

Heterocyclic Tricycles as Internal N-Glycosides from 2-Methyl-5-nitro-6-(2-nitrophenyl)-4-phenyl(2-furyl)tetrahydropyrans

Lutz Götze¹, Manfred Michalik², Klaus Peseke^{1*}, José Quinoces^{3,4} and Helmut Reinke¹

¹Fachbereich Chemie der Universität Rostock, D-18051 Rostock, Germany

Fax: +49-381 498 1763, E-mail: klaus.peseke@chemie.uni-rostock.de,

URL: <http://www.fb-chemie.uni-rostock.de/organik/peseke/index.html>

²Institut für Organische Katalyseforschung an der Universität Rostock, Buchbinderstr. 5-6, D-18055 Rostock, Germany

³Centro Bioactivos Quimicos, Universidad Central de Las Villas, Santa Clara, Cuba

⁴Departamento de Farmacia e Bioquímica, Universidade Bandeirante de Sao Paulo (UNIBAN), Rua Maria Candida, 1813 Vila Guilherme Sao Paulo-SP, Brasil, CEP: 02071-013

* Author to whom correspondence should be addressed.

Received: 10 February 2000 / Accepted: 14 March 2000 / Published: 16 March 2000

Abstract: 1-Methyl-10-nitro-11-phenyl(2-furyl)-2-aza-13-oxa-tricyclo[7.3.1.0^{3,8}]trideca-3,5,7-trienes **3** were synthesized *via* the reduction of the aromatic 2-nitro group of 2-methyl-5-nitro-6-(2-nitrophenyl)-4-phenyl(2-furyl)tetrahydropyrans **2** and subsequent condensation with their anomeric OH group. As by-products, the corresponding 6-(2-aminophenyl)-2-methyl-5-nitro-4-phenyl(2-furyl)tetrahydropyrans **4** were isolated.

Keywords: pyran derivatives, tricyclo[7.3.1.0^{3,8}]trideca-3,5,7-trienes, N-glycosides.

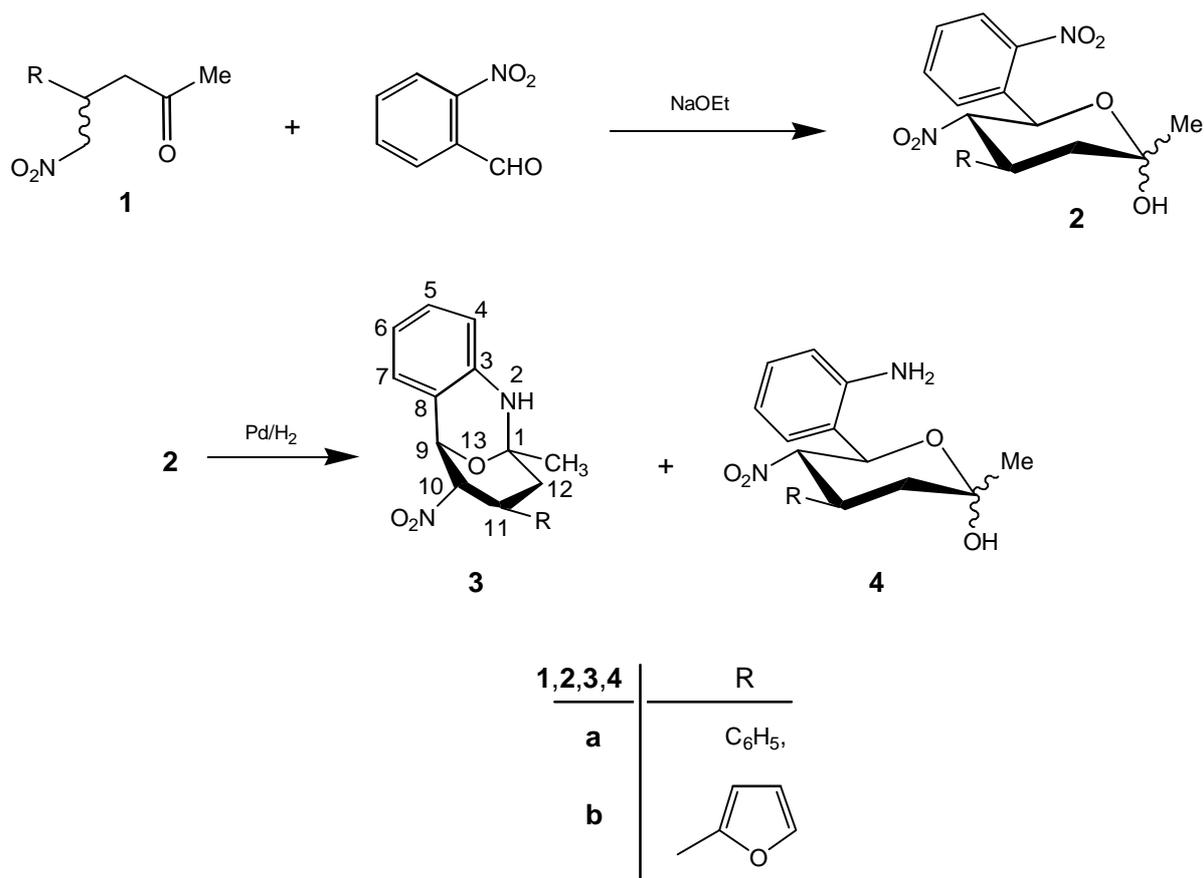
Introduction

Recently we published a new method for the preparation of some tetrahydro-2-pyrans by nitroal-dol reaction of *g*-nitro ketones with various aromatic aldehydes and subsequent cyclization [1]. The anomeric OH group of these tetrahydro-2-pyrans underwent the Fischer-glycosidation by refluxing

in methanol with a catalytic amount of concentrated hydrochloric acid to furnish the corresponding α -methyl glycosides. In this paper, we describe the use of an internal N-glycosidation based on 2-methyl-5-nitro-6-(2-nitrophenyl)-4-phenyl(2-furyl)tetrahydropyranols (**2**) to prepare new tricyclic compounds.

Results and Discussion

The [2*RS*-(**2a**, **4b**, **5a**, **6b**)]-(\pm)-3,4,5,6-tetrahydro-2-methyl-5-nitro-6-(2-nitrophenyl)-4-phenyl(2-furyl)-2*H*-pyran-2-ols **2a,b** were synthesized by treatment of (*RS*)-(\pm)-5-nitro-4-phenyl(2-furyl)-2-pentanones (**1a,b**) with 2-nitrobenzaldehyde in the presence of sodium ethoxide in dry ethanol at room temperature [1]. The reduction of compounds **2** with palladium on charcoal in ethyl acetate yielded mixtures of (1*RS*, 9*RS*, 10*RS*, 11*RS*)-(\pm)-1-methyl-10-nitro-11-phenyl(2-furyl)-2-aza-13-oxa-tricyclo-[7.3.1.0^{3,8}]trideca-3,5,7-trienes **3a,b** and of [2*RS*-(**2a**, **4b**, **5a**, **6b**)]-(\pm)-6-(2-aminophenyl)-3,4,5,6-tetrahydro-2-methyl-5-nitro-4-phenyl(2-furyl)-2*H*-pyran-2-ols **4a,b**. By separation with column chromatography we obtained as main products the tricycles **3a** and **3b** as crystalline solids in 57 and 54% yields (Scheme 1). The 6-(2-aminophenyl)-3,4,5,6-tetrahydro-2-methyl-5-nitro-4-phenyl(2-furyl)-2*H*-pyran-2-ols **4a,b** could be isolated as by-products in yields of 28 and 26%, respectively.



Scheme 1.

Although all compounds are racemates only one isomer is shown in Scheme 1. The analytical data of the isolated tricycles **3** are in agreement with these structures. On the other hand, the coupling constants in the ^1H NMR spectra and an X-ray crystal structure investigation of compound **3b** showed that during the reduction of the aromatic nitro group and the subsequent condensation the pyranoid ring system is forced into a boat conformation (Figure 1, Table 1). To our knowledge tricycles of this kind containing a pyranosidic ring system anellated to an aromatic ring in 1- and 2-position over a NH-function are not yet described in the literature.

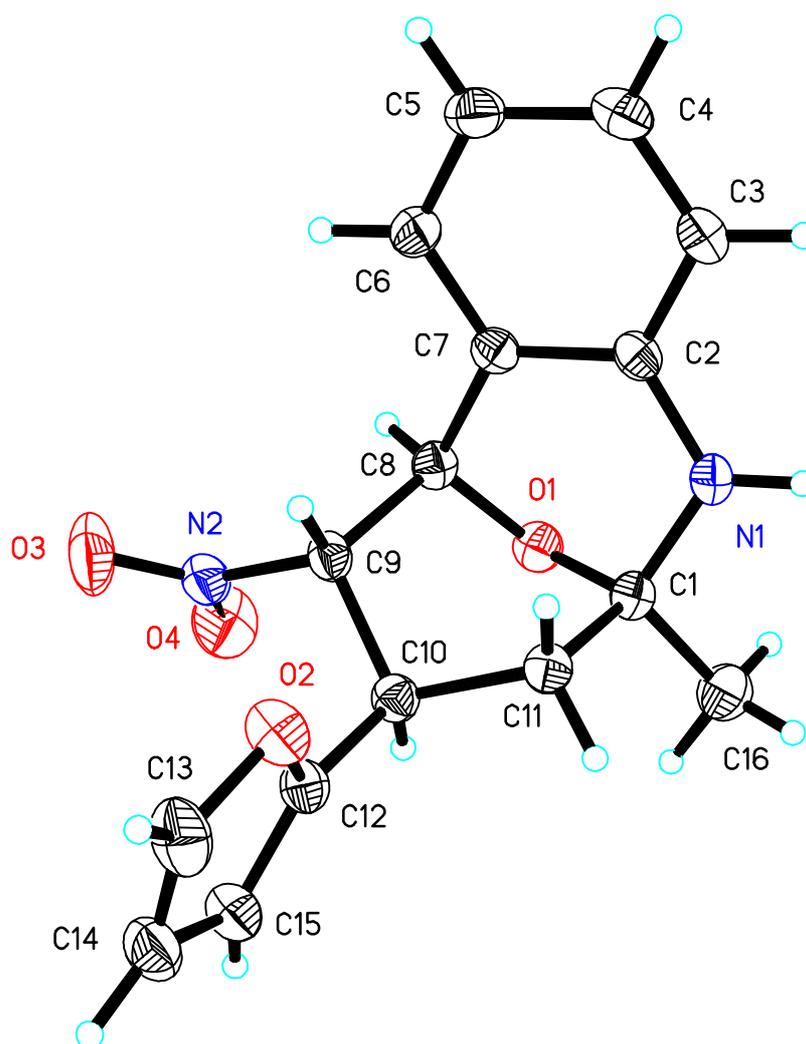


Figure 1. Molecular structure of **3b**.

Table 1. Crystal-structure data.

Empirical formula	C ₁₆ H ₁₆ N ₂ O ₄
Formula weight	300.31
Unit cell dimensions [Å]	a = 7.5790(10) b = 18.069(2) c = 21.553(2) α = 90° β = 90° γ = 90°
Volume [Å ³]	2951.6(6)
ρ (calculated) [g cm ⁻³]	1.352
Z	8
Crystal system	Orthorhombic
Space group	Pbca
F (000)	1264
(Mo-Kα) [mm ⁻¹]	0.098
Radiation	0.71073
Crystal size [mm]	0.94 x 0.44 x 0.05
Data collecting mode	ω-scan
2θ range	4.5/45
hkl range	-1/8, -1/19, -1/23
Measured refl.	2561
Unique refl.	1917
Observed refl.	1474
Completeness to Θ = 22.50°	99.6%
Data / restraints / parameters	1917 / 0 / 200
R1 for observed	0.0409
R1 for all	0.0590
wR2 for all	0.1104
GoF ²	1.046
ρ (max/min) [e.Å ⁻³]	0.292 / -0.183

The corresponding 5-amino-2-methyl-6-(2-nitro-phenyl)-4-phenyl(2-furyl)tetrahydropyrans are interesting owing to the biological activity of a variety of 5-amino-tetrahydro-2-pyrans [2-4]. Although there are many literature methods for conversion of an aliphatic nitro group into an amino function the 5-amino-tetrahydro-2-pyranol could not be obtained, neither by means of reducing agents like Zn/hydrochloric acid nor by refluxing with LiAlH₄ in tetrahydrofuran [5].

Due to the 1,3-interaction of the bulky aryl groups the compounds **4**, like the corresponding 2-methyl-5-nitro-6-(2-nitro-phenyl)-4-phenyl(2-furyl)tetrahydropyrans **2**, possess a 1,4-chair conformation. The J values for the couplings between the protons 3_{ax} -H, 4-H; 4-H, 5-H and 5H, 6-H are 10 - 13 Hz. Therefore, in all known cases the R, NH₂ and o-nitrophenyl groups are oriented in the preferred equatorial arrangement. Other diastereomers were not identified. According to the anomeric effect and the long-range coupling of the OH group with an axial proton of the ethylene group observed in the ¹H NMR spectra of **4a** and further investigated compounds [6] the OH group in **4** should be in axial position.

Conclusion

We have presented a method for the one-pot preparation of 1-methyl-10-nitro-11-phenyl(2-furyl)-2-aza-13-oxa-tricyclo[7.3.1.0^{3,8}]trideca-3,5,7-trienes from (2-nitrophenyl)pyran-2-oles by successful reduction of nitro group followed by internal N-glycosidation.

Experimental

General

Melting points were obtained on a Boëtius melting point apparatus. ¹H NMR and ¹³C NMR spectra were recorded on Bruker ARX 300 and AC 250 instruments with DMSO-d₆ as solvent. The calibration of spectra was carried out by means of solvent peaks (DMSO-d₆: δ ¹H= 2.50; δ ¹³C= 39.7). Signal assignment was confirmed by DEPT and/or ¹H, ¹³C COSY experiments. Mass spectra were recorded on an AMD 402/3 spectrometer (AMD Intectra GmbH). TLC was performed on silica gel foils 60 F₂₅₄ (Merck) with detection by charring with sulphuric acid. For column chromatography silica gel 60 (230-400 mm) (Merck) was used. Elemental analyses were carried out with a Leco CHNS-932 apparatus. Table 1 provides a summary of the crystallographic data of compound **3b**. A crystal of **3b** was sealed onto a glass fiber and mounted on a Siemens P4 automated four circle diffractometer (Mo-K_α radiation; $\lambda = 0.71073$ Å) with graphite monochromator and measured at $T = 293$ K. The structure was solved by direct methods (Siemens SHELXTL, version 4.2 for MS-DOS, Siemens Analytical Xray Inst. Inc.) and refined by the full-matrix least-squares method of SHELXL-97. Non-H atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed into theoretical positions and were refined by using the riding model. Crystallographic data (excluding structure factors) reported in this paper for structure **3b** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC-139912. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: int. code +(1223) 336-033; e-mail:deposit@ccdc.cam.ac.uk).

Method

The [2*RS*-(**2a**, **4b**, **5a**, **6b**)]-(±)-3,4,5,6-tetrahydro-2-methyl-5-nitro-6-(2-nitrophenyl)-4-phenyl(2-

furyl)-2H-pyran-2-ols **2a,b** (3 mmol) were dissolved in ethyl acetate (20 mL). A small portion of palladium on charcoal (10% Pd) was added. The vessel was filled three times with hydrogen under stirring at normal pressure. After prolongation of the stirring for 48 h the solution was filtrated over Celite. Elution with ethyl acetate (3x10 mL), solvent evaporation under reduced pressure and column chromatographic separation (toluene/ ethyl acetate = 5 : 1, v/v) afforded compounds **3** and **4**.

(1RS, 9RS, 10RS, 11RS)-(±)-1-Methyl-10-nitro-11-phenyl-2-aza-13-oxa-tricyclo[7.3.1.0^{3,8}]trideca-3,4,5-triene (**3a**)

Yield 0.53 g (57%).- *m.p.* 193-194°C (ether).- ¹H NMR (250.1 MHz, DMSO-d₆): δ/ppm = 7.32-7.10 (m, 7H, C₆H₅, H-5, H-7), 6.80 (m, 1H, H-6), 6.79 (s, 1H, NH), 6.70 (m, 1H, H-4), 5.45 (br s, 1H, H-9), 4.93 (dd, 1H, *J*_{10,11} = 10.4 Hz, *J*_{9,10} = 0.9 Hz, H-10), 3.35 (ddd, 1H, H-11), 2.05 (dd, 1H, *J*_{12,12'} = 14.3 Hz, *J*_{11,12} = 4.3 Hz, H-12), 1.66 (dd, 1H, *J*_{11,12} = 14.0 Hz, H-12'), 1.58 (s, 3H, CH₃).- ¹³C NMR (62.9 MHz, DMSO-d₆): δ/ppm = 140.1(C-3), 139.7 (*i*-C₆H₅), 128.8 (*m*-C₆H₅), 128.4, 127.4, 126.1 (C-5, C-7, *p*-C₆H₅), 127.6 (*o*-C₆H₅), 121.9 (C-8), 118.4 (C-6), 117.0 (C-4), 95.5 (C-10), 81.3 (C-1), 72.5 (C-9), 39.4 (C-12), 38.6 (C-11), 26.6 (CH₃).- IR(nujol), $\tilde{\nu}_{\max}$ /cm⁻¹ = 3402 (NH), 1548, 1378 (NO₂). - MS (70 eV, EI): *m/z* (%) = 310 (100, M⁺). For C₁₈H₁₈N₂O₃ (310.1) calcd.: C 69.65 H 5.85 N 9.03; found C 69.43 H 5.81 N 8.87.

(1RS, 9RS, 10RS, 11RS)-(±)-11-(2-Furyl)-1-methyl-10-nitro-2-aza-13-oxa-tricyclo[7.3.1.0^{3,8}]trideca-3,4,5-triene (**3b**)

Yield 0.48 g (54%).- *m.p.* 137-138°C (ether).- ¹H NMR (250.1 MHz, DMSO-d₆): δ/ppm = 7.45 (dd, 1H, *J*_{4-Fur,5-Fur} = 1.8 Hz, *J*_{3-Fur,5-Fur} = 0.6 Hz, H-5-Fur), 7.16 (m, 1H, H-7), 7.08 (m, 1H, H-5), 6.74 (m, 1H, H-6), 6.73 (s, 1H, NH), 6.62 (m, 1H, H-4), 6.26 (dd, 1H, *J*_{4-Fur,3-Fur} = 3.4 Hz, H-4-Fur), 6.16 (dd, 1H, H-3-Fur), 5.45 (br s, 1H, H-9), 4.94 (dd, 1H, *J*_{10,11} = 8.9 Hz, *J*_{9,10} = 0.9 Hz, H-10), 3.60 (ddd, 1H, H-11), 2.23 (dd, 1H, *J*_{12,12'} = 14.5 Hz, *J*_{11,12} = 4.6 Hz, H-12), 1.71 (dd, 1H, *J*_{11,12} = 12.3 Hz, H-12'), 1.55 (s, 3H, CH₃).- ¹³C NMR (62.9 MHz, DMSO-d₆): δ/ppm = 152.8 (C-2-Fur), 142.4 (C-5-Fur), 140.4 (C-3), 128.4, 125.9 (C-5, C-7), 120.7 (C-8), 118.1 (C-6), 116.5 (C-4), 110.5 (C-4-Fur), 105.5 (C-3-Fur), 91.8 (C-10), 80.7 (C-1), 72.3(C-9), 36.3 (C-12), 26.9 (C-11), 25.9 (CH₃).- IR(nujol), $\tilde{\nu}_{\max}$ /cm⁻¹ = 3409 (NH), 1548, 1367 (NO₂). - MS (70 eV, EI): *m/z* (%) = 310 (100, M⁺). For C₁₆H₁₆N₂O₄ (300.1) calcd. C 63.98 H 5.37 N 9.33; found C 63.98 H 5.21 N 9.25.

[2RS-(**2a**, **4b**, **5a**, **6b**)-(±)-6-(2-Aminophenyl)-3,4,5,6-tetrahydro-2-methyl-5-nitro-4-phenyl-2H-pyran-2-ol (**4a**)

Yield 0.27 g (28%).- *m.p.* 147-148°C (ethanol).- ¹H NMR (250.1 MHz, DMSO-d₆): δ/ppm = 7.30-7.15 (m, 5H, C₆H₅), 7.07-6.94 (m, 2H, H-4-C₆H₄, H-6-C₆H₄), 6.71 (dd, 1H, *J*_{3-C₆H₄,4-C₆H₄} = 8.0 Hz, *J*_{3-C₆H₄,5-C₆H₄} = 0.9 Hz, H-3-C₆H₄), 6.50 (ddd, 1H, *J*_{5-C₆H₄,6-C₆H₄} = *J*_{5-C₆H₄,3-C₆H₄} = 7.5 Hz, H-5-C₆H₄), 6.42 (d, 1H, *J*_{3ax,OH} = 1.5 Hz, OH), 5.50-5.30 (m, 2H, H-5, H-6), 5.05 (s, 2H, NH₂), 3.85 (ddd, 1H, *J*_{3ax,4} = 13.0 Hz, *J*_{4,5} = 10.7 Hz, *J*_{3eq,4} = 4.0 Hz, H-4), 2.18 (ddd, 1H, H-3ax), 1.93 (dd, 1H, *J*_{3ax,3eq} = 13.5 Hz, H-3eq), 1.44 (s, 3H,

CH_3)- ^{13}C NMR (62.9 MHz, DMSO- d_6): $\delta/ppm = 147.2$ (C-2- C_6H_4), 139.6 (*i*- C_6H_5), 129.5, 129.0 (C-4- C_6H_5 , C-6- C_6H_5), 128.8 (*m*- C_6H_5), 128.3 (*p*- C_6H_5), 127.5 (*o*- C_6H_5), 118.9 (C-1- C_6H_4), 116.3, 116.1 (C-3- C_6H_4 , C-5- C_6H_4), 95.6 (C-2), 88.5 (C-5), 72.7 (C-6), 42.6 (C-4), 41.4 (C-3), 28.4 (CH_3)- IR(KBr), $\tilde{\nu}_{max}/cm^{-1} = 3395, 3321$ (NH_2), 1545, 1336 (NO_2). - MS (70 eV, EI): m/z (%) = 328 (88, M^+). For $C_{18}H_{20}N_2O_4$ (328.1) calcd. C 65.83 H 6.14 N 8.53; found C 65.60 H 5.94 N 8.41.

[2*RS*-(**2a**, **4b**, **5a**, **6b**)]-(±)-6-(2-Aminophenyl)-4-(2-furyl)-3,4,5,6-tetrahydro-2-methyl-5-nitro-2H-pyran-2-ol (**4b**)

Yield 0.24 g (26%).- *m.p.* 153-154°C (ether).- 1H NMR (250.1 MHz, DMSO- d_6): $\delta/ppm = 7.58$ (dd, 1H, $J_{5-Fur,4-Fur} = 2.2$ Hz, $J_{5-Fur,3-Fur} = 0.8$ Hz, H-5-Fur), 7.05 (ddd, 1H, H-4- C_6H_4), 6.92 (dd, 1H, $J_{6-C_6H_4,5-C_6H_4} = 7.6$ Hz, $J_{6-C_6H_4,4-C_6H_4} = 1.5$ Hz, H-6- C_6H_4), 6.71 (dd, 1H, $J_{3-C_6H_4,4-C_6H_4} = 8.0$ Hz, $J_{3-C_6H_4,5-C_6H_4} = 0.9$ Hz, H-3- C_6H_4), 6.51 (ddd, 1H, $J_{5-C_6H_4,4-C_6H_4} = 7.6$ Hz, H-5- C_6H_4), 6.48 (br, 1H, OH), 6.39 (dd, 1H, $J_{3-Fur,4-Fur} = 3.4$ Hz, H-4-Fur), 6.27 (dd, 1H, H-3-Fur), 5.33-5.22 (m, 2H, H-5, H-6), 5.02 (br, 2H, NH_2), 4.00 (m, 1H, H-4), 2.20-2.00 (m, 2H, H-3ax, H-3eq), 1.46 (s, 3H, CH_3)- ^{13}C NMR (62.9 MHz, DMSO- d_6): $\delta/ppm = 152.9$ (C-2-Fur), 147.2 (C-2- C_6H_4), 142.8 (C-5-Fur), 129.6, 129.2 (C-4- C_6H_4 , C-6- C_6H_4), 118.6 (C-1- C_6H_4), 116.4, 116.3 (C-3- C_6H_4 , C-5- C_6H_4), 110.6 (C-4-Fur), 106.6 (C-3-Fur), 95.4 (C-2), 86.8 (C-5), 72.8 (C-6), 38.7 (C-3), 35.9 (C-4), 28.2 (CH_3)- IR(nujol), $\tilde{\nu}_{max}/cm^{-1} = 3391, 3321$ (NH_2), 1546, 1367 (NO_2). - MS (70 eV, EI): m/z (%) = 316 (18, M^+). For $C_{16}H_{16}N_2O_5$ (316.1) calcd. C 60.74 H 5.10 N 8.86; found C 60.86 H 5.03 N 8.79.

Acknowledgment: We would like to thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support. José Quincoes is grateful to FAPESP, Sao Paulo, Brasil, for financial support.

References and Notes

1. Peseke, K.; Götze, L.; Reinke, H.; Cedeno, Q. A.; Suarez, J. Q.; Andreu, M. G.; Castro, H. V. Synthesis of Substituted Tetrahydro-2-pyrans. *J. prakt. Chem.* **1997**, *339*, 656-659.
2. Kuhn, R. Aminozucker. *Angew. Chem.* **1957**, *69*, 23-33.
3. Balazs, E. A.; Jeanloz, R. W. *The Amino Sugars*; Academic Press: New York, 1966.
4. Brimacombe, J. S. Synthesen von Antibiotica-Zuckern. *Angew. Chem.* **1971**, *83*, 261-300.
5. Gibson, M. S. In: *The chemistry of functional groups*; Patai, S., Ed.; *The chemistry of the amino group*, Feuer, H., Ed.; Wiley & Sons: New York, 1986; Vol. 1, Chapter 2, p 37.
6. Götze, L.; Peseke, K.; Michalik, M. *unpublished results*.

Samples Availability: Available from the authors.