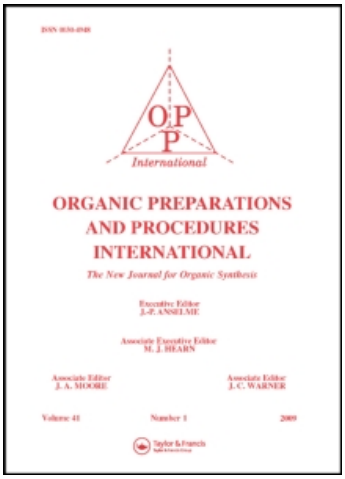


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

FORMATION OF A 1,2-DIHYDROPYRAZINE USING AN AMINO ACID AND D-GLUCOSE

C. W. Yuan[ab]; J. Beauhaire[a]; C. Marty[a]; J. L. Fourrey[c]; H. Richard[a]
[a] Department de Biochimie Industrielle, ENSIA, Massy, FRANCE [b] Department of Biomedical Engineering, Southeast University, Nanjing, PR China [c] ICSN CNRS, Gif/Yvette, FRANCE

To cite this Article Yuan, C. W. , Beauhaire, J. , Marty, C. , Fourrey, J. L. and Richard, H.(1992) 'FORMATION OF A 1,2-DIHYDROPYRAZINE USING AN AMINO ACID AND D-GLUCOSE', Organic Preparations and Procedures International, 24: 6, 665 — 669
To link to this Article: DOI: 10.1080/00304949209356241
URL: http://dx.doi.org/10.1080/00304949209356241

27. C. J. Pouchert, *The Aldrich Library of NMR Spectra*, 2nd Ed., Aldrich Chem. Co, Milwaukee, 1983.

28. C. J. Pouchert, *The Aldrich Library of Infrared Spectra*, 3rd Ed., Aldrich Chem. Co, Milwaukee, 1981.

****

FORMATION OF A 1,2-DIHYDROPYRAZINE USING AN AMINO ACID AND D-GLUCOSE

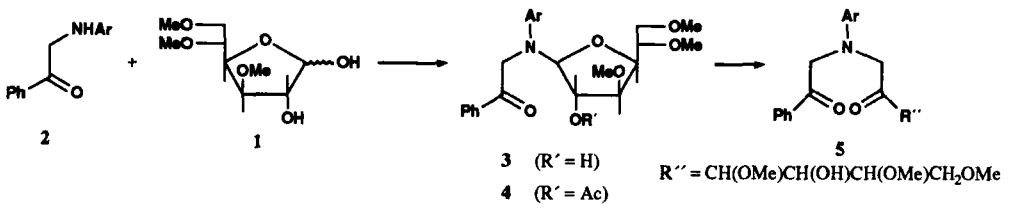
Submitted by (12/17/91) C. W. Yuan*†, J. Beauhaire†, C . Marty†, J. L. Fourrey‡ and H. Richard†

† *Departement de Biochimie Industrielle, ENSIA 1, Avenue des Olympiades, 91305 Massy, FRANCE*

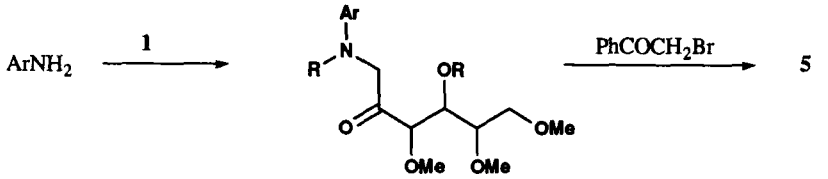
‡ *ICSN CNRS, 91190 GifYvette, FRANCE*

Pyrazines, the most important flavored compounds in food,[1] may have dihydropyrazines as precursors which are currently considered to be produced from complex interactions between amino acids and carbohydrates.[2] However, to our knowledge, such dihydropyrazines have never been isolated and identified due to their instability. A previous paper[3] reported that *antiaromatic* 1,4-dihydropyrazines can be synthesized only if the ring substituents are electron-deficient or hinder the conjugation of the 8p electron system by steric repulsion. Usually, the poorly stable 1,4-dihydropyrazines undergo a 1,3-sigmatropic rearrangement to form relatively stable 1,2-dihydropyrazines. In order to explore the pathway leading to the formation of pyrazines in the Maillard reaction, we undertook the synthesis of dihydropyrazines in which carbohydrate and amino acid moieties were combined.

3,5,6-Tri-O-methyl-D-glucose (**1**), ethyl glycine, *p*-toluidine and phenacyl bromide were chosen as starting materials in order to enhance the stability of reaction products. The D-glucose derivative **1**[4] and N-phenacyl-*p*-toluidine (**2**)[3] were prepared as reported previously. Reaction between **1** and **2** did not occur at room temperature and the decomposition of **1** became a serious problem with increasing reaction temperatures. Since Lewis acids[5] catalyze the condensation of aldehydes or ketones with secondary amines to form enamines, this led us to utilize zinc chloride ($ZnCl_2$). The reaction proceeded rapidly to give a 46% yield of N-phenacyl-N-*p*-tolyl-3,5,6-tri-O-methyl-D-glucofuranosylamine **3** (Method A). Structural elucidation was based on the interpretation of the physical data of its acetyl derivative **4**. In acidic medium, compound **3** underwent the Amadori rearrangement to provide its isomer **5**.

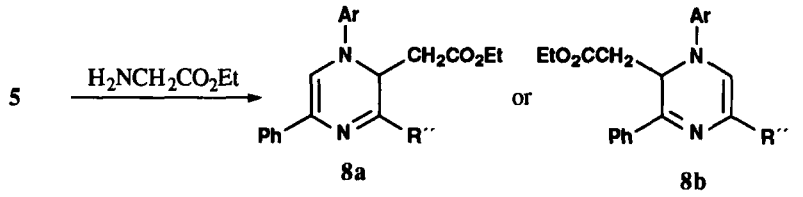


The synthesis of **5** was also achieved by reaction of *p*-toluidine with 1, followed by the treatment of the resulting product with phenacyl bromide (Method B). The reaction mechanism for the first step is well-known.[6] The condensation product between **1** and *p*-toluidine underwent the Amadori rearrangement in the presence of acetic acid to give 1-*p*-toluidino-1-deoxy-3,5,6-tri-O-methyl-D-fructose (**6**). Structural assignment was based on the spectral data of its acetyl derivative **7**. The substitution reaction between **6** and phenacyl bromide was facilitated by using phase-transfer catalysis.[7] The final product was identical with that obtained by the method A.

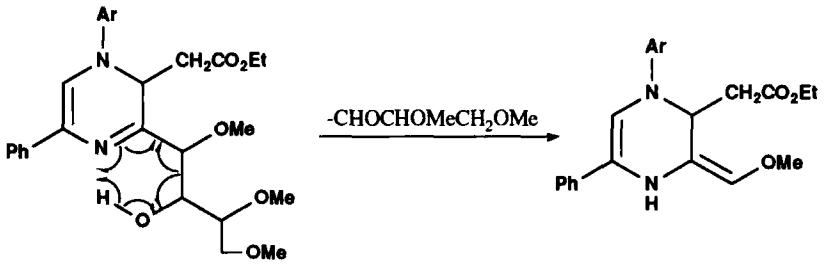


6 R = H
7 R''' = Ac

Reaction of **5** with ethyl glycine afforded a 1,2-dihydropyrazine derivative, most likely resulting from a 1,3-sigmatropic rearrangement of the intermediate 1,4-dihydropyrazine derivative. Its structure was deduced from its ^{1}H NMR, high resolution mass spectrum (HRMS) and chemical ionization mass spectrum. Two structures: 1-N-*p*-tolyl-2-(ethoxycarbonylmethyl)-3-(D-arabino-2'-hydroxy-1',3',4'-trimethoxybutyl)-5-phenyl-1,2-dihydropyrazine **8a** and its isomer **8b** could be attributed to this compound.



Further examination of the HRMS data revealed a fragment peak (m/z 378.1911, 24.8%) representing $C_{23}H_{26}N_2O_3$. A reasonable mechanism for the formation of this fragment can be proposed from the structure **8a**. An attempt to determine the exact position of ring substituent CH_2CO_2Et by chemical reactivity, *e. g.* formation of a lactone ring between this group and R_2 for the structure **8a**, failed because of its sensitivity to acids, bases and heat.



EXPERIMENTAL SECTION

Melting points were determined with a Reichert hot-stage microscope and are uncorrected. UV-visible spectra were measured in ethanol on a Kontron Uvikon 810 spectrophotometer. IR spectra were recorded on a Perkin-Elmer 297 instrument. High and low resolution electron impact (EI) mass spectra were obtained with an A.E.I MS 50 instrument. Chemical ionisation (CI) mass spectra (isobutane) were obtained with an AEI MS 9 instrument. ^{1}H NMR spectra were obtained on Brucker WP-80 (80 MHz), WP-200-SY (200 MHz) and WM-400 (400 MHz) spectrometers. ^{13}C NMR spectra were recorded on a Brucker WP-200-SY spectrometer operating at 50.30 MHz in the pulsed f.t. mode. Benzene and toluene were dried over calcium hydride (CaH_2) and distiled under atmospheric pressure.

N-Phenacyl-N-*p*-tolyl-3,5,6-tri-O-methyl-D-glucofuranosylamine (3).- A solution of **1** (111 mg, 0.5 mmol) in benzene (0.6 mL) was added under argon to a stirring suspension of **2** (112 mg, 0.5 mmol) in benzene (1 mL). $ZnCl_2$ (19 mg, 0.1 mmol), dissolved in absolute ethanol (0.2 mL), was added to the above mixture. After 45 min, benzene was removed under reduced pressure at 40°. Purification on a silica gel column with CH_2Cl_2:MeOH ratio of 99:1 as eluent gave **3** as an unstable yellow oil (100 mg, 46%), which was converted to its acetyl derivative **4**.

N-Phenacyl-N-*p*-tolyl-2-O-acetyl-3.5,6-tri-O-methyl-D-glucofuranosylamine (4).- To a solution of **3** (157.0 mg, 0.366 mmol) in pyridine (0.5 mL) was added acetic anhydride (0.05 mL, 0.53 mmol). After 12 hrs at room temperature, pyridine was removed under reduced pressure. The residue was purified by column chromatography over silica gel (CH_2Cl_2:MeOH, 99:1). A yellow oil (98 mg, 57%) was obtained.

Anal. Calcd. for $C_{26}H_{33}NO_7$: C, 66.22; H, 7.05; N, 2.97. Found: C, 66.01; H, 7.03; N, 2.89

UV λ_{max} (EtOH): 206.3 (ε = 33160), 245 (29340) and 276 nm (5795); IR: 1740 (CH_3C=O) and 1700 cm^{-1} (PhC=O); ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): δ 4.65 (1H, d, $J_{A,B}$ = 19Hz, $COCH_AH_BN$), 5.21 (1H, d, $J_{A,B}$ = 19Hz, $COCH_AH_BN$), 5.68 (1H, d, J = 2Hz, C(1)H) 5.13 (1H, d, J = 2Hz, C(2)H), 3.60 (1H, d, J = 3Hz, C(3)H), 3.93 (1H, q, J= 9Hz, C(4)H), 3.48 (3H, s, C(3)OCH_3), 3.46 (3H, s, c(5)OCH_3), 3.26 (3H, s, C(6)OCH_3), 2.26 (3H, s, PhCH_3), 2.09 (3H, s, $COCH_3$), 6.80-8.10 (9 aromatic protons), 3.43-3.80 (3H, C(5)H and C(6)H_2). ^{13}C NMR: δ (50.30 MHz, $CDCl_3$) 197.33 (PhCO), 169.86 (MeCO), 54.09 ($COCH_2N$), 95.37 (C(1)), 72.62 (C(6)), 76.50, 77.14, 77.77, 83.14 (C(2), C(3), C(4), C(5)), 20.98 (PhCH_3), 20.45 ($COCH_3$), 57.39, 58.36, 59.52 (3 other CH_3), 129.58, 116.52, 128.03, 135.96, 146.77, 128.78, 129.73, 133.11 (12 aromatic carbons); MS: m/z (EI) 471

(M^+,24%), 382 (1.9, M-$CHOMeCH_2OMe$), 3.66 (18.3, M-PhCO), 2.47 (49.9, M-$PhCOCH_2NPhMe$), 89 (100, $CHOMeCH_2OMe$).

1-(N-Phenacyl)-*p*-toluidino-1-deoxy-3,5,6-tri-O-mehyl-D-fructose 5 (Method A).- A solution of **3** (961 mg, 2.24 mmol) in benzene (2 mL) with ten drops of acetic acid was kept at 55° for 4 hrs. After removal of the solvents, the crude product was purified by chromatography on a silica gel column with ethyl acetate and hexane (40:60). A yellowish solid (192.4 mg, 20%, or total yield 9%) was obtained, mp. 122-124° (from EtOEt and hexane 1:1).

Anal. Calcd. for $C_{24}H_{31}NO_6$: C, 67.11; H, 7.28; N, 3.26. Found: C, 66.83; H, 7.27; N, 3.31

UV: λ_{max} (EtOH) 204.4 (ε = 42020) and 248.2 nm (31430); IR: 3400(OH), 1700 (PhC=O) and 1730 cm^{-1} (C=O); ^1H NMR: δ (200 MHz $CDCl_3$ Me_4Si), 4.70 (2H, s, $COCH_2N$), 4.40 (2H, s, C(1)H), 3.45 (3H, s, $C(3)OCH_3$), 3.26 (6H, s, $C(5)OCH_3$ and $C(6)OCH_3$), 2.08 (3H, s, $PhCH_3$), 6.38-8.00 (aromatic protons), 3.32-3.90 (other protons); MS: m/z (EI high resolution) 429.2160 (M^+, 17.12%, $C_{24}H_{31}NO_6$ requires 429.2152), 324.1757 (70, M-PhCO), 238.1187 (100, M-$COCHOMeCHOHCHOMeCH_2OMe$).

1-*p*-Toluidino-1-deoxy-3,5,6-tri-O-methyl-D-fructose 6.- To a benzene solution (3 mL) of **1** (1.377 g, 6.223 mmol) were added molecular sieves, *p*-toluidine (0.6589 g, 6.401 mmol) in benzene (2 mL) and seven drops of acetic acid. The mixture was stirred at room temperature for 4 hrs. After removal of benzene the crude product was purified on a silica gel column. Elution with methanol and dichloromethane (1:99) gave **6** (725 mg, 38%), MS: m/z (CI) 312(MH^+). **6** was treated immediately with a EtOEt-HCl solution and was stored as its hydrochloride.

1-(N-Acetyl)-*p*-toluidino-1-deoxy-4-O-acetyl-3,5,6-tri-O-methyl-D-fructose 7.- A mixture of **6** (200 mg, 0.643 mmol) and acetic anhydride (0.2 mL, 2.115 mmol) in pyridine (0.5 mL) was kept at room temperature overnight. Purification on a silica gel column (methanol and dichloromethane 1:99) gave the product **7** as a yellowish oil (222.8 mg, 88%).

Anal. Calcd. for $C_{20}H_{29}NO_7$: C, 60.74; H, 7.39; N, 3.54. Found: C, 60.49; H, 7.36; N, 3.58

UV: λ_{max} EtOH) 212 (ε = 7866) and 221 nm(7049); IR: ν_{max} 1730 (OC=O), 1725 (C=O), 1640 cm^{-1} (NC=O), ^1H NMR: δ (80MHz, $CDCl_3$, Me_4Si), 4.58 (2H, s, C(1)H), 4.21 (1H, d, J = 3Hz, C(3)H), 5.25 (1H, q, J = 3Hz, J = 8Hz, C(4)H), 2.35 (3H, s, $PhCH_3$), 1.85 (3H, s, $NC=OCH_3$), 1.90 (3H, s, $OC=OCH_3$), 3.51 (3H, s, $C(3)OCH_3$), 3.38 (6H, s, $C(5)OCH_3$ and $C(6)OCH_3$), 7.18 (4 aromatic protons), 3.5-3.7 (3H, C(5)H and $C(6)H_2$); MS: m/z (CI) 396 (MH^+).

1-(N-Phenacyl)-*p*-toluidino-1-deoxy-3,5,6-tri-O-methyl-D-fructose 5 (Method B).- Compound **6** (361 mg, 1.161 mmol) in its hydrochloride was dissolved in dichloromethane (5 mL) and treated with potassium bicarbonate solid ($KHCO_3$) (696 mg, 6.96 mmol). After adding phenacyl bromide (1.155 g, 5.805 mmol) and tetrabutylammonium hydrogen sulfate (11.8 mg, 0.035 mmol), the organic solvent was evaporated. The residue was then maintained at 65° for 20 min. The crude product was extracted with dichloromethane and purified on a silica gel column, yield 225.4 mg (45%, or total yield 17%).

1-N-*p*-Tolyl-2-(ethoxycarbonymethyl)-3-(D-arabino-2′-hydroxy-1′,3′,4′-tri-methoxy-butyl)-5-phenyl-1,2-dihydropyrazine 8a or 8b.- Ethyl glycine was liberated from its hydrochloride as described by Chambers *et al.*[8] Under argon, a benzene solution (2.5 mL) of **5** (134 mg, 0.314 mmol)

was introduced with a syringe into a mixture containing ethyl glycine (64 mg, 0.628 mmol) in benzene (0.5 mL) and sodium sulfate (Na_2SO_4) as drying agent. This mixture was then kept at 78° for 40 min. The product was isolated and purified by thin layer chromatography using successively three solvent systems: 1. acetone and hexane (35:65), 2. ethyl acetate and hexane (1:1), 3. methanol and dichloromethane (3:97), yield 1.1 mg (0.7%), UV: λ_{max} (EtOH), 204.7 (ε = 29200), 253.5 (16540) and 404.5 nm (7142); ^{1}H NMR: δ (400 MHz, C_6D_6, Me_4Si), 4.03 (1H, q, $J_{1,A}$ = 8Hz, $J_{1,B}$ = 5Hz C(1)H), 2.46 (1H, q, $J_{B,1}$ = 5 Hz, $J_{A,B}$ =16Hz, C(1)CH_B), 2.90 (1H, q, $J_{A,1}$ = 8Hz, $J_{A,B}$ = 16Hz, C(1)CH_A), 6.34 (1H, s, C(6)H), 3.76 (3H, s, C(1')OCH_3), 3.51 (3H, s, C(3')OCH_3), 3.44 (3H, s, C(4')OCH_3), 5.20 (1H, s, C(2')OH), 2.26 (3H, s, PhCH_3), 3.95 (2H, q, CO_2CH_2), 0.93 (3H, t, $CO_2CH_2CH_3$), 7.14, 7.26, 8.08 (aromatic protons), 4.21, 4.60, 6.10 (other 5 protons); MS: m/z (CI) 497(MH^+); m/z (EI high resolution), 496.2550 (M^+, 3.91%, $C_{28}H_{36}N_2O_6$ requires 496.2575), 409.2099 (46.04, M-CH_2CO_2Et), 378.1911 (24.8,M-HCOCHOMeCH_2OMe), 377.1877 (100, M-CHOHCHOMeCH_2OMe).

REFERENCES

† Present address: Department of Biomedical Engineering, Southeast University, Nanjing, 210018, P. R. China.

1. J. A. Maga, *CRC Crit. Rev. Food Sci. Nutri.*, **16**, 1 (1982).

2. G. Vernin, "*Chemistry of Heterocyclic Compounds in Flavors and Aromas*", J. Wiley & Sons, New York, NY (1982).

3. J. L. Fourrey, J.Beauhaire and C. W. Yuan, *J. Chem. Soc. Perkin Trans. 1*, 1841 (**1987**).

4. G. Just and D. Crosilla, *Can. J. Chem.*, **58**, 2523 (1980).

5. W. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967).

6. J. E. Hodge, *J. Agr. Food Chem.*, **1**, 928 (1953).

7. E. V. Dehmlow, R. Thieser, Y. Sasson and H. A. Zahaalka, *Tetrahedron Lett.*, **26**, 297 (1985).

8. R. W. Chambers and F. H. Carpenter, *J. Am. Chem. Soc.*, **77**, 1522 (1955).

****