A Practical Synthesis of Ethyl 1,2,4-Triazole-3-Carboxylate and its use in the Formation of Chiral 1′,2′-*seco*-Nucleosides of Ribavirin [1]

Purushotham Vemishetti, Robert W. Leiby,
Elie Abushanab*, and Raymond P. Panzica*

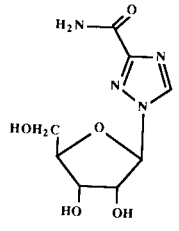
Departments of Medicinal Chemistry and Chemistry, University of Rhode Island,
Kingston, Rhode Island 02881

Received September 15, 1987

A practical and efficient synthesis of ethyl 1,2,4-triazole-3-carboxylate (**6a**, R″ = H) from ethyl carboethoxyformimidate hydrochloride (**7**) is described. Alkylation of this heterocycle with the chloromethyl ethers of 1,3-*O*-dibenzylbutane-1,2*R*,3*S*-triol (**8a**) and 1,3,4-*O*-tribenzylbutane-1,2*R*,3*S*,4-tetrol (**8b**), followed by conversion of the ester function to the amide and deprotection, furnished the chiral 1′,2′-*seco*-nucleosides of ribavirin, **11a** and **11b**, respectively.

J. Heterocyclic Chem., **25**, 651 (1988).

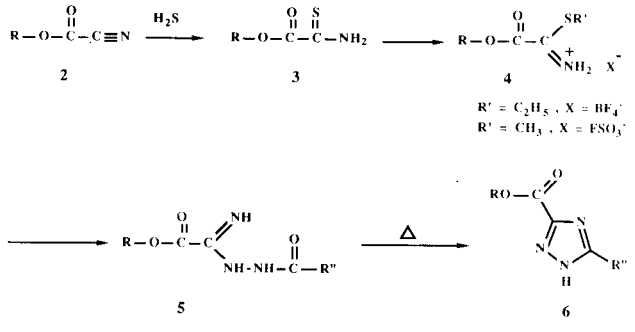
In an attempt to find additional broad-spectrum antiviral agents like ribavirin (**1**, 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide), synthetic programs were initiated involving chemical modifications of this nucleoside [2]. Some of these studies focused on altering the sugar moiety and a variety of *N*(1)-pentofuranosyl analogues were prepared [2]. A more recent addition to this category was an acyclic *N*(1)-derivative possessing the DHPG-type side chain [3]. In an effort to synthesize additional acyclic analogues of ribavirin, especially those which retain the chirality and carbon framework of the natural pentoses, we undertook the preparation of 1′,2′-*seco*-nucleosides **11** of **1**. During this synthetic study, we became aware that a practical, chemical route to 1,2,4-triazole-3-carboxylic esters was needed. Such heterocycles are valuable synthons in the chemical synthesis of ribavirin analogues [4,5]. Methods for the preparation of such esters exist [5,6], but a shorter and more efficient approach to these heterocycles was desired. We now wish to describe a convenient synthesis of ethyl 1,2,4-triazole-3-carboxylate **6a**, (R″ = H) and its use in the preparation of 1′,2′-*seco*-analogues of ribavirin.



1

A literature search concerning the syntheses of 1,2,4-triazole esters revealed that ethyl 5-methyl-1,2,4-triazole-3-carboxylate **6a** (R″ = CH_3) [7] could be prepared in 34% overall yield starting with ethyl 2-thiooxamate (**3a**, Scheme 1). Alkylation of **3a** with either triethyloxonium tetrafluoroborate or methyl fluorosulfonate

Scheme 1

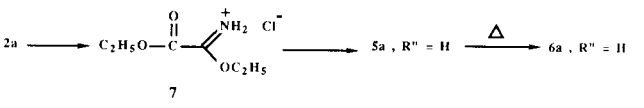


a series : R = C_2H_5 , b series : R = $CH_2C_6H_5$

afforded the corresponding thioformimidates **4a** [8] which were then reacted with acethydrazide to furnish the amidrazone **5a** (R″ = CH_3). This intermediate upon thermal cyclization provided **6a** (R″ = CH_3). The same synthetic methodology was used by Ohno and coworkers [5] to prepare benzyl 1,2,4-triazole-3-carboxylate (**6b**, R″ = H). However, their synthesis started with benzyl cyanoformate (**2b**) [10] and they subsequently reacted **4b** (R′ = C_2H_5 and X = BF_4^-) with formyl hydrazine instead of acethydrazide to obtain **5b** (R″ = H).

The present procedure (Scheme 2) is shorter and avoids the thiation-alkylation steps. It uses the hydrochloride **7** of ethyl carboethoxyformimidate [11] which can be conveniently synthesized from ethyl cyanoformate [12]. Reaction

Scheme 2

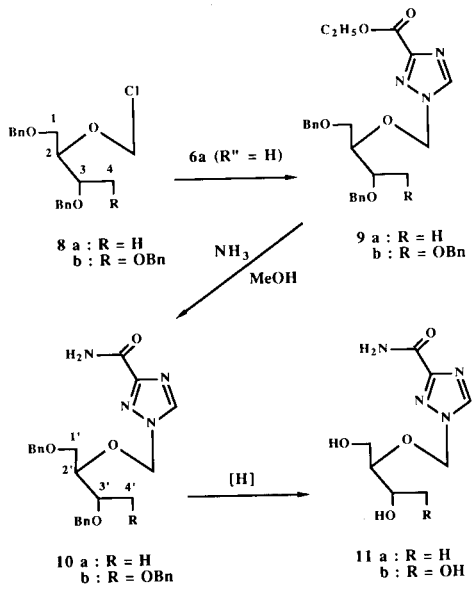


of **7** with formyl hydrazine at 5° furnished **5a** (R″ = H, 99%) which when heated at 165° cyclized to **6a** (R″ = H)

in near-quantitative yield [13].

We now turned our attention to coupling this synthon with the protected, chiral chloromethyl ethers **8a** and **8b** (Scheme 3). The corresponding precursors of **8a** and **8b**, *i.e.*, 1,3-*O*-dibenzylbutane-1,2*R*,3*S*-triol and 1,3,4-*O*-tribenzylbutane-1,2*R*,3*S*,4-tetrol, were prepared from D-isoascorbic acid [14]. Chloromethylation of these chirons was carried out with paraformaldehyde and hydrogen chloride gas in dichloromethane at 0° [15a]. The percent purity of **8a** and **8b** was determined by integration of the

Scheme 3



Bn = Benzyl

characteristic OCH_2Cl resonance which appears approximately at δ 5.6 in the ^1H nmr spectrum. In our hands, we found the percent of chloromethylation to range between 80 to 90% [15b]. Treatment of **8a** and **8b** with silylated **6a** (R'' = H) furnished the blocked 1′,2′-*seco*-nucleosides **9a** and **9b**, respectively. In each case, a small amount of the 5-carboxylate isomer was isolated from the reaction mixture.

The site of alkylation on the 1,2,4-triazole ring was determined by ^1H nmr spectroscopy. The 1′,2′-*seco*-nucleosides prepared in this study followed the same trend observed for 3- and 5-substituted 1-β-D-ribofuranosyl-1,2,4-triazoles [16]. The C(3)H proton chemical shift of the 5-substituted isomer is more shielded (*ca.* δ 7.9) then than the C(5)H signal of the 3-substituted isomer (*ca.* δ 8.2) whereas the proton chemical shift for OCH_2N methylene of the 3-isomer appears at higher field (*ca.* δ 5.6) as compared to the signal of the 5-substituted isomer (*ca.* δ 6.0). This spectral feature provides a rapid and convenient method to assign the site of attachment of similar acyclic chains on the 1,2,4-triazole-3-carboxylic ester ring.

The ester function of **9a** and **9b** was easily converted to the carboxamide moiety using methanolic ammonia at room temperature. Debenzylation of the acyclic side chain was accomplished by transfer hydrogenation over Pearlman's catalyst [17]. These last two steps were near-quantitative and provided the desired 1′,2′-*seco*-nucleosides **11a** and **11b** in reasonable overall yields.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting apparatus and are uncorrected. The ^1H nmr spectra were obtained with a Varian EM-390 spectrometer. The chemical shifts are expressed in parts per million with respect to TMS. Thin layer chromatography was run on precoated (0.2 mm) silica gel 60 F-254 plates manufactured by EM Laboratories, Inc., and short-wave ultraviolet light (254 nm) was used to detect the uv-absorbing spots. Silica gel (Merck, 230-400 mesh, 60A) suitable for chromatographic use was employed for column chromatography. All solvent proportions are by volume unless otherwise stated. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

Ethyl carboethoxyformimidate hydrochloride (**7**) was obtained according to reference [12] with minor modifications. Therefore, we have included our procedure for the synthesis of **7**.

Ethyl Carboethoxyformimidate Hydrochloride (**7**).

Ethyl cyanoformate (Aldrich, 16.5 g, 167 mmoles) was added to a solution of absolute ethanol (7.8 g, 170 mmoles) and anhydrous diethyl ether (25 ml). The solution was stirred and maintained between -35° and -15°. Dry hydrogen chloride gas was bubbled into the reaction mixture until 18 g were absorbed. The reaction flask was tightly stoppered and placed in a freezer for six days. The precipitated solid was collected by filtration, washed with dry ether, and dried in a vacuum desiccator over sodium hydroxide/phosphorus pentoxide to furnish 23.9 g of **7** (79%).

Ethyl β-Formyloxalamidrazone (**5a**, R'' = H).

To a cold solution (5°) of formyl hydrazine (Aldrich, 3.31 g, 55.1 mmoles) in dry, AR-methanol (50 ml) was added a cold solution of **7** (10.0 g, 55.1 mmoles) in AR-methanol (25 ml). The reaction mixture was stirred at 5° for 10 minutes and then neutralized with reagent grade sodium bicarbonate (4.63 g, 55.1 mmoles) which was previously dissolved in water (30 ml). The solution was filtered, concentrated *in vacuo* to near-dryness, and the precipitated product collected by filtration (8.67 g, 98.9%; mp 149-151°). Recrystallization from ethyl acetate provided the pure amidrazone, mp 152-153°; ^1H nmr (DMSO-d_6): δ 1.25 (t, 3, CH_3), 4.20 (q, 2, CH_2), 6.20-6.60 (m, 2, NH), 8.43 (s, 1, C*H*O), 10.20 (s, 1, NH).

Anal. Calcd. for $C_5H_9N_3O_3$: C, 37.73; H, 5.70; N, 26.40. Found: C, 37.88; H, 5.45; N, 26.30.

Ethyl 1,2,4-Triazole-3-carboxylate (**6a**, R'' = H).

Compound **5a** (R'' = H, 4.44 g, 27.9 mmoles) was placed in a sublimation apparatus and heated at 165° (oil bath) under vacuum. After heating for 10 minutes, the molten material solidified and was allowed to cool. The crystalline residue was recrystallized from absolute ethanol to afford **6a** (R'' = H) (3.80 g, 97%), mp 169-171°; ^1H nmr (DMSO-d_6): δ 1.32 (t, 3, CH_3), 4.30 (q, 2, CH_2), 8.51 (s, 1, C(5)H), 14.69 (br s, 1, NH).

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.77. Found: C, 42.34; H, 4.90; N, 29.60.

2*R*-Chloromethoxy-1,3*S*-dibenzyloxybutane (**8a**).

1,3-*O*-Dibenzylbutane-1,2*R*,3*S*-triol [14b] (10.74 g, 37 mmoles) was dissolved in 65 ml of dry dichloromethane (distilled from phosphorus pentoxide) to which 1.7 g of paraformaldehyde was added. The reaction mixture was cooled in an ice bath and hydrogen chloride gas (dried through concentrated sulfuric acid) was passed through the stirred solution for 4 hours. Next, anhydrous calcium chloride was added and the

suspension stirred for 5 minutes. It was then filtered and the filtrate was concentrated under diminished pressure to furnish 12.68 g of an oily material, which contains 84% of the chloromethyl ether **8a** as indicated by ^{1}H nmr spectroscopy.

2*R*-Chloromethoxy-1,3*S*,4-tribenzyloxybutane (**8b**).

Treatment of 1,3,4-tribenzyloxy-D-erythritol [14b] (15.86 g, 40 mmoles) with paraformaldehyde (1.83 g) in the presence of hydrogen chloride gas, as described for **8a**, afforded 17.81 g of a liquid product. The ^{1}H nmr indicated that it contained 81% of the title chloromethyl ether **8b**.

Ethyl 1-[(1,3*S*-Dibenzyloxy-2*R*-butoxy)methyl]-1,2,4-triazole-3-carboxylate (**9a**).

Ethyl 1,2,4-triazole-3-carboxylate (3.53 g, 25 mmoles) and ammonium sulfate in hexamethyldisilazane (HMDS, 90 ml) were heated at reflux for 5 hours. The excess HMDS was distilled off under reduced pressure and the silylated triazole ester was treated with **8a** (9.54 g, 24 mmoles) in acetonitrile (155 ml) and in the presence of tetraethylammonium iodide (38 mg). The resulting mixture was stirred at reflux for 4.5 hours and then 3 days at room temperature. The acetonitrile was removed *in vacuo* and the remaining residue was dissolved in dichloromethane (40 ml). This solution was washed with water, a 10% sodium thiosulfate solution, water, and brine, and then dried over anhydrous magnesium sulfate. The solvent was removed under diminished pressure and the resulting syrup (9.94 g) was applied to a silica gel column (200 g) and the column eluted with hexane-ethyl acetate (65/35, v/v). Fractions containing uv-active material were pooled and evaporated to afford pure ethyl 1-[(1,3*S*-dibenzyloxy-2*R*-butoxy)methyl]-1,2,4-triazole-5-carboxylate (0.09 g, 0.8%) and **9a** (7.02 g, 64%). Physical constants of **9a** are: $[\alpha]_D$ = -0.21 (c = 2.405, ethanol); ^{1}H nmr (deuteriochloroform): δ 1.08 (d, 3, CH_3), 1.37 (t, 3, OCH_2CH_3), 3.3-4.08 (m, 4), 4.23-4.63 (m, 6, $CH_2C_6H_5$ and OCH_2CH_3), 5.68 (s, 2, OCH_2N), 7.25 (br s, 10, $CH_2C_5H_5$), 8.27 (s, 1, C(5)H).

Anal. Calcd. for $C_{24}H_{29}N_3O_5$: C,65.59; H, 6.65; N, 9.56. Found: C, 65.40; H, 6.72; N, 9.53.

Ethyl 1-[(1,3*S*,4-tribenzyloxy-2*R*-butoxy)methyl]-1,2,4-triazole-3-carboxylate (**9b**).

The synthetic procedure was identical to that described for **9a**. Ethyl 1,2,4-triazole-3-carboxylate (1.19 g, 8.43 mmoles) was silylated and condensed with **8b** (6.66 mmoles as based on percent purity) in acetonitrile (60 ml) containing tetraethylammonium iodide (16 mg). Work-up and chromatography provided 310 mg (6.8%) of ethyl 1-[(1,3*S*,4-tribenzyloxy-2*R*-butoxy)methyl]-1,2,4-triazole-5-carboxylate and 1.52 g (33%) of the title compound **9b** [18] as colorless gums. Physical constants for **9b** are: $[\alpha]_D^{25}$ = -3.22 (c = 1.645, ethanol); ^{1}H nmr (deuteriochloroform): δ 1.37 (t, 3, CH_2CH_3), 3.17-4.2 (m, 6), 4.27-4.73 (m, 8, $CH_2C_6H_5$ and CH_2CH_3), 5.63 (s, 2, OCH_2N), 7.25 (s, 15, $CH_2C_6H_5$), 8.2 (s, H, C(5)H).

Anal. Calcd. for $C_{31}H_{35}N_3O_6$: C, 67.54; H, 6.42; N, 7.65. Found: C, 67.52; H, 6.54; N, 7.80.

1-[(1,3*S*-Dibenzyloxy-2*R*-butoxy)methyl]-1,2,4-triazole-3-carboxamide (**10a**).

A solution of **9a** (4.7 g, 10 mmoles) in 100 ml of methanolic ammonia (previously saturated at -10°) was allowed to stand at room temperature for 3 days in a sealed flask. The solvent was removed under diminished pressure to provide crystalline **10a** (4.33 g, 98%). An analytical sample was prepared by recrystallization from ethanol, mp 124-125°; $[\alpha]_D^{25}$ = -2.19 (c = 1.184, chloroform); ^{1}H nmr (deuteriochloroform): δ 1.1 (d, 3, CH_3), 3.33-4.12 (m, 4), 4.43 (q_{AB} J = 12 Hz, 2, $CH_2C_6H_5$), 4.43 (s, 2, $CH_2C_6H_5$), 5.68 (s, 2, OCH_2N), 6.78-7.07 (br s, 2, $CONH_2$, deuterium oxide exchangeable), 7.25 (br s, 10, $CH_2C_6H_5$), 8.2 (s, 1, C(5)H).

Anal. Calcd. for $C_{22}H_{26}N_4O_4$: C, 64.38; H, 6.38; N, 13.65. Found: C, 64.65; H, 6.37; N, 13.58.

1-[(1,3*S*,4-Tribenzyloxy-2*R*-butoxy)methyl]-1,2,4-triazole-3-carboxamide (**10b**).

The synthetic procedure was similar to that described for **10a**. Compound **9b** (889 mg, 1.63 mmoles) afforded the title compound **10b** (770 mg, 92%) as a gum, $[\alpha]_D^{25}$ = -5.90 (c = 1.365, ethanol); ^{1}H nmr (deuteriochloroform): δ 3.2-4.22 (m, 6), 4.33-4.78 (m, 6, $CH_2C_6H_5$), 5.6 (s, 2, OCH_2N), 6.8-7.67 (m, 17, $CH_2C_6H_5$ and NH_2 (deuterium oxide exchangeable)), 8.18 (s, 1, C(5)H).

Anal. Calcd. for $C_{29}H_{32}N_4O_5$: C, 67.43; H, 6.24; N, 10.85. Found: C, 67.38; H, 6.54; N, 11.07.

1-[(1,3*S*-dihydroxy-2*R*-butoxy)methyl]-1,2,4-triazole-3-carboxamide (**11a**).

Compound **10a** (4.07 g, 9.92 mmoles) was dissolved in absolute ethanol (75 ml) and to this solution was added 20% Palladous hydroxide/C (1.1 g) and cyclohexene (19 ml). This mixture was heated at reflux for 6 hours and, while hot, filtered through a celite pad. The pad was washed with hot ethanol, the wash and filtrate were combined, and evaporated to dryness to furnish a quantitative yield of **11a** as a gum. This material was dissolved in a minimal amount of distilled water and lyophilized to provide a colorless solid, mp 79-84°; $[\alpha]_D$ = -7.8 (c = 2.75, ethanol); ^{1}H nmr (DMSO-d_6): δ 0.88 (d, 3, CH_3), 3.17-3.8 (m, 4), 4.45-4.83 (m, 2, OH, deuterium oxide exchangeable), 5.67 (s, 2, OCH_2N), 7.62 (br d, 2, NH_2, deuterium oxide exchangeable), 8.73 (s, 1, C(5)H).

Anal. Calcd. for $C_6H_{14}N_4O_4$: C, 41.76; H, 6.13; N, 24.34. Found: C, 42.00; H, 6.17; N, 24.19.

1-[(1,3*S*,4-Trihydroxy-2*R*-butoxy)methyl]-1,2,4-triazole-3-carboxamide (**11b**).

Transfer hydrogenation of 679 mg (1.32 mmoles) of **10b** was carried out as described in the preceding experiment. A quantitative yield of **11a** was obtained. This material was dissolved in water and lyophilized to a white solid, mp 71-73°; $[\alpha]_D$ = -9.47 (c = 1.995, ethanol); ^{1}H nmr (DMSO-d_6): δ 2.93-3.78 (m, 6), 3.96-4.87 (m, 3, OH, deuterium oxide exchangeable), 5.63 (s, 2, OCH_2N), 7.59 (br d, 2, NH_2, deuterium oxide exchangeable), 8.68 (s, 1, C(5)H).

Anal. Calcd. for $C_6H_{14}N_4O_5$: C, 39.03; H, 5.73; N, 22.76. Found: C, 39.21; H, 5.80; N, 22.54.

Acknowledgments.

This work was supported by U. S. Army Contract No. DAMD-86-C-6012. We thank Dr. Joseph T. Witkowski (Schering) for helpful discussions and Mr. H. El-Sabbagh for technical assistance.

REFERENCES AND NOTES

[1] Presented in part at the 194th National Meeting of the American Chemical Society, New Orleans, Louisiana, August, 1987, MEDI 10.

[2] "Ribavirin: A Broad Spectrum Antiviral Agent", R. A. Smith and W. Kirkpatrick, eds, Academic Press, New York, 1980, pp 3-8.

[3] T.-S. Lin and M.-C. Lin, *Tetrahedron Letters*, **25**, 611 (1984).

[4] J. T. Witkowski, R. K. Robins, R. W. Sidwell, and L. N. Simon, *J. Med. Chem.*, **15**, 1150 (1972).

[5] Y. Ito, Y. Nii, S. Kobayashi, and M. Ohno, *Tetrahedron Letters*, 2521 (1979).

[6] G. E. Cipens and V. Grinsteins, *Chem. Abstr.*, **63**, 13243 (1965); *Chem. Abstr.*, **64**, 5074 (1966).

[7] J. E. Oliver and P. E. Sonnet, *J. Org. Chem.*, **38**, 1437 (1973).

[8] Using a similar approach, Schmidt and Heerman [9] also prepared the thioformimidate **4a** (R' = CH_3 and X = FSO_3^-) in 90% yield and employed this reagent in their synthesis of ribavirin (**1**).

[9] R. R. Schmidt and D. Heerman, *Chem. Ber.*, **114**, 2825 (1981).

[10] Y. Nii, K. Okano, S. Kobayashi, and M. Ohno, *Tetrahedron Letters*, 2517 (1979).

[11] E. Gomez, C. Avendano, and A. McKillop, *Tetrahedron*, **42**, 2625 (1986).

[12] G. I. Braz, G. V. Myasnikova, A. Ya. Yakubovich and V. P. Bazov, *Chem. Abstr.*, **62**, 562 (1965).

[13] The methyl ester was synthesized using the transesterification procedure cited in reference [7]. It was identical to an authentic sample

which was generously supplied to us by Drs. Roland K. Robins and Ganapathi R. Revankar of the Nucleic Acid Research Institute, Costa Mesa, California.

[14a] E. Abushanab, M. Bessodes, and K. Antonakis, *Tetrahedron Letters*, **25**, 3841 (1984); [b] E. Abushanab, P. Vemishetti, R. W. Leiby, H. K. Singh, A. B. Mikkilineni, A. F. Cichy, D. C.-J. Wu, and R. P. Panzica, Abstracts, 194th National Meeting of the American Chemical Society, New Orleans, Louisiana, August 1987, ORGN 279.

[15a] W. T. Ashton, L. F. Canning, G. F. Reynolds, R. L. Tolman, J. D. Karkas, R. Liou, M. E. M. Davies, C. M. DeWitt, H. C. Perry, and A. K. Fields, *J. Med. Chem.*, **28**, 926 (1985); [b] K. K. Ogilvie, R. G. Hamilton, M. F. Gillen, B. K. Radatus, K. O. Smith, and K. S. Galloway, *Can. J. Chem.*, **62**, 16 (1984).

[16] G. P. Kreishman, J. T. Witkowski, R. K. Robins, and M. P. Schweizer, *J. Am. Chem. Soc.*, **94**, 5894 (1972).

[17] K. K. Ogilvie, U. O. Cheriyan, B. K. Radatus, K. O. Smith, K. S. Galloway, and W. L. Kennell, *Can. J. Chem.*, **60**, 3005 (1982).

[18] Alkylation of methyl 1,2,4-triazole-3-carboxylate (2.57 g, 20 mmoles) with 8.9 g of **8b** (81% pure, 16.4 mmoles) furnished methyl 1-[(1,3*S*,4-tribenzyloxy-2*R*-butoxy)methyl]-1,2,4-triazole-5-carboxylate (2.05 g, 19%) and methyl 1-[(1,3*S*,4-tribenzyloxy-2*R*-butoxy)methyl]-1,2,4-triazole-3-carboxylate (3.34 g, 31%). Physical data for the 5-carboxylate are: $[\alpha]_D^{25}$ = -1.9 (c = 2.105, ethanol); ^{1}H nmr (deuteriochloroform): δ 3.3-3.75 (m, 5), 3.85 (s, 3, OCH_3), 4.02-4.25 (m, 1), 4.32-4.68 (m, 6, $CH_2C_6H_5$), 5.97 (s, 2, OCH_2N), 7.23 (br s, 15, $CH_2C_6H_5$), 7.87 (s, 1, C(3)H).

Anal. Calcd. for $C_{30}H_{33}N_3O_6$: C, 67.79; H, 6.26; N, 7.90. Found: C, 68.08; H, 6.03; N, 7.90.

Physical constants of the 3-carboxylate are: $[\alpha]_D^{25}$ = -3.66 (c = 1.91, ethanol); ^{1}H nmr (deuteriochloroform): δ 3.25-4.23 (m, 6), 3.87 (s, 3, OCH_3), 4.27-4.75 (m, 6, $CH_2C_6H_5$), 5.6 (s, 2, OCH_2N), 7.22 (br s, 15, $CH_2C_6H_5$), 8.17 (s, 1, C(5)H).

Anal. Calcd. for $C_{30}H_{33}N_3O_6$: C, 67.79; H, 6.26; N, 7.90. Found: C, 67.74; H, 6.01; N, 7.90.