OPTICALLY ACTIVE FURANOIDS CONTAINING CYTOSINE-, ADENINE- AND NICOTINAMIDE-LIKE MOIETIES

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3-Hydroxymethyl-5-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)-2-methylfuran (**2**) prepared from 3-ethoxycarbonyl derivative **1** was converted to 3-chloromethyl-5-(2,3-*O*-isopropylidene-β-D-erythro-furanosyl)-2-methylfuran (**3**). Compound **3** reacted with cytosine, adenine, 6-chloropurine, 6-mercaptopurine, and nicotinamide to corresponding optically active heterocyclic derivatives **5–10** and **14**. The 6-chloro derivative **9** was converted to 6-alkoxy derivatives **11** and **12** by the reaction with methanol or ethanol, respectively, in the presence of diazabicyclooctane. Dithionite reduction of quaternary chloride **14** gave 1,4-dihydropyridine derivative **15** capable to transform ethyl phenylglyoxylate to optically active ethyl mandelate.

Key words: 5-Deoxy-β-D-ribofuranose derivatives; NADH model reduction.

In connection with our interest in biologically active chiral heterocycles we decided to investigate some optically active furanoids. A number of these compounds are easily available from various pentoses and simple 1,3-dicarbonyl reaction partners[1]. In this communication we attempt to connect a chiral furanoid system with biochemically important cytosine-, adenine- and nicotinamide-like moieties. It has been believed[2] that optically active substances containing such fragments may exhibit antiviral and cytostatic activities.

Ethyl 5-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)-2-methylfuroate (**1**) prepared by two-step synthesis from D-glucose and ethyl acetoacetate[3] was used as starting material. By its reduction with lithium aluminium hydride the 3-hydroxymethyl derivative **2** was obtained which with tosyl chloride under mild conditions gave the corresponding 3-chloromethyl-5-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)-2-methylfuran (**3**) instead of expected 3-toluenesulfonyl ester **4**. Such uncommon behaviour may be explained by the following two-step process (Eq. (*1*)):

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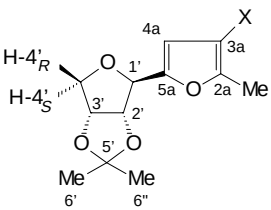
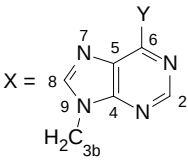
$$\mathbf{2} + \mathrm{TsCl} + \mathrm{Py} \rightarrow \mathbf{4} + \mathrm{PyH^+\,Cl^-} \rightarrow \mathbf{3} + \mathrm{PyH^+\,OTs^-}\,. \qquad (1)$$

Similar unexpected behaviour has been so far observed, to our knowledge, only in one case of tosylation at elevated temperature[4]. An useful approach to 3-chloromethyl derivative **3** has finally been worked up on the basis of a direct reaction of alcohol **2** with thionyl chloride.

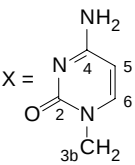
Compound **3** was sensitive to hydrolysis with moist air and therefore it was allowed to react with cytosine, adenine, 6-chloro- and 6-mercaptopurine without any purification. Nucleophilicity of the reactants has been enhanced prior to the substitution by transformation to corresponding sodium salts using sodium hydride in dimethylformamide[5]. It was found that the reaction with cytosine gave exclusively compound **5** substituted at the position 1, similarly to other alkylations[6] of this substrate. On the other

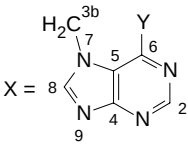




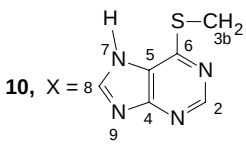
6, Y = NH_2
9, Y = Cl
11, Y = OMe
12, Y = OEt
13, Y = $N^{\oplus}(CH_2CH_2)_3N$ $Cl^{\ominus}$

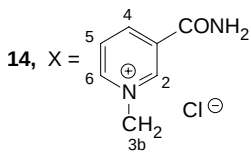
1, X = CO_2Et
2, X = CH_2OH
3, X = CH_2Cl
4, X = CH_2OTs

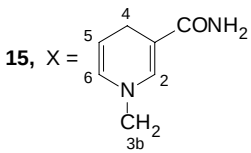




7, Y = NH_2
8, Y = Cl







hand, mixtures of 9- and 7-substituted regioisomers **6**, **7** and **8**, **9**, respectively, were obtained from adenine and 6-chloropurine. The isomers were separated by column chromatography and their structure was assigned by NMR spectroscopy by comparison with the published data[7]. 6-Mercaptopurine gave exclusively the *S*-substituted product **10**. The ambiguous *N*-nucleophilic behaviour of adenines[6,7] as well as the typical *S*-nucleophilicity of mercaptopurines[6] were already reported.

6-Methoxy- and 6-ethoxypurin-9-yl derivatives **11** and **12** were prepared using 1,4-diazabicyclo[2.2.2]octane (DABCO)–potassium carbonate reagent[8] in methanol and ethanol, respectively. The quaternary intermediate[8] **13** formed in the course of this reaction was isolated and characterized. Yields, optical activity and analytical data of products **5**–**12** are given in Table I.

TABLE I
Characteristic data of the compounds **5–12**

Compound	M.p., °C	Yield, % $[\alpha]_D$ (*c* 1, $CHCl_3$)	Formula M.w.	Calculated/Found		
				% C	% H	% N
5	206–207	75	$C_{17}H_{21}N_3O_5$	58.76	6.10	12.10
		–72.6	347.1	58.59	6.25	11.92
6	143–145	54	$C_{18}H_{21}N_5O_4$	58.20	5.70	18.86
		–58.2[a]	371.2	58.10	5.83	18.59
7	131–133	54	$C_{18}H_{21}N_5O_4$	58.20	5.70	18.86
		–62.3	371.2	57.98	5.73	18.65
8[b]	49–50 (dec.)	46	$C_{18}H_{19}ClN_4O_4$	55.37	4.91	14.36
		–57.2	390.1	55.35	5.20	14.17
9[c]	47–50 (dec.)	46	$C_{18}H_{19}ClN_4O_4$	55.37	4.91	14.36
		–53.7	390.1	55.37	5.02	14.12
10	34–37 (dec.)	45	$C_{19}H_{22}N_4O_5$	59.04	5.74	14.50
		–54.9	386.2	59.30	6.00	14.35
11	37–40 (dec.)	53	$C_{20}H_{24}N_4O_5$	59.97	6.04	14.00
		–59.6	400.2	59.70	6.27	13.78
12[d]	140–141	62	$C_{18}H_{20}N_4O_4S$	55.65	5.19	14.43
		–60.9	388.1	55.67	5.29	14.31

[a] Measured at *c* 0.5. [b] Calculated: 8.96% Cl, found: 8.71% Cl. [c] Calculated: 8.96% Cl, found: 9.02% Cl. [d] Calculated: 8.24% S, found: 8.01% S.

The success in preparation of the above mentioned compounds prompted us to investigate the reaction of 3-chloromethyl derivative **3** with nicotinamide to obtain corresponding NAD model. Such types of compounds have been widely investigated[9–11] especially in connection with general mechanistic problems of enzymatic reactions. As expected, 3-carbamoyl-1-[5-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)-2-methyl-3-furylmethyl]pyridinium chloride (**14**) was isolated in 70% yield as a stable crystalline substance.

NAD models are usually converted to the corresponding NADH models by the dithionite reduction[12]. We attempted to perform the conversion with the quaternary salt **14** and thus 1-[5-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)-2-methyl-3-furylmethyl]-1,4-dihydropyridine-3-carboxamide (**15**) was prepared as strongly hygroscopic substance which had to be stored at low temperature under nitrogen. Nevertheless, the reduction ability of the optically active NADH model was verified.

A number of optically active NADH models has been found to reduce prochiral substrates to optically active products in variable enantiomeric excesses (e.e.) and different stereochemical interaction models have been proposed[11]; it is thus only a minimum possible to predict considering a priori the molecular structure of our NADH model **15**.

Reductive ability and enantioselectivity of 1,4-dihydropyridine derivative **15** were verified by one of the standard procedures based on the reaction with ethyl phenylglyoxylate catalyzed with magnesium perchlorate. The reaction rate was monitored by decrease of the absorption maximum at 352 nm corresponding to 1,4-dihydropyridine chromophore. Interconversion of the components proceeded in acetonitrile at 22 °C and was completed after 4 h. The isolated ethyl mandelate was slighty optically active exhibiting only ca 2% e.e. of its (*R*)-(–)-enantiomer. The low e.e. value conforms to a considerable distance between the chiral and reaction sites in the molecule **15**. On the other hand, the fact that the asymmetric induction has been really observed for such a long range effect within the molecule **15** might be surprising. However, any error was excluded by repeated experiments.

Molecular structures of all studied compounds are confirmed by assignments of their ^{1}H and ^{13}C NMR spectra (Tables II and III), where signals typical for chiral, furan and aza-heterocyclic moieties in the molecules of all synthesized compounds **1**–**15** (proton signals) and pyrimidine and purine nucleosides **5**–**12** (carbon signals) can be easily recognized. Thus, the chiral part exhibits more or less developed ABCMX proton system characterized by no interaction between H-1′ and H-2′ (the proton at the position 1′ forms in all cases where distinguished clear singlet) and thus H-2′ signal is doublet with coupling constant J(2′,3′) between 6.0 and 6.6 Hz. No coupling interaction is observable also in the case of H-4′$_R$ and H-3′. The signal of H-3′ thus became simple dd, as well as one of H-4′$_S$. The value of spin–spin coupling constant J(3′,4′$_S$) ranges from 2.9 to 3.6 Hz (Table II).

TABLE II

^{1}H NMR spectra (δ, ppm; J, H_2) of the synthesized furanoids **1–15**

Compound	H-1′(s)	H-2′(d) J(2′3′)	H-3′(dd) J(3′2′), J(3′4$_S$′)	H-4$_R$′(d) J(4$_R$′4$_S$′)	H-4$_S$′(dd) J(4$_S$′4$_R$′), J(4$_S$′3′)	H-6′(s)	H-6″(s)	H-4a(s)	H-3b(s)	CH_3-2a(s)	Substituent at C-3b[a]	
1	5.11	5.03 6.2	4.99 6.2, 3.8	4.13 10.6	3.97 10.6, 3.8	1.32	1.54	6.49	–	2.55	4.27	1.33
2	5.00	4.94 5.6	4.90 6.2, 3.8	4.02 10.7	3.88 10.7, 3.8	1.34	1.53	6.21	4.34	2.24	1.83	–
3	4.98	4.93 6.2	4.90 6.2, 3.8	4.03 10.6	3.91 10.6, 3.7	1.35	1.53	6.22	4.38	2.26	–	–
4	5.01	5.02 6.0	4.91 6.2, 3.7	4.05 10.5	3.81 10.5, 3.7	1.36	1.55	6.23	4.40	2.28	2.50	–
5	4.94	4.88[b]	4.88[b]	3.98 10.3	3.87 10.4, 3.3	1.34	1.52	6.14	4.64	2.28	5.75	7.15
6	4.96	4.88[b]	4.88[b]	4.01 10.5	3.83 10.5, 3.3	1.29	1.48	6.12	5.09	2.30	8.39[c]	7.72
7	4.94	4.87[b]	4.87[b]	3.99 10.5	3.86 10.5, 2.9	1.30	1.44	6.20	5.29	2.36	8.05	7.97
8	4.94	4.87[b]	4.87[b]	4.00 10.7	3.87 10.7, 2.9	1.32	1.51	6.08	5.42	2.33	8.86	8.17

TABLE II
(*Continued*)

Compound	H-1′(s)	H-2′(d) $J(2'3')$	H-3′(dd) $J(3'2')$, $J(3'4_S')$	H-4$_R$′(d) $J(4_R'4_S')$	H-4$_S$′(dd) $J(4_S'4_R')$, $J(4_S'3')$	H-6′(s)	H-6″(s)	H-4a(s)	H-3b(s)	CH_3-2a(s)	Substituent at C-3b[a]	
9	4.88	4.82[b]	4.82[b]	3.93	3.81	1.26	1.45	6.12	5.16	2.33	8.75	8.05
				10.7	10.8, 3.0							
10	4.97	4.92	4.88	4.00	3.90	1.35	1.54	6.23	4.39	2.35	8.80	8.28
		6.6	6.6, 3.5	10.4	10.7, 3.5							
11	4.93	4.86[b]	4.86[b]	3.98	3.80	1.32	1.50	6.14	5.12	2.34	8.55[d]	7.84
				10.5	10.5, 3.5							
12	4.93	4.85[b]	4.85[b]	3.98	3.85	1.31	1.50	6.12	5.11	2.35	8.52[e]	7.83
				10.4	10.4, 3.0							
13	4.93	4.86[b]	4.86[b]	3.99	3.86	1.20	1.52	6.10	5.06	2.33	8.36	7.64
				10.4	10.5, 2.8							
14	4.88[b]	4.88[b]	4.88[b]	3.84	3.70	1.20	1.40	6.58	5.72	2.42	9.65[f]	9.16
				10.7	10.7, 2.4							
15	4.89[b]	4.89[b]	4.89[b]	3.83	3.70	1.36	1.55	6.12	4.03	2.25	7.08[g]	5.68
				10.7	10.7, 2.8							

[a] For compound **1** signals of the methylene and methyl group, for compound **4** methyl group (phenyl: 7.2 and 7.9 2 × d, 2 × 2 H, J = 8.4), for compound **5** signals H-5 and H-6 (J = 7.7), for **6–13** H-2 and H-8, for **14**, **15** H-2 and H-6, respectively. [b] Multiplet. [c] 5.67 brs, 2 H (NH_2). [d] 4.17 s, 3 H (CH_3). [e] 1.48 t, 3 H (CH_3); 4.64 q, 2 H (CH_2). [f] 8.26 dd, 1 H, J(5,4) = J(5,6) = 5.6 (H-5); 8.19 and 8.89 2 × brs, 2 H (NH_2); 9.03 d, 1 H, J(4,5) = 5.6 (H-4). [g] 3.14 m, 2 H (H-4); 4.72 m, 1 H (H-5); 5.13 brs, 2 H (NH_2).

EXPERIMENTAL

Temperature data are uncorrected and were determined on a Boetius block. NMR spectra (δ, ppm and *J*, Hz) were measured in deuteriochloroform (unless stated otherwise) using TMS as internal standard on a GEMINI 300 instrument at 297 K. IR spectra (ν, cm^{-1}) were recorded on a Bruker IFS 88 spectrometer. TLC was performed using SILUFOL UV_{254} plates (Kavalier, Czech Republic), HPLC (methanol–water 9 : 1) on an instrument LCP 4000 (Ecom, Czech Republic) with the column Nucleosil 120 (C_{18}, 5 μm; Macherey–Nagel, Germany). Optical rotation data were measured on a JASCO DIP-370 polarimeter at the temperature 20 °C.

Ethyl 5-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)-2-methyl-3-furoate (**1**) was prepared according to the described procedure[3]. Its ^{1}H NMR spectrum is given in Table II.

TABLE III
^{13}C NMR spectra of compounds **5–12**

Carbon	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
2a	151.18	152.22	152.07	152.03	151.36	151.08	152.60	152.60
3a	115.65	115.37	114.09	114.27	114.47	116.21	115.27	115.60
4a	109.90	109.74	109.70	108.87	109.32	110.88	109.72	109.68
5a	150.67	151.43	151.51	151.19	151.37	150.25	151.25	151.22
1′	84.15	84.35	84.27	84.24	84.10	84.41	84.20	84.47
2′	81.73	81.88	81.79	81.75	81.62	81.98	81.90	81.89
3′	80.26	80.44	80.35	80.34	80.18	80.54	80.48	80.56
4′	73.26	73.54	73.49	73.55	73.33	73.49	73.39	73.46
5′	113.34	113.61	113.58	113.67	113.40	113.51	113.60	113.57
6′	25.46	25.66	25.59	25.58	25.42	25.72	25.76	25.69
6″	27.05	27.21	27.15	27.14	26.98	27.26	27.22	27.44
Me-2a	12.30	12.47	12.55	12.60	12.32	12.62	12.60	12.52
3b	44.03	38.99	45.09	43.13	39.51	24.37	39.17	39.25
2	157.37	154.37	153.80	153.28	151.63	152.12	152.86	152.87
4	166.60	[a]	[a]	143.69	151.54	[a]	[a]	151.15
5	95.60	121.05	120.23	123.13	132.06	[a]	122.21	122.04
6	145.03	155.12	156.60	162.75	152.75	[a]	161.77	161.51
8	–	142.17	140.43	149.11	145.40	142.00	141.20	141.96
Other	–	–	–	–	–	–	54.80 (CH_3)	63.80 (CH_2), 15.18 (CH_3)

[a] Signal not observed.

3-Hydroxymethyl-5-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)-2-methylfuran (**2**)

The reported procedure[3] was modified in the following manner: A solution of ethyl ester **1** (9.5 g, 32 mmol) in anhydrous ether (100 ml) was added dropwise to a suspension of lithium aluminium hydride (2.0 g, 53 mmol) in the same solvent (50 ml). The reaction was completed in 4 h according to HPLC. The resulting reaction mixture was decomposed with aqueous 4% NaOH (8 ml) and filtered. The filtrate was washed with anhydrous ether, evaporated and dried to yield the alcohol **2** (7.2 g, 90%) as a colourless oil, $[\alpha]_D$ –81° (*c* 1, $CHCl_3$), the value reported in ref.[3]: $[\alpha]_D$ –71° (*c* 1, $CHCl_3$). For $C_{13}H_{18}O_5$ (254.1) calculated: 61.39% C, 7.14% H; found: 61.36% C, 7.36% H. ^{1}H NMR spectrum is given in Table II, ^{13}C NMR spectrum in Table III. IR spectrum ($CHCl_3$): 3 610 (OH), 1 634 (furan ring), 1 379 (Me_2C).

3-Chloromethyl-5-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)-2-methylfuran (**3**)

Method A. A solution of thionyl chloride (0.3 g, 2.5 mmol) in dichloromethane (5 ml) was added dropwise to a stirred mixture of 3-hydroxymethyl derivative **2** (0.5 g, 1.9 mmol), pyridine (0.2 g, 2.5 mmol) and dichloromethane (5 ml) in 30 min. After 1 h stirring, the reaction mixture was decomposed with water (5 ml) under ice-cooling, the organic layer was separated and the aqueous layer was repeatedly extracted with dichloromethane. The combined organic extracts were dried with sodium sulfate and evaporated under reduced pressure. Yield 0.42 g (80%) of 3-chloromethyl derivative **3** as a yellowish viscous oil, $[\alpha]_D$ –84° (*c* 1, $CHCl_3$). ^{1}H NMR spectrum is given in Table II, ^{13}C NMR spectrum in Table III. IR spectrum ($CHCl_3$): 1 691 (furan ring), 1 376 (Me_2C).

Method B. A cold mixture (0 °C) of tosyl chloride (0.446 g, 5.8 mmol) and triethylamine (1.0 ml, 7.2 mmol) in dichloromethane (25 ml) was added to a solution of 3-hydroxymethyl derivative **2** (1.08 g, 4.2 mmol) in the same solvent (10 ml). The reaction mixture was worked up as shown above.Yield 0.58 g (50%) of compound **3** which exhibited the same spectral properties as above mentioned preparate.

Preparation of Furanoids **5**, **6**, **7**, **8**, **9** and **10**. General Procedure

The corresponding heterocyclic base (1.4 mmol) was added to a suspension of sodium hydride (55 mg, 1.4 mmol) in dimethylformamide (10 ml) and the mixture was stirred under nitrogen at 70 °C for 1 h. Then a solution of crude 3-chloromethyl derivative **3** (720 mg, 28 mmol) in dimethylformamide (5 ml) was added dropwise and the resulting reaction mixture was heated to 60 °C for 7 h and then filtered while hot. The precipitate was washed with dimethylformamide and the collected filtrates were co-distilled with toluene. The residue was extracted with chloroform and chromatographed on a silica gel column (chloroform–methanol 9 : 1 followed by chloroform–acetone 2 : 1). The composition of individual fractions was monitored using HPLC and ^{1}H NMR spectra. In the case of regioisomers **6**, **7** and **8**, **9** the less polar products were characterized as the 9-isomers, while to the more polar ones the 7-substitution was assigned. Isolated substances were purified by crystallization from the chloroform–ether mixture. The results are summarized in Table I. The NMR spectra are given in Tables II and III.

Preparation of Furanoids **11** and **12**. General Procedure

The 6-chloro derivative **9** (390 mg, 1 mmol) was heated with DABCO (10 mg) and potassium carbonate (138 mg, 1 mmol) in corresponding alcohol (2 ml) at 70 °C for 1 h. After cooling the reaction mixture was filtered and the precipitate was washed with ether. The collected filtrates were evaporated in vacuo and the residue was chromatographed on a silica gel column (chloroform–acetone 2 : 1). Yields of the hygroscopic products **11** and **12** are given in Table I and their NMR spectra in Tables II and III.

1-{9-[5-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)-2-methyl-3-furylmethyl]purin-6-yl}-4-aza-1-azoniabicyclo[2.2.2]octane chloride (**13**)

A mixture of the 3-chloromethyl derivative **3** (0.5 g, 1.8 mmol) and DABCO (0.4 g, 3.6 mmol) in anhydrous dimethylformamide (15 ml) was stirred at 25 °C for 2 h. The precipitate of the compound **13** was then filtered, washed with cold DMF and dried in vacuo to give a hygroscopic substance **13** in almost quantitative yield. ^{1}H NMR spectrum of the DABCO moiety: 2.70 brs, 4 H; 2.81 t, 2 H, J = 6.6; 3.65 t, 2 H, J = 6.6 and 4.35 brs, 4 H (6 × CH_2). Chemical shifts of other protons are given in Table II.

3-Carbamoyl-1-[5-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)-2-methyl-3-furylmethyl]pyridinium chloride (**14**)

A solution of the 3-chloromethyl derivative **3** (0.5 g, 1.8 mmol) in dimethylformamide (15 ml) was added to nicotinamide (0.12 g, 1 mmol) in the same solvent (5 ml) under nitrogen. After 10 days, the reaction mixture exhibited no nicotinamide according to TLC (ethanol–aqueous ammonia–water 95 : 5 : 5). The solvent was co-distilled with toluene and the residue afforded a crude product, which after thorough washing with ethanol afforded white crystals of quaternary salt **14**. Yield 1.053 g (70%), m.p. 218–220 °C, $[\alpha]_D$ –53.7° (*c* 1, DMF). For $C_{19}H_{23}ClN_2O_5$ (394.9) calculated: 57.85% C, 5.88% H, 8.87% Cl, 7.11% N; found: 57.48% C, 5.65% H, 8.75% Cl, 7.00% N. ^{1}H NMR spectrum is given in Table II. IR spectrum (KBr): 3 388 and 3 296 (NH_2), 1 700 ($CONH_2$), 1 649 (furan ring), 1 392 (Me_2C).

1-[5-(2,3-*O*-Isopropylidene-β-D-*erythro*-furanosyl)-2-methyl-3-furylmethyl]-1,4-dihydropyridine-3-carboxamide (**15**)

The quaternary pyridinium salt **14** (0.1 g, 0.25 mmol) was added to a saturated and cold (0 °C) aqueous solution of sodium bicarbonate (0.18 g, 2.2 mmol) which was saturated with nitrogen. After 5 min a saturated solution of sodium dithionite (0.24 g, 1.4 mmol) in cold water was dropwise added and the reaction mixture became yellow. Stirring was continued for further 20 min at room temperature and then at 0 °C for 3 h. After washing with chloroform (10 ml), the aqueous phase was separated and repeatedly extracted with chloroform (15 ml). The collected organic layers were dried over sodium sulfate, filtered and evaporated at reduced pressure at 0 °C. The yellow solid, yield 0.04 g (45%), with m.p. 68–73 °C (dec.), $[\alpha]_D$ –58° (*c* 1, $CHCl_3$) was stored at –5 °C under nitrogen. ^{1}H NMR spectrum: 7.08 s, 1 H (H-2); 5.68 m, 1 H (H-6); 5.13 brs, 2 H (H_2N); 3.14 m, 2 H (H-4). ^{13}C NMR spectrum ($(CD_3)_2SO$): 174.80 C ($CONH_2$), 143.32 CH (C-2), 135.11 CH (C-6), 107.49 CH (C-5), 106.09 C (C-3), 28.17 CH (C-4). Other proton and carbon signals not assigned to 1,4-dihydronicotinamide moiety, see Table II.

Reduction of Ethyl Phenylglyoxylate with NADH Model **15**

Reaction was performed in the dark under dry nitrogen at the temperature of 22 °C and monitored by measurement of UV absorption in the region of 200 to 500 nm. Reaction products were analyzed by ^{1}H NMR spectra. A freshly prepared solution of 1,4-dihydropyridine derivative **15** (90 mg, 0.25 mmol) in acetonitrile (10 ml) was added to a solution of ethyl phenylglyoxylate (45 mg, 0.25 mmol) and magnesium perchlorate (62 mg) in the same solvent (5 ml). After 4 h the absorption maximum of the compound **15** at 352 nm completely disappeared and the reaction was stopped by addition of water (3 ml). Acetonitrile was distilled off under reduced pressure and the residue was extracted with dichloromethane (20 ml). The aqueous phase was evaporated and the residue exhibited ^{1}H NMR patterns similar to those in salt **14**: 9.24 s, 1 H (H-2); 8.82 d, 1 H, J = 8.6 (H-6); 8.63 d, 1 H, J = 4.4 (H-4, pyridine ring); 8.01 dd, 1 H, J = 4.4 and 8.6 (H-5); 7.69 brs (NH); 7.05 brs (NH); 6.34 s, 1 H

(H-4, furan ring); 5.60 s, 2 H (H-3b); 4.94–3.84 m, 3 H (H-1′, H-2′ and H-3′); 4.89 m, 2 H (H-4′); 2.36 s, 3 H (Me-2a); 1.48 s, 3 H and 1.30 s, 3 H (Me_2C). The organic extract was dried over magnesium sulfate, filtered, evaporated, treated with chloroform and chromatographed on a short silica gel column. All collected eluents afforded only a mixture (40 mg) of ethyl mandelate (65%) and ethyl phenylglyoxylate (35%). The both esters were carefully separated on a silica gel column (40 g SiO_2) and gave 26 mg of ethyl mandelate as colourless oil of $[\alpha]_D$ –2.61° (*c* 0.5, $CHCl_3$), in repeated experiment $[\alpha]_D$ –2.80° (*c* 0.5, $CHCl_3$), corresponding to 1.81% e.e. (1.95% e.e., respectively) of (*R*)-(–)-enantiomer. ^{1}H NMR spectrum: 7.25 s, 5 H (Ph); 4.15 m, 2 H (CH_2); 3.51 brs, 1 H (OH); 1.16 t, 3 H (Me).

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