H_2C), 24.65 (NCH_3).

(10a*S*)-2-(Naphthalen-1-yl)-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**10**): Prepared from **4** by Procedure 1 and from **2a** and naphthalen-1-yl isocyanate in the same way as **8a** by Procedure 2. The yield of brownish product obtained by Procedure 1 was practically quantitative, that in Procedure 2 was 96 %. According to NMR, the product is a mixture of two diastereoisomers. Due to the hindered rotation around the N(2)–C(Ar) bond, the molecule exhibits atropoisomerism. The proportion of the diastereoisomers calculated from the integral intensities is **I**/**II** = 5 : 4. Mp 213-215°C, $[\alpha]_D^{20}$ –117.0° (*c* 1, $CHCl_3$). *Anal*. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 77.04; H, 4.98; N, 8.51.

Diastereoisomer **I**: ^{1}H NMR (δ/ppm, $CDCl_3$): 7.92-7.17 (11H, m, arom.), 5.15 (1H, d, H(5a), ^2J=16.8), 4.48 (1H, d, H(5b), ^2J=16.8), 4.33 (1H, dd, H(11), ^3J=4.7, ^3J=11.6), 3.43 (1H, dd, H(10a), ^2J=15.4, ^3J=4.7), 3.16 (1H, dd, H(10b), ^2J=15.4, ^3J=11.6). ^{13}C NMR (δ/ppm, $CDCl_3$): 172.28 (C**C**ON), 154.70 (NCON), 130.96, 130.69, (2xC_q, isoquin., arom.), 134.38, 129.85 a 127.66 (3xC_q, arom.), 130.03, 129.49, 128.58, 127.45, 127.26, 127.15, 126.67, 126.64, 126.46, 125.36 121.75 (11xCH, arom.), 55.10 (**C**HCO), 41.95 (Ar**C**H_2N), 31.52 (Ar**C**H_2C).

Diastereoisomer **II**: ^{1}H NMR ((δ/ppm, $CDCl_3$): 7.92-7.17 (11H, m, arom.), 5.10 (1H, d, H(5a), ^2J=17.0), 4.40 (1H, d, H(5b), ^2J=17.0), 4.40 (1H, dd, H(11), ^3J=4.6, ^3J=11.6), 3.36 (1H, dd, H(10a), ^2J=15.4, ^3J=4.6), 3.04 (1H, dd, H(10b), ^2J=15.4, ^3J=11.6). ^{13}C NMR (δ/ppm, $CDCl_3$): 172.30 (C**C**ON), 154.78 (NCON), 131.14, 130.69 (2xC_q, isoquin., arom.), 134.40, 129.82 a 127.70 (3xC_q, arom.), 129.96, 129.41, 128.54, 127.41, 127.24, 127.10, 126.74, 126.67, 126.50, 125.35, 122.15 (11xCH, arom.), 54.98 (**C**HCO), 41.92 (Ar**C**H_2N), 31.10 (Ar**C**H_2C).

(10a*S*)-2-Cyclohexyl-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**11**): Prepared from methyl (3*S*)-*N*-cyclohexylcarbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**6**) by Procedure 1. The

yield was practically quantitative; m.p. of white solid 126-128°C, $[\alpha]_D^{20}$ –167.9° (*c* 1, $CHCl_3$). *Anal*. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.90; H, 7.05; N, 10.15.

^{1}H NMR (δ/ppm, $CDCl_3$): 7.25-7.15 (4H, m, arom.), 4.98 (1H, d, H(5a), ^2J=16.5), 4.36 (1H, d, H(5b), ^2J=16.5), 3.97 (1H, dd, H(11), ^3J=4.6 Hz, ^3J=11.8), 3.22 (1H, dd, H(10a), ^2J=15.5, ^3J=4.6 Hz), 2.77 (1H, dd H(10b), ^2J=15.5, ^3J=11.8), 3.97-3.91 (1H, m, CHN, cyclohexyl), 2.15-2.12 (2H, m, cyclohexyl), 1.83-1.63 (4H, m, cyclohexyl), 1.32-1.22 (4H, m, cyclohexyl). ^{13}C NMR (δ/ppm, $CDCl_3$): 172.89 (C**C**ON), 155.43 (NCON), 131.22, 130.96 (2xC_q, arom.), 129.34, 127.22, 127.18, 126.57 (4xCH, arom.), 54.10 (**C**HCO), 51.44 (NCH-cyclohexyl), 41.52 (Ar**C**H_2N), 30.95 (Ar**C**H_2C), 29.43, 29.29, 26.02, 25.17, 25.05 (cyclohexyl).

(10a*S*)-2-[(1*S*)-1-methylbenzyl]-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**12**): Prepared from carbamoyl derivative (**5**) by Procedure 3 with the yield 93%. The integral intensities indicate the proportion of diastereoisomers in the product isolated to be **I**/**II** = 2/1, mp 149-156°C, $[\alpha]_D^{20}$ +27.2° (*c* 1, $CHCl_3$). The ring closure of compound (**5**) by means of catalytic amount of NEt_3 in ether solution at r.t. for 3 days gave hydantoin (**12**) in quantitative yield. The ^{1}H a ^{13}C NMR spectra only exhibit the signals of diastereoisomer **I**, mp 139-140°C, $[\alpha]_D^{20}$ +68.3° (*c* 1, $CHCl_3$). For the mixture of diastereoisomers: *Anal*. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.23; H, 6.08; N, 9.00.

Diastereoisomer **I**: ^{1}H NMR (δ/ppm, $CDCl_3$): 7.48-7.25 (5H, m, phenyl), 7.27-7.14 (4H, m, arom., isoquin.), 5.38 (1H, q, C**H**CH_3, ^3J=7.3), 4.97 (1H, d, H(5a), ^2J=16.9), 4.35 (1H, d, H(5b), ^2J=16.9), 4.01(1H, dd, H(11),), ^3J=4.5, ^3J=11.7), 3.20 (1H, dd, H(10a), ^2J=15.5, ^3J=4.5), 2.74 (1H, dd, H(10b), ^2J=15.5, ^3J=11.7), 1.87 (3H, d, CHC**H**$_3$, ^3J=7.3). ^{13}C NMR (δ/ppm $CDCl_3$): 172.64 (C**C**ON), 155.15 (NCON), 140.08 (C_q, phenyl, arom.), 131.09 130.82 (2xC_q, isoquin., arom.), 128.45, 127.27 (2x2xCH, phenyl, arom.), 129.38, 127.70, 127.33, 127.10, 126.57 (5xCH, arom.), 54.18 (**C**HCO), 50.36 (Ar**C**HNH), 41.51 (Ar**C**H_2N), 30.84 (Ar**C**H_2C), 17.25 (CH**C**H_3).

Diastereoisomer **II**: ^{1}H NMR (δ/ppm, $CDCl_3$): 7.48-7.25 (5H, m, phenyl), 7.27-7.14, (4H, m, arom., isoquin.), 5.39 (1H, q, C**H**CH_3, ^3J=7.3), 4.97 (1H, d, H(5a), ^2J=16.9), 4.35 (1H, d, H(5b), ^2J=16.9), 3.98 (1H, dd, H(11), ^3J=4.6, ^3J=11.6), 3.23 (1H, dd, H(10a), ^2J=15.3, ^3J=4.6), 2.78 (1H, dd, H(10b), ^2J=15.3, ^3J=11.6), 1.87 (3H, d, CHC**H**$_3$, ^3J=7.3). ^{13}C NMR (δ/ppm, $CDCl_3$): 172.61 (C**C**ON), 155.15 (NCON), 140.05 (C_q, phenyl), 131.09, 130.82 (2xC_q, isoquin., arom.), 128.45, 127.27 (2x2xCH, phenyl), 129.38, 127.73, 127.33, 127.10, 126.57 (5xCH, arom.), 54.18 (**C**HCO), 50.30 (Ar**C**HNH), 41.47 (Ar**C**H_2N), 30.88 (Ar**C**H_2C), 17.09 (CH**C**H_3).

(10a*S*)-2-(4-Methylphenyl)-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**13**): Prepared from ester (**2a**) and 4-methylphenyl isocyanate in the same way as compound (**8a**) by Procedure 2.

Yield 98%, mp 189-191°C, $[\alpha]_D^{20}$ –223.0° (*c* 1, $CHCl_3$). *Anal*. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 73.98; H, 5.64; N, 9.47.

^{1}H NMR (δ/ppm, $CDCl_3$): 7.33-7.18 (8H, m, arom.), 5.09 (1H, d, H(5a), ^2J=16.9), 4.48 (1H, d, H(5b), ^2J=16.9), 4.23 (1H, dd, H(11), ^3J=4.5, ^3J=11.7), 3.34 (1H, dd, H(10a), ^2J=15.7, ^3J=4.5), 2.98 (1H, dd, H(10b), ^2J=15.7, ^3J=11.7), 2.37 (3H, s, $ArCH_3$). ^{13}C NMR (δ/ppm, $CDCl_3$): 171.80 (C**C**ON), 154.48 (NCON), 138.21, 128.87 (2xC_q, 4-methylphenyl, arom.), 131.02, 130.83 (2xC_q, isoquin., arom.), 129.71, 126.65 (2x2xCH-4-methylphenyl, arom.), 129.45, 127.38, 127.23, 125.92 (4xCH-isoquin., arom.), 54.61 (**C**HCO), 41.83 (Ar**C**H_2N), 31.00 (Ar**C**H_2C), 21.15 (Ar**C**H_3).

(10a*S*)-2-(3-Methylphenyl)-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**14**): Prepared from ester (**2a**) and 3-methylphenyl isocyanate in the same way as compound (**8a**) by Procedure 2. Yield 96%, mp 190-192°C, $[\alpha]_D^{20}$ –208.1° (*c* 1, $CHCl_3$). *Anal*. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 73.75; H, 5.75; N, 9.49.

^{1}H NMR (δ/ppm, $CDCl_3$): 7.36-7.17 (8H, m, arom.), 5.10 (1H, d, H(5a), ^2J=16.7), 4.49 (1H, d, H(5b), ^2J=16.7), 4.24 (1H, dd, H(11), ^3J=4.5, ^3J=11.9), 3.35 (1H, dd, H(10a), ^2J=15.6 Hz, ^3J=4.5), 2.99 (1H, dd, H(10b), ^2J=15.6, ^3J=11.9), 2.38 (3H, s, $ArCH_3$). ^{13}C NMR (δ/ppm, $CDCl_3$): 171.79 (C**C**ON), 154.48 (NCON), 139.13, 131.36 (2xC_q, 3-methylphenyl, arom.), 131.00, 130.81 (2xC_q, isoquin., arom.), 129.46, 129.12, 128.91, 127.42, 127.27, 126.76, 126.67, 123.25 (8xCH, arom.), 54.66 (**C**HCO), 41.86 (Ar**C**H_2N), 31.02 (Ar**C**H_2C), 21.34 (Ar**C**H_3).

(10a*S*)-2-(4-Chlorophenyl)-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**15**): Prepared from ester (**2a**) and 4-chlorophenyl isocyanate in the same way as compound (**8a**) by Procedure 2. Yield 90%, mp 232-234°C, $[\alpha]_D^{20}$ –212.4° (*c* 1, $CHCl_3$). *Anal*. Calcd for $C_{17}H_{13}N_2O_2Cl$: C, 65.29; H,4.19; N, 8.96; Cl, 11.34. Found: C, 65.24; H, 4.19, N, 8.92; Cl, 11.14.

^{1}H NMR (δ/ppm, $CDCl_3$): 7.42-7.21 (8H, m, arom.), 5.09 (1H, d, H(5a), ^2J=16.9), 4.49 (1H, d, H(5b), ^2J=16.9), 4.24 (1H, dd, H(11), ^3J=4.7, ^3J=11.9), 3.35 (1H, dd, H(10a), ^2J=15.5, ^3J=4.7 Hz), 2.98 (1H, dd, H(10b), ^2J=15.5, ^3J=11.9). ^{13}C NMR (δ/ppm, $CDCl_3$): 171.40 (C**C**ON), 153.93 (NCON), 137.78, 130.14 (2xC_q, 4-chlorophenyl), 130.82, 130.65 (2xC_q, isoquin., arom.), 129.24, 127.06 (2x2xCH, 4-chlorophenyl), 129.48, 127.50, 127.35, 126.68 (4xCH-isoquin., arom.), 54.64 (**C**HCO), 41.88 (Ar**C**H_2N), 30.96 (Ar**C**H_2C).

(10a*S*)-2-(2,4-Dichlorophenyl)-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**16**): Prepared from ester (**2a**) and 2,4-dichlorophenyl isocyanate in the same way as compound (**8a**) by Procedure 2. After recrystallisation from a benzene-cyclohexane mixture, yield 91%, mp 157-161°C, $[\alpha]_D^{20}$ –135.3° (*c* 1, $CHCl_3$). *Anal*. Calcd for $C_{17}H_{12}N_2O_2Cl_2$: C, 58.81; H, 3.48; N, 8.07; Cl, 20.42. Found: C, 58.63; H, 3.59; N, 8.25; Cl, 20.36.

The product is a mixture of two diastereoisomers. Due to the hindered rotation around the N(2)–C(Ar) bond, the molecule exhibits atropoisomerism. According to the integral intensities, the proportion of isomers in the mixture isolated is **I**/**II** = 7/5.

Diastereoisomer **I**: ^{1}H NMR (δ/ppm, $CDCl_3$): 7.53-7.19 (7H, m, arom.), 5.08 (1H, d, H(5a), ^2J=17.0), 4.48 (1H, d, H(5b), ^2J=17.0), 4.27 (1H, dd H(11), ^3J=4.5, ^3J=11.7), 3.36 (1H, dd, H(10a), ^2J=15.4, ^3J=4.5), 3.06 (1H, dd, H(10b), ^2J=15.4, ^3J=11.7). ^{13}C NMR (δ/ppm, $CDCl_3$): 170.98 (C**C**ON), 153.45 (NCON), 136.28, 133.94 (2xC_q, isoquin., arom.), 131.23, 130.34, 129.52, 128.25, 127.50, 127.33, 126.63 (7xCH, arom.), 128.70, 127.89, 127.83 (3xC_q, arom.), 55.16 (**C**HCO), 41.84 (Ar**C**H_2N), 31.13 (Ar**C**H_2C).

Diastereoisomer **II**: ^{1}H NMR (δ/ppm, $CDCl_3$): 7.55-7.19 (7H, m, arom.), 5.13 (1H, d, H(5a), ^2J=16.7), 4.52 (1H, d, H(5b), ^2J=16.7), 4.34 (1H, dd, H(11), ^3J=4.7, ^3J=11.6), 3.36 (1H, dd, H(10a), ^2J=15.8, ^3J=4.7), 3.02 (1H, dd, H(10b), ^2J=15.8, ^3J=11.6). ^{13}C NMR (δ/ppm, $CDCl_3$): 170.98 (C**C**ON), 153.45 (NCON), 136.15, 133.77 (2xC_q, isoquin., arom.), 131.10, 130.41, 129.45, 128.09, 127.53, 127.36, 126.68 (7xCH, arom.), 128.69, 127.95, 127.70 (3xC_q, arom.), 54.96 (**C**HCO), 41.97 (Ar**C**H_2N), 30.91 (Ar**C**H_2C).

(10a*S*)-2-(4-Methoxyphenyl)-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**17**): Prepared from ester (**2a**) and 4-methoxyphenyl isocyanate in the same way as compound (**8a**) by Procedure 2. Yield 87%, mp 226-228°C, $[\alpha]_D^{20}$ –206.6° (*c* 1, $CHCl_3$). *Anal*. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.17; H, 5.32; N, 8.83.

^{1}H NMR (δ/ppm, $CDCl_3$): 7.32 (2H, m, methoxyphenyl), 6.97 (2H, m, methoxyphenyl), 7.29-7.18 (4H, m, isoquin., arom.), 5.09 (1H, d, H(5a), ^2J=16.9), 4.50 (1H, d, H(5b), ^2J=16.9), 4.23 (1H, dd, H(11), ^3J=4.6, ^3J= 11.9), 3.34 (1H, dd, H(10a), ^2J=15.6, ^3J=4.6), 2.98 (1H, dd, H(10b), ^2J=15.6, ^3J=11.9), 3.81 (3H, s, OCH_3). ^{13}C NMR (δ/ppm, $CDCl_3$): 171.94 (C**C**ON), 154.60 (NCON), 159.21, 124.11 (2xC_q, methoxyphenyl, arom.), 130.99, 130.79 (2xC_q isoquin., arom.), 127.45, 114.41 (arom, 2x2xCH, methoxyphenyl, arom.), 129.45, 127.39, 127.24, 126.65 (4xCH, isoquin., arom.), 55.47 (OCH_3), 54.59 (**C**HCO), 41.82 (Ar**C**H_2N), 30.99 (Ar**C**H_2C).

(10a*S*)-2-(5-Chloro-2-methoxyphenyl)-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**18**): Prepared from ester (**2a**) and 5-chloro-2-methoxyphenyl isocyanate in the same way as compound (**8a**) by Procedure 2. Yield 85%, mp 205-207°C, $[\alpha]_D^{20}$ –138.8° (*c* 1, $CHCl_3$). *Anal*. Calcd for $C_{18}H_{15}N_2O_3Cl$: C, 63.07; H, 4.41; N, 8.17, Cl, 10.34. Found: C, 63.17; H, 4.45; N, 8.02; Cl, 10.46.

The NMR analysis showed that the product is a mixture of two diastereoisomers. Due to the hindered rotation around the N–C(Ar) bond, the molecule exhibits atropoisomerism. The proportion of isomers in the mixture isolated is **I**/**II** = 6/5.

Diastereoisomer **I**: ^{1}H NMR (δ/ppm, $CDCl_3$): 7.38-6.90 (7H, m, arom.), 5.06 (1H, d, H(5a), ^2J=16.7), 4.50 (1H, d, H(5b), ^2J=16.7), 4.22 (1H, dd, H(11), ^3J=4.5, ^3J=11.7), 3.33 (1H, dd, H(10a), ^2J=15.3, ^3J=4.5 Hz), 3.01 (1H, dd, H(10b), ^2J=15.3, ^3J=11.7), 3.76 (3H, s, OCH_3). ^{13}C NMR (δ/ppm, $CDCl_3$): 171.71 (C**C**ON),

154.00 (NCON), 131.00, 130.78 (2xC_q, isoquin., arom.), 130.61, 129.92, 129.41, 127.31, 127.12, 126.58, 112.96 (7xCH, arom.), 153.97, 125.38, 120.87 (3xC_q, arom.), 56.13 (O**C**H_3), 54.89 (**C**HCO), 41.67 (Ar**C**H_2N), 30.99 (Ar**C**H_2C).

Diastereoisomer **II**: ^{1}H NMR (δ/ppm, $CDCl_3$): 7.38-6.90 (7H, m, arom.), 5.11(1H, d, H(5a), ^2J=16.6), 4.45 (1H, d, H(5b), ^2J=16.6), 4.48 (1H, dd, H(11), ^3J=4.6, ^3J=11.7), 3.33 (1H, dd, H(10a), ^2J=14.9, ^3J=4.6), 2.98 (1H, dd, H(10b), ^2J=14.9, ^3J=11.7), 3.82 (3H, s, OCH_3). ^{13}C NMR (δ/ppm, $CDCl_3$): 171.51 (C**C**ON), 154.13 (NCON), 130.90, 130.66 (2xC_q, isoquin., arom.), 130.48, 129.73, 129.38, 127.34, 127.18, 126.59, 113.08 (7xCH, arom.), 153.94, 125.29, 120.72 (3xC_q, arom.), 56.15 (O**C**H_3), 54.84 (**C**HCO), 41.85 (Ar**C**H_2N), 30.92 (Ar**C**H_2C).

(10a*S*)-2-(3-Chloro-4-ethoxyphenyl)-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione (**19**): Prepared from ester (**2a**) and 3-chloro-4-ethoxyphenyl isocyanate in the same way as compound (**8a**) by Procedure 2. Yield 93%, mp 208-209°C, $[\alpha]_D^{20}$ –174.2° (*c* 1, $CHCl_3$). *Anal*. Calcd for $C_{19}H_{17}N_2O_3Cl$: C, 63.96; H, 4.80; N, 7.85; Cl, 9.94. Found: C, 63.86; H, 4.93; N, 7.73; Cl, 9.87.

^{1}H NMR (δ/ppm, $CDCl_3$): 7.46 (1H, d, H(2′), ^4J=2.5), 7.27 (1H, dd, H(6′),^3J=8.8, ^4J=2.5), 7.30-7.17 (4H, m, isoquin., arom.), 6.96 (1H, d, H(5′), ^3J=8.8), 5.07 (1H, d, H(5a), ^2J=16.9), 4.47 (1H, d, H(5b), ^2J=16.9), 4.22 (1H, dd, H(11), ^3J=4.6, ^3J=11.7), 3.33 (1H, dd, H(10a), ^2J= 15.6, ^3J=4.6), 2.96 (1H, dd, H(10b), ^2J= 15.6, ^3J=11.7), 4.11 (2H, q, OCH_2, ^3J=7.0), 1.46 (3H, t, ^3J=7.0). ^{13}C NMR (δ/ppm, $CDCl_3$): 171.60 (C**C**ON), 154.21 (NCON), 130.80, 130.63 (2xC_q, isoquin., arom.), 129.43, 128.04, 127.42, 127.27, 126.63, 125.49, 112.98 (7xCH, arom.), 154.15, 124.23, 123.01 (3xC_q, arom.), 54.91 (OCH_2), 54.57 (**C**HCO), 41.81 (Ar**C**H_2N), 30.91 (Ar**C**H_2C), 14.58 (CH_3).

(10a*S*)-2-Phenyl-3-thioxo-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline-1-one (**20a**): A suspension of hydrochloride of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2a**) (0.50 g, 2.20 mmol) in dry Et_2O (20 mL) was vigorously stirred, cooled, and treated with dry NEt_3 (0.22 g, 2.18 mmol) followed by fast addition of phenyl isothiocyanate (0.30 g, 2.22 mmol) in dry CH_2Cl_2 (2 mL). After 3 h vigorous stirring, the solid portion was collected by suction and washed with Et_2O (5 mL) and H_2O (10 mL). The crude product was purified by flash chromatography (silica gel 60 μm, CH_2Cl_2). The residue was recrystallised from a benzene-cyclohexane mixture to give 0.59 g (91%), yellow solid, mp 226-229°C, $[\alpha]_D^{20}$ –323.7° (*c* 1, $CHCl_3$). *Anal*. Calcd for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52; S, 10.89. Found: C, 69.53; H, 4.75; N, 9.36; S, 10.78.

^{1}H NMR (δ/ppm, $CDCl_3$): 7.51-7.35, (5H, m, phenyl), 7.26-7.19 (4H, m, isoquin., arom.), 5.48 (1H, d, H(5a), ^2J= 17.6), 4.61 (1H, d, H(5b), ^2J= 17.6), 4.32 (1H, dd, H(11), ^3J=4.5, ^3J=12.2), 3.33 (1H, dd, H(10a), ^2J=15.6, ^3J=4.5), 3.02 (1H, dd, H(10b), ^2J=15.6, ^3J=12.2). ^{13}C NMR (δ/ppm, $CDCl_3$): 180.87 (CS), 172.39 (CO), 128.24 (C_q, phenyl,), 130.86, 130.30 (2xC_q, isoquin., arom.), 129.13, 128.34 (2x2xCH, phenyl), 129.27, 129.20, 127.65, 127.41, 126.74 (5xCH, arom.), 57.86 (**C**HCO), 46.24 (Ar**C**H_2N), 30.92 (Ar**C**H_2C).

(10a±)-2-Phenyl-3-thioxo-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline-1-one (**20b**): Prepared from ester (**2a**) and phenyl isothiocyanate in the same way as compound (**8a**) by Procedure 2. Yield 89%, mp 197-199°C, (benzene-cyclohexane), (ref.[18] mp 214-215°C, acetone). The ^{1}H and ^{13}C NMR spectra ($CDCl_3$) were identical with those of compound (**20a**).

(10a*S*)-2-Methyl-3-thioxo-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline-1-one (**21a**): Prepared from ester (**2a**) and methyl isothiocyanate in the same way as compound (**20a**). Compound (**21a**) is soluble in Et_2O and was isolated from the ethereal solution by distilling off the solvent until dry. After recrystallisation from a cyclohexane-hexane mixture yield 82 %, yellow solid mp 192-193°C, $[\alpha]_D^{20}$ –156.3° (*c* 1, $CHCl_3$). *Anal*. Calcd for $C_{12}H_{12}N_2OS$: C, 62.04; H, 5.21; N, 12.06; S, 13.80. Found: C, 62.29; H, 5.14; N, 11.88; S, 13.84.

^{1}H NMR (δ/ppm, $CDCl_3$): 7.33-7.21 (4H, m, arom.), 5.49 (1H, d, H(5a), ^2J=17.6), 4.63 (1H, d, H(5b), ^2J=17.6), 4.17 (1H, dd, H(11), ^3J=4.7, ^3J=12.7), 3.35 (1H, dd, H(10a), ^2J=15.9, ^3J=4.7), 2.93 (1H, dd, H(10b), ^2J=15.9, ^3J=12.7), 3.35 (3H, s, CH_3). ^{13}C NMR (δ/ppm, $CDCl_3$): 181.33 (CS), 173.02 (CO), 130.86, 130.30 (2xC_q, arom.), 129.18, 127.50, 127.27, 126.68 (4xCH, arom.), 57.47 (**C**HCO), 45.96 (Ar**C**H_2N), 30.62 (Ar**C**H_2C), 27.78 (CH_3).

(10a±)-2-Methyl-3-thioxo-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline-1-one (**21b**): Prepared from ester (**2a**) and methyl isothiocyanate in the same way as compound (**8a**) by Procedure 2. Yield of the yellow solid 92%, mp 162-164°C (cyclohexane-hexane), (ref.[18]: mp 175-176°C, acetone). The ^{1}H and ^{13}C NMR spectra ($CDCl_3$) were identical with those of compound (**21a**).

(10a*S*)-2-Ethyl-3-thioxo-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline-1-one (**22a**): Prepared from ester (**2a**) and ethyl isothiocyanate in the same way as compound (**20a**). Yield of the yellow solid 91%, mp 118-120°C (cyclohexane-hexane), $[\alpha]_D^{20}$ –293.8° (*c* 1, $CHCl_3$). (In the sample exhibiting $[\alpha]_D^{20}$ –209.0 (*c* 1, $CHCl_3$), the content of *R*-enantiomer determined by HPLC was 15.6 % (Figure 4), which means that the sample exhibiting $[\alpha]_D^{20}$ –293.8° (*c* 1, $CHCl_3$) contains 1.6 % of *R*-enantiomer.

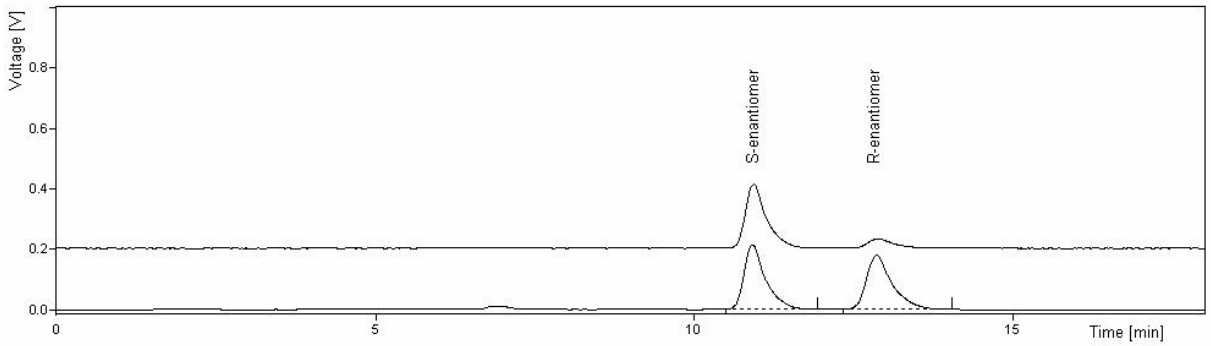


Figure 4. Chiral HPLC separation of 2-ethyl-3-thioxo-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline-1-one (**22**) enantiomers. Lower chromatogram represents separation of racemic mixture and upper chromatogram represents the mixture of enantiomers containing 84.4% (10a*S*)-2-ethyl-3-thioxo-

1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline-1-one (**22a**) and 15.6% (10a*R*) enantiomer. HPLC conditions are described in Experimental section.

Anal. Calcd for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37; S, 13.02. Found: C, 63.66; H, 5.78; N, 11.18; S, 12.86.

^{1}H NMR (δ/ppm, $CDCl_3$): 7.29-7.20 (4H, m, arom.), 5.46 (1H, d, H(5a), ^2J=17.5), 4.58 (1H, d, H(5b), ^2J=17.5), 4.15 (1H, dd, H(11), ^3J=4.6, ^3J=12.6), 3.28 (1H, dd, H(10a), ^2J=15.4, ^3J=4.6), 2.87 (1H, dd, H(10b), ^2J=15.4, ^3J=12.6), 3.94 (1H, dq, (NCHa), ^2J=13.3, ^3J=7.2), 3.90 (1H, dq, (NCHb), ^2J=13.3, ^3J=7.2), 1.26 (3H, t, CH_3, ^3J=7.2). ^{13}C NMR (δ/ppm, $CDCl_3$): 180.77 (CS), 172.84 (CO), 130.94, 130.35 (2xC_q, arom.), 129.18, 127.48, 127.26, 126.66 (4xCH, arom.), 57.36 (**C**HCO), 45.83 (Ar**C**H_2N), 36.44 (NCH_2), 30.63 (Ar**C**H_2C), 13.02 (CH_3).

(10a±)-2-Ethyl-3-thioxo-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline-1-one (**22b**): Prepared from ester (**2a**) and ethyl isothiocyanate in the same way as compound (**8a**) by Procedure 2. Yield 88% mp 122-124°C (EtOH), (ref.[18]: mp 125-126°C, EtOH). The ^{1}H and ^{13}C NMR spectra ($CDCl_3$) were identical with those of compound (**22a**).

(10a*S*)-2-Allyl-3-thioxo-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline-1-one (**23a**): Prepared from ester (**2a**) and allyl isothiocyanate in the same way as compound (**20a**). Yield of the yellow solid 83%, mp 110-113°C (cyclohexane-hexane), $[\alpha]_D^{20}$ –273.5° (*c* = 1, $CHCl_3$). *Anal*. Calcd for $C_{14}H_{14}N_2OS$: C, 65.09; H, 5.46; N, 10.85; S, 12.41. Found: C, 65.18; H, 5.60; N, 10.70; S, 12.47.

^{1}H NMR (δ/ppm, $CDCl_3$): 7.30-7.21 (4H, m, arom.), 5.86 (1H, m, CH_2C**H**=, ^3J =5.8, $^3J_{cis}$ =10.3, $^3J_{trans}$ =17.1), 5.25 (1H, m, =CH, ^2J=1.2, $^3J_{trans}$ =17.1), 5.19 (1H, m, =CH, ^2J=1.2, $^3J_{cis}$ =10.3), 4.47 (1H, m, NCHa, ^2J=1.4, ^3J=5.8), 4.46 (1H, m, NCHb, ^2J=1.4, ^3J=5.8), 5.47 (1H, d, H(5a), ^2J=17.5), 4.61 (1H, d, H(5b), ^2J=17.5), 4.19 (1H, dd, H(11), ^3J=4.6 Hz, ^3J=12.6), 3.30 (1H, dd, H(10a), ^2J=15.6, ^3J=4.6**),** 2.89 (1H, dd, H(10b), ^2J=15.6, ^3J=12.6). ^{13}C NMR (δ/ppm, $CDCl_3$): 180.70 (CS), 172.70 (CO), 130.94, 130.34 (2xC_q, arom.), 130.82 (CH_2**C**H=CH_2), 129.24, 127.58, 127.36, 126.72 (4xCH, arom.), 118.44 (CH=**C**H_2), 57.45 (**C**HCO), 46.01 (Ar**C**H_2N), 43.38 (N**C**H_2CH), 30.77 (Ar**C**H_2C).

(10a±)-2-Allyl-3-thioxo-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline-1-one (**23b**): Prepared from ester (**2a**) and allyl isothiocyanate in the same way as compound (**8a**) by Procedure 2. Yield 85%, mp 75-77°C (cyclohexane-hexane), (ref.[18]: mp 86-87°C, EtOH). The ^{1}H and ^{13}C NMR spectra ($CDCl_3$) were identical with those of compound (**23a**).

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REFERENCES

1. A. Hätzelt, S. Laschat, P. G. Jones, and J. Grunenberg, *Eur. J. Org. Chem*., 2002, **23**, 3936.
2. M. W. Kazmierski, Z. Urbanczyk-Lipkowska, and V. J. Hruby, *J. Org. Chem*., 1994, **59**, 1789.
3. D. Alagille, B. Pfeiffer, E. Scalbert, G. Ferry, J. A. Boutin, and P. Renard, *J. Enzyme Inhib. Med. Chem*., 2004, **19**, 137.
4. H. Nakagawa, N. Nihonmatsu, S. Ohta, and M. Hirobe, *Biochem. Biophys. Res. Comm*., 1996, **225**, 1027.
5. S. Vendeville, F. Goossens, M.-A. Debreu-Fontaine, V. Landry, E. Davioud-Charvet, P. Grellier, S. Scharpe, and C. Sergheraert, *Bioorg. Med. Chem.,* 2002, **10**, 1719.
6. H. Matter, M. Schudok, W. Schwab, W. Thorwart, D. Barbier, G. Billen, B. Haase, B. Neises, K.-U. Weithmann, and T. Wollmann, *Bioorg. Med. Chem*., 2002, **10**, 3529.
7. H. Matter, M. Knauf, W. Schwab, and E. F. Paulus, *J. Am. Chem. Soc*., 1998, **120**, 11512.
8. S. E. Gibson, N. Guillo, J. O. Jones, I. M . Buck, S. B. Kalindjian, S. Roberts, and M. J. Tozer, *Eur. J. Med. Chem.,* 2002, **37**, 379.
9. G. R. Marshall, *Biopolymer,* 2001, **60**, 246.
10. J. F. Corcho, M. Filizola, and J. J. Perez, *Chem. Phys. Lett*., 2000, **319**, 65.
11. E. Mannekens, M. Crisma, S. Cauwenberghe, and D. Tourwe, *Eur. J. Org. Chem*., 2003, **17**, 3300.
12. Z. Salamon, V. J. Hruby, G. Tollin, and S. Cowell, *J. Peptide Res*., 2002, **60**, 322.
13. L. M. Bolla, V. E. Azevedo, J. M. Smith, R. E. Taylor, D. K. Ranjit, A. M. Segall, and R. S. McAlpine, *Org. Lett*., 2003, **5**, 109.
14. J. E. Tarver, A. J. Pfizenmayer, and M. M. Joullie, *J. Org. Chem*., 2001, **66**, 7575.
15. M. Sedlák, R. Keder, J. Hanusek, and A. Růžička *J. Heterocycl. Chem.,* 2005, **42**, 899 and references cited therein.
16. J. Charton, S. Delarue, S. Vendeville, M.-A. Debreu-Fontaine, S. Girault-Mizzi, and C. Sergheraert, *Tetrahedron Lett*., 2001, **42**, 7559.
17. J. Charton, A. Cazenave Gassiot, P. Melnyk, S. Girault-Mizzi, and C. Sergheraert, *Tetrahedron Lett.,* 2004, **45**, 7081.
18. E. C. Weir, I. Niopas, and G. A. Smail, *Chimika Chronika, New Series,* 1989, **18**, 3.
19. P. Jansa, V. Macháček, and V. Bertolasi, *Heterocycles,* 2006, **68**, 59.
20. T. J. Schwan, M. M. Goldenberg, and A. C. Ilse, *J. Pharm. Sci.,* 1978, **67**, 718.
21. N. Albanoudi, C. Gabrieli, and I. Niopas, I. *Sci. Pharm*., 1990, **58**, 259.
22. I. Niopas and G. A. Smail, *Collect. Czech. Chem. Commun*., 1990, **55**, 540.
23. I. Niopas and G. A. Smail, *J. Chem. Soc., Perkin Trans 1,* **1991**, 113.
24. I. Niopas and G. A. Smail, *J. Chem. Soc., Perkin Trans 1,* **1991**, 119.
25. J. Kaválek, V. Macháček, G. Svobodová, and V. Štěrba, *Collect. Czech. Chem. Commun*., 1986, **51**,

375.

26. F. A. Carey and R. J. Sundberg, "Advanced Organic Chemistry", Part A, 3rd Ed., pp. 467-468, Plenum Press, New York, **1990**.
27. J. March, "Advanced Organic Chemistry," 4th Ed., pp. 381-382, 421, Wiley, New York, **1992**.
28. M. N. Burnett and C. K. Johnson, "ORTEP-III, Report ORNL-6895", Oak Ridge National Laboratory, Oak Ridge, TN, **1996**.
29. H. D. Flack, *Acta Crystallogr. Sect. A*, 1983, **39**, 876.
30. D. Cremer and J. A. Pople, *J. Am. Chem. Soc*., 1975, **97**, 1354.
31. G. R. Desiraju and T. Steiner, "The Weak Hydrogen Bond in Structural Chemistry and Biology," Oxford University Press, Oxford, **1999**.
32. J. Hanusek, M. Sedlák, P. Jansa, and V. Štěrba, *J. Phys. Org. Chem*., 2006, **19**, 61.
33. F. G. Bordwell and H. E. Fried, *J. Org. Chem*., 1991, **56**, 4218.
34. A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. Moliterni, G. Polidori, and R. Spagna, *J. Appl. Crystallogr*., 1999, **32**, 115.
35. G. M. Sheldrick, *SHELXL-97,* "Program for Refinement of Crystal Structures", University of Göttingen, Germany, **1997**.
36. K. Hayashi, Y. Ozaki, K. Nunami, and N. Yoneda, *Chem. Pharm. Bull*., 1983, **31**, 312.
37. G. L. Grunewald, D. J. Sall, and J. A. Monn, *J. Med. Chem*., 1988, **31**, 824.
38. A. K. Saxena, P. C. Jain, and N. Anand, *Indian J. Chem*., 1975, **13**, 230.