

SYNTHESIS AND CHIROPTICAL PROPERTIES  
OF 1-(4-, 5-PYRIMIDYL)ETHYLAMINES\*

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The isomeric 1-(4-,5-pyrimidyl)ethylamines *I* and *II* were synthesised and resolved into the optical antipodes. The preferred conformations of both compounds were determined using empirical potential functions as well as the EHT method. For these conformations optical rotatory strengths for the  $n-\pi^*$  and  $\pi-\pi^*$  transitions were calculated directly on the basis of CNDO/S wave functions. The calculated values agree with the experimental data obtained by decomposition of the CD spectra into the Gaussian bands.

In our previous papers<sup>1,2</sup> we studied chiroptical properties of optically active flexible aromatic compounds of the 1-arylethanol type. Using semiempirical quantum chemical methods we tried to find the reasons why changes of position of chiral substituents on an aromatic nucleus evoke changes in the signs of the Cotton effects. In the course of these investigations we needed model compounds in which the symmetry of the aromatic chromophore is lowered by introduction of a hetero atom. This reduction of symmetry results in an increase of the value of the transition moments which might cause an increase also of the optical rotatory strength; such an increase leads to higher reliability of the calculations employed. In this respect, pyrimidine derivatives substituted with 1-hydroxyethyl or 1-aminoethyl group appear to be suitable models.

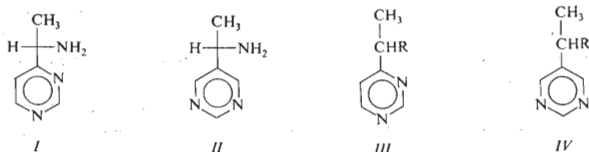
In a preliminary communication<sup>3</sup> we described asymmetric reductions of 2-, 4- and 5-acetylpyrimidines leading to partially optically active dextrorotatory alcohols of the absolute configuration *R*. However, low optical purity of these compounds did not allow to perform CD measurements and therefore we turned our attention to the corresponding amino derivatives *I* and *II* which are the subject of this study.

Both the racemic 1-(4-pyrimidyl)ethylamine, *III* ( $R = NH_2$ ) and 1-(5-pyrimidyl)ethylamine, *IV* ( $R = NH_2$ ), were prepared from the corresponding ethyl derivatives of pyrimidine described already in the literature<sup>4,5</sup>. The ethylpyrimidines *III* and *IV* ( $R = H$ ) were first converted by radical bromination with *N*-bromosuccinimide

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into the bromides *III* and *IV* ( $R = Br$ ) in which the bromine atom was replaced by azide in a nucleophilic substitution. Catalytic hydrogenation of the obtained azides *III*, *IV* ( $R = N_3$ ) afforded in an acceptable yield racemic aminoethylpyrimidines *III* and *IV* ( $R = NH_2$ ) which were resolved *via* diastereoisomeric salts with (+)-dibenzoyltartaric and (+)-tartaric acids, respectively. Thus we obtained the levorotatory amines *I*,  $[\alpha]_D^{20} -10.6^\circ$  ( $c$  2.0, ethanol), 7% optical purity, and *II*,  $[\alpha]_D^{20} -37.3^\circ$  ( $c$  2.0, ethanol), 100% optical purity. We assume that the absolute configuration of both the optically active amines *I* and *II* is *S*, analogously as in the case of the previously studied aryl-1-ethylamines and aryl-1-ethanols.



The CD spectra of the amines *I* and *II* are given in Fig. 1. Both the curves exhibit in the region 250 nm a distinct positive Cotton effect, accompanied with the corresponding absorption maximum in the UV spectrum. This band can be unequivocally assigned to the  $^1L_b$  transition of the pyrimidine nucleus. The other observed Cotton effects can obviously be ascribed to the  $n-\pi^*$  transitions. Their assignment is, however, difficult since in the region of long wavelengths the pyrimidine chromophore exhibits two different  $n-\pi^*$  transitions the sequence of which is hitherto unknown. Moreover, according to calculations carried out recently by the CNDO/S (ref.<sup>6</sup>) and by INDO/CI (ref.<sup>7</sup>) methods, in the pyrimidine molecule there is a further,

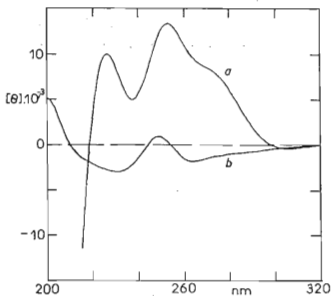


FIG. 1  
CD Spectrum of *a*) (*S*)-(-)-1-(4-Pyrimidyl)-ethylamine (*I*), *b*) (*S*)-(-)-1-(5-Pyrimidyl)-ethylamine (*II*)

Measured in methanol.

forbidden,  $n-\pi^*$  transition at 220 nm which has not hitherto been experimentally confirmed.

The resolution of the CD spectra of both compounds into the Gaussian bands is influenced by the still unknown assignment of the  $n-\pi^*$  transitions. In addition to the Cotton effect in the region of the  ${}^1L_b$  band at 251 nm (compound *I*) or at 248.5 nm (compound *II*), two Cotton effects were identified at longer wavelengths (285 and 275 nm for the compound *I* and 270 and 249 nm for the compound *II*). However, for the region of shorter wavelengths the set of parameters obtained by the decomposition of the experimental curves into the Gaussian bands is not consistent. The CD maximum found in the CD spectrum of the compound *I* at about 220 nm can be described as a distinct Cotton effect whereas a similar maximum in the spectrum of *II* can be described as a component of a broad CD band related to the  $n-\pi^*$  transition at 249 nm. This discrepancy is obviously connected with the unfavourable signal to noise ratio in the region under 240 nm and with the necessity of taking separate parts of the spectrum in several different cells. It causes relatively great differences in the wavelengths of the mutually corresponding  $n-\pi^*$  transitions in both compounds. For this reason only the rotatory strengths of the three experimentally found Cotton effects at the longest wavelengths will be compared with the calculated values.

Preferred conformations of both compounds were studied using the empirical potential functions and the EHT method, analogously as in the case of pyridine derivatives<sup>2</sup>. The initial orientations of the (*R*)-(+)-enantiomers of these compounds in which the angles  $\alpha$  and  $\beta$  equal zero are depicted in Fig. 2. As seen from Figs 3 and 4, the shapes of the curves of non-bonding, as well as electrostatic, interactions for the compound *I* remind those of 1-(2-pyridyl)ethanol<sup>2</sup>.

The preferred conformations, calculated on the basis of non-bonding interactions, are in the region  $\alpha = 60^\circ - 180^\circ$  and  $300^\circ$ . Calculations of the electrostatic interactions show energy minima at  $\alpha = 180^\circ$  for  $\beta = 0 - 120^\circ$  and at  $\alpha = 300^\circ$  for  $\beta = 240^\circ$  (in this conformation the hydrogens of the amino group are turned away from the aromatic nucleus). Total energy minima for  $\alpha = 160^\circ$  (*Ia*) and  $300^\circ$



FIG. 2  
Initial Geometry of the (*R*)-(+)-Enantiomers of Compounds *I* and *II*

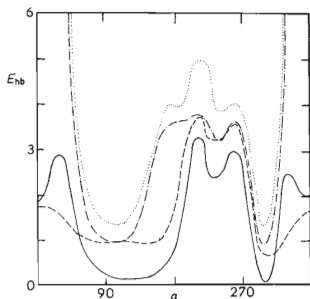


FIG. 3

Dependence of Non-bonding Interactions ( $\text{kcal mol}^{-1}$ ) in the Molecule of (*R*)-(+)-1-(4-Pyrimidyl)ethylamine (*I*) on the Angles  $\alpha$  and  $\beta$

$\beta$ :  $0^\circ$  .....;  $60^\circ$  —;  $120^\circ$  - - - -;  $140^\circ$  - · - · -

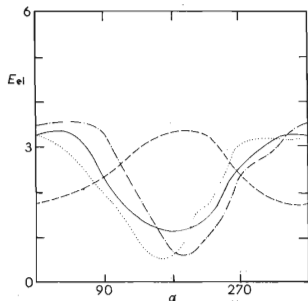


FIG. 4

Dependence of Electrostatic Interactions ( $\text{kcal mol}^{-1}$ ) in the Molecule of (*R*)-(+)-1-(4-Pyrimidyl)ethylamine (*I*) on the Angles  $\alpha$  and  $\beta$

$\beta$ :  $0^\circ$  .....;  $60^\circ$  —;  $120^\circ$  - · - · -;  $240^\circ$  - - - -

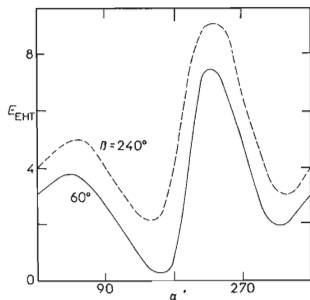


FIG. 5

Dependence of Total Energy of the Molecule of (*R*)-(+)-1-(4-Pyrimidyl)ethylamine (*I*) ( $\text{kcal mol}^{-1}$ ) on the Angles  $\alpha$  and  $\beta$ , as Calculated by the EHT Method

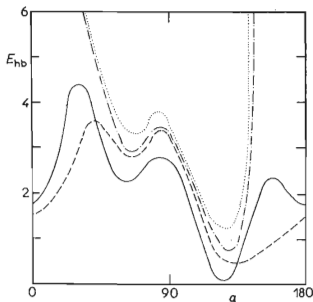


FIG. 6

Dependence of Non-bonding Interactions ( $\text{kcal mol}^{-1}$ ) in the Molecule of (*R*)-(+)-1-(5-Pyrimidyl)ethylamine (*II*) on the Angles  $\alpha$  and  $\beta$

$\beta$ :  $0^\circ$  .....;  $60^\circ$  —;  $120^\circ$  - · - · -;  $240^\circ$  - - - -

(*Ib*) were found by the EHT method (Fig. 5). In the molecule of the compound *I* conformations of the amino group with the hydrogens oriented toward the heterocyclic system ( $\beta = 60^\circ$ ) are preferred. According to EHT method, the conformation *Ia* ( $\alpha = 160^\circ$ ,  $\beta = 60^\circ$ ) is only by  $1.5 \text{ kcal mol}^{-1}$  more stable than the conformation *Ib* ( $\alpha = 300^\circ$ ,  $\beta = 60^\circ$ ) and therefore we must expect that in a solution both these conformations are present.

The non-bonding interaction curves of (*R*)-(+)-1-(5-pyrimidyl)ethylamine (*II*) exhibit only one minimum at  $\alpha = 120^\circ$  (Fig. 6, 7) as compared with the minimum at  $\alpha = 135^\circ$ , calculated by the EHT method (Fig. 8). The position of this minimum is independent of the angle  $\beta$ , however, lower energy values are found for  $\beta \sim 60^\circ$  (conformation *IIa*). These preferred conformations were used in the calculations of the optical rotatory strengths of the  $n-\pi^*$  and  $\pi-\pi^*$  transitions by direct calculation on the basis of CNDO/S wave functions. Technical details of these calculations are given in our previous communications<sup>1,2</sup>. In addition to the conformations *Ia*, *Ib* and *IIa*, also the conformations *Ic* and *IIb* were investigated. These conformations can be important in methanolic solution where the lone electron pairs of the pyrimidine nucleus are solvated. The results are summarised in Table I.

For the conformations *Ib* and *Ic* the sign of the Cotton effect in the region  $^1L_b$  agrees with the sign found experimentally. In both cases also the numerical values of the calculated rotatory strengths agree very well with the experimental values. The rotatory strengths of the  $n-\pi^*$  transitions for these two conformations have the right signs but the numerical values agree not so well. The experimentally found rotatory strength of the Cotton effect of the corresponding  $^1L_b$  band for compound *II* is in accord with the conformation *IIb*. The rotatory strength of this band in *II* is much more sensitive to the change of the angle  $\beta$  than in *I*. The signs of the Cotton effects of  $n-\pi^*$  transitions agree with the experiment, however, the worse accord

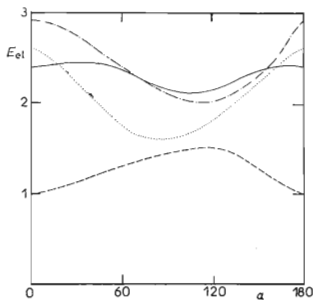


FIG. 7

Dependence of Electrostatic Interactions ( $\text{kcal mol}^{-1}$ ) in the Molecule of (*R*)-(+)-1-(5-Pyrimidyl)ethylamine (*II*) on the Angles  $\alpha$  and  $\beta$

$\beta$ :  $0^\circ$  - - - - -;  $60^\circ$  ———;  $120^\circ$  ·····;  $240^\circ$  - · - · - ·.

between the numerical values makes a reliable interpretation difficult. In the conformations *Ib*, *Ic* and *IIb*, no intramolecular hydrogen bonding can take place.

TABLE I  
Optical Rotatory Strength of the (*R*)-(+)-Enantiomers of the Amines *I* and *II*

Con-formation	Transition	$\lambda_{\text{exp}}^a$	$\lambda_{\text{calc}}^a$	$f_{\text{calc}}^b$	$f_{\text{exp}}^b$	$R_{\text{calc}}^c$	$E_{\text{exp}}^c$
<i>Ia</i>	$n-\pi^*$	285	297.9	$8.8 \cdot 10^{-3}$		-3.41	4.37
	$n-\pi^*$	275	285.5	$1.0 \cdot 10^{-3}$		0.92	-10.8
	$\pi-\pi^*$	251	256.6	$5.6 \cdot 10^{-2}$	$7.0 \cdot 10^{-2}$	0.44	-5.49
<i>Ib</i>	$n-\pi^*$	285	297.1	$8.8 \cdot 10^{-3}$		12.8	4.37
	$n-\pi^*$	275	281.2	$1.0 \cdot 10^{-4}$		-1.03	-10.8
	$\pi-\pi^*$	251	255.9	$5.3 \cdot 10^{-2}$	$7.0 \cdot 10^{-2}$	-4.58	-5.49
<i>Ic</i>	$n-\pi^*$	285	296.8	$8.6 \cdot 10^{-3}$		11.8	4.37
	$n-\pi^*$	275	284.4	$2.0 \cdot 10^{-4}$		-0.16	-10.9
	$\pi-\pi^*$	251	259.9	$5.6 \cdot 10^{-2}$	$7.0 \cdot 10^{-2}$	-3.93	-5.49
<i>IIa</i>	$n-\pi^*$	270	306.9	$5.6 \cdot 10^{-3}$		0.14	-0.96
	$n-\pi^*$	249	279.6	$1.0 \cdot 10^{-4}$		1.81	7.50
	$\pi-\pi^*$	248.5	266.6	$8.9 \cdot 10^{-2}$	$4.5 \cdot 10^{-2}$	0.51	-2.69
<i>IIb</i>	$n-\pi^*$	270	304.6	$5.3 \cdot 10^{-3}$		-0.33	-0.96
	$n-\pi^*$	249	278.0	$2.0 \cdot 10^{-4}$		0.87	7.50
	$\pi-\pi^*$	248.5	266.6	$8.8 \cdot 10^{-2}$	$4.5 \cdot 10^{-2}$	-0.11	-2.69

<sup>a</sup> Wavelength in nm; <sup>b</sup> oscillator strength; <sup>c</sup> optical rotatory strength  $R \cdot 10^{40}$  (cgs).

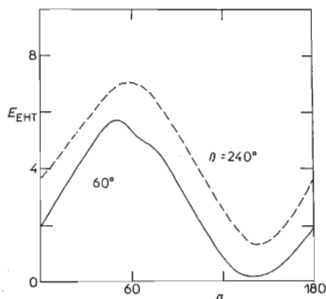
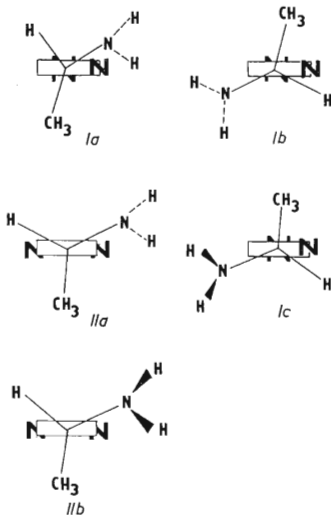


FIG. 8  
Dependence of Total Energy of the Molecule of (*R*)-(+)-1-(5-Pyrimidyl)ethylamine (*II*) ( $\text{kcal mol}^{-1}$ ) on the Angles  $\alpha$  and  $\beta$ , as Calculated by the EHT Method

Since the measurements were performed in methanol in which obviously the lone electron pairs of the pyrimidine nucleus are solvated, the assumption that the molecules of the studied compounds *I* and *II* exist in the mentioned conformations seems to be justified.



## EXPERIMENTAL

The temperature data are uncorrected. The IR spectra were measured on a UR-10 instrument in tetrachloromethane. <sup>1</sup>H-NMR spectra were taken on a Varian XL-100 instrument in deuteriochloroform using tetramethylsilane as internal standard. The CD measurements were performed on a Roussel Jouan CD 185/II dichrograph, the optical rotations were measured on a Zeiss Opton polarimeter.

### 1-(4-Pyrimidyl)ethyl Bromide (*III*, *R* = Br)

A mixture of 4-ethylpyrimidine (*III*, *R* = H) (20 g; 185 mmol), N-bromosuccinimide (33 g; 186 mmol), benzoyl peroxide (0.48 g; 2 mmol) and tetrachloromethane (360 ml) was refluxed under stirring. After the succinimide had been precipitated, the mixture was heated for 1 h, the succinimide was filtered and washed with tetrachloromethane. The crude product (about 35 g of an oily, skin irritating liquid) was obtained by evaporation of the solvent. <sup>1</sup>H-NMR spectrum,  $\delta$ : 2.08 (3 H, *J* = 6.75 Hz), 5.25 (1 H, *J* = 6.75 Hz), 7.70 (1 H, *J* = 5.6 Hz), 8.98 (1 H, *J* = 5.6 Hz), 9.21 (1 H).

1-(4-Pyrimidyl)ethyl Azide (*III*, R = N<sub>3</sub>)

A mixture of the crude bromo derivative *III*, R = Br (35 g), sodium azide (24 g; 370 mmol) and ethanol (80 ml) was refluxed for 6 h under stirring. The ethanol was evaporated, the residue dissolved in water (130 ml) and extracted with ether. After drying over magnesium sulphate the ether was evaporated leaving 30 g of a liquid. Distillation of a small sample afforded 330 mg of a yellow liquid, b.p. 95–98°C/15 Torr. IR spectrum,  $\text{cm}^{-1}$ : 3040 (m), 2980 (s), 2935 (m), 2870 (m), 2100 (s). 1585 (s), 1560 (s), 1470 (s), 1393 (s), 1335 (s), 1295 (s), 1260 (s), 1070 (s). <sup>1</sup>H-NMR spectrum,  $\delta$ : 1.62 (3 H,  $J = 7.1$  Hz), 4.62 (1 H,  $J = 7.1$  Hz), 7.39 (1 H,  $J = 5.2$  Hz), 8.80 (1 H,  $J = 5.2$  Hz), 9.23 (1 H).

1-(4-Pyrimidyl)ethylamine (*III*, R = NH<sub>2</sub>)

The crude azide *III*, R = N<sub>3</sub> (30 g) in methanol (400 ml) was hydrogenated over PtO<sub>2</sub> (1 g) for 8 h in an open apparatus. The reaction course was followed by thin-layer chromatography (commercial Silufol UV plates, chloroform–benzene–acetone 4 : 1 : 4). The methanol was evaporated, the residue treated with a 10% sodium hydroxide solution (100 ml) and the liberated base taken up into ether and dried over potassium carbonate. Distillation afforded 5 g (22% based on the ethyl derivative *III*, R = H) of a yellowish liquid, b.p. 96–100°C/18 Torr. For C<sub>6</sub>H<sub>9</sub>N<sub>3</sub> (126.2) calculated: 58.51% C, 7.37% H, 34.12% N; found: 59.11% C, 7.56% H, 32.08% N. <sup>1</sup>H-NMR spectrum,  $\delta$ : 1.46 (3 H,  $J = 7$  Hz), 1.90 (2 H), 4.14 (1 H,  $J = 7$  Hz), 7.38 (1 H,  $J = 6$  Hz), 8.68 (1 H,  $J = 6$  Hz), 9.15 (1 H).

*(S)*-(–)-1-(4-Pyrimidyl)ethylamine (*I*)

The racemic amine *III*, R = NH<sub>2</sub> (3.67 g; 30 mmol) and (+)-dibenzoyltartaric acid monohydrate (10.42 g; 30 mmol) were mixed in a hot mixture of ethanol (200 ml) and methanol (100 ml). The precipitated salt (6 g; m.p. 177–181°C) was crystallised from methanol and decomposed with 20% sodium hydroxide solution (10 ml). The product was taken up in chloroform, dried over potassium carbonate and isolated by distillation. Yield 0.58 g of a yellow liquid, b.p. 92 to 93°C/12 Torr;  $[\alpha]_{\text{D}}^{20} -10.65^\circ$  ( $c$  2, ethanol). For C<sub>6</sub>H<sub>9</sub>N<sub>3</sub> (123.2) calculated: 58.51% C, 7.37% H; found: 58.54% C, 7.35% H.

1-(5-Pyrimidyl)ethyl Bromide (*IV*, R = Br)

A solution of 5-ethylpyrimidine (*IV*, R = H) (10 g; 92 mmol), N-bromosuccinimide (16.4 g; 93 mmol) and benzoyl peroxide (0.3 g; 1 mmol) in tetrachloromethane (600 ml) was irradiated for 30 minutes by an 80 W mercury lamp, inserted into the reaction mixture (quartz jacket). After cooling the separated succinimide was filtered and washed with tetrachloromethane. Evaporation of the filtrate afforded 17.2 g of the crude product. <sup>1</sup>H-NMR spectrum,  $\delta$ : 2.05 (3 H,  $J = 7.5$  Hz), 9.20 (2 H), 5.23 (1 H,  $J = 7.5$  Hz), 9.52 (1 H).

1-(5-Pyrimidyl)ethyl Azide (*IV*, R = N<sub>3</sub>)

Sodium azide (30 g; 460 mmol) was added to a solution of the crude bromo derivative *IV*, R = Br (43.2 g; 230 mmol) in ethanol (100 ml) and the mixture was heated for 4.5 h under stirring. The ethanol was distilled off and chloroform (100 ml) and water (80 ml) were added to the residue. The reaction of the aqueous layer was adjusted to pH 10 by 10% sodium hydroxide, the product was extracted with chloroform, the extract dried over potassium carbonate and taken down.



A sample of the azide (*IV*, R = N<sub>3</sub>) was distilled, b.p. 78–83°C/15 Torr. IR-spectrum, cm<sup>-1</sup>: 3050 (m), 3020 (m), 2980 (s), 2930 (s), 2880 (s), 2100 (s), 1592 (s), 1417 (s), 1410 (s), 1385 (s), 1355 (m), 1318 (s), 1295 (s), 1240 (s), 1190 (s), 1160 (s), 1118 (s), 1039 (s). <sup>1</sup>H-NMR spectrum, δ: 1.65 (3 H, *J* = 7 Hz), 4.72 (1 H, *J* = 7 Hz), 8.74 (2 H), 9.19 (1 H).

1-(5-Pyrimidyl)ethylamine (*IV*, R = NH<sub>2</sub>)

A solution of the crude azide *IV*, R = N<sub>3</sub> in methanol (200 ml) was hydrogenated over PtO<sub>2</sub> (1.5 g) in a stream of hydrogen for 11 h. The course of the reaction was followed by thin-layer chromatography, similarly as in the case of the compound *III*. The catalyst was filtered off, the filtrate was saturated with gaseous carbon dioxide and taken down. The residue was dissolved in water (200 ml), made alkaline with 5M-NaOH (100 ml) and the product was extracted with chloroform. After drying over potassium carbonate and evaporation of the solvent the amine was yielding 5.5 g (19% based on the ethyl derivative *IV*) of a yellow liquid, boiling at 90–95°C/15 Torr. For C<sub>6</sub>H<sub>9</sub>N<sub>3</sub> (123.2) calculated: 58.50% C, 7.37% H; 34.12% N; 58.94% C, 7.60% H, 33.05% N. IR spectrum, cm<sup>-1</sup>: 3390 (w), 3300 (w), 3050 (m), 3020 (m), 2970 (s), 2930 (s), 2870 (m), 1580 (s), 1560 (s), 1450 (s), 1435 (s), 1405 (s), 1370 (s), 1320 (m), 1185 (m), 1165 (m), 1120 (s). <sup>1</sup>H-NMR spectrum, δ: 1.46 (3 H, *J* = 6.8 Hz), 1.59 (2 H), 4.24 (1 H, *J* = 6.8 Hz), 8.78 (2 H), 9.12 (1 H).

(*S*)-(-)-1-(5-Pyrimidyl)ethylamine (*II*)

The racemic amine *IV*, R = NH<sub>2</sub> (3 g) was added to a solution of tartaric acid (3.66 g) in hot ethanol (15 ml). The separated solid (5.13 g; m.p. 166–175°C) was crystallised three times from ethanol–water (7 : 1). The obtained salt, m.p. 188–191°C was decomposed with 20% sodium hydroxide solution (7.5 ml) under cooling. The product was taken up in ether and the solution dried over potassium carbonate. Distillation afforded 0.47 g of a liquid, b.p. 100–105°C/20 Torr; [α]<sub>D</sub><sup>20</sup> -37.3° (*c* 3.06, ethanol). For C<sub>6</sub>H<sub>9</sub>N<sub>3</sub> (123.2) calculated: 58.51% C, 7.37% H; found: 58.49% C, 7.40% H.

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