

Synthesis of 6-Oxa-1,5-Pentamethylenetetrazoles (Sugar Tetrazoles)

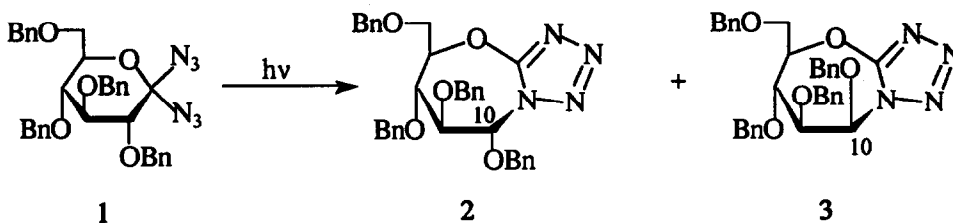
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Abstract: *Some sugar tetrazoles have been synthesized by the photolysis or the thermolysis of D-glucopyranosylidene diazide or D-galactopyranosylidene diazide. The reaction mechanism is discussed.*

1,5-Pentamethylenetetrazole (Leptazol or Metrazole) has been known as a stimulant for the central nervous system.¹ This drug is more effective when administered parenterally than orally due to a slow absorption from the stomach. Herein we present the synthesis of some tetrazoles having a sugar moiety (sugar tetrazoles) in order to increase the water-solubility necessary for more biologically active tetrazoles.

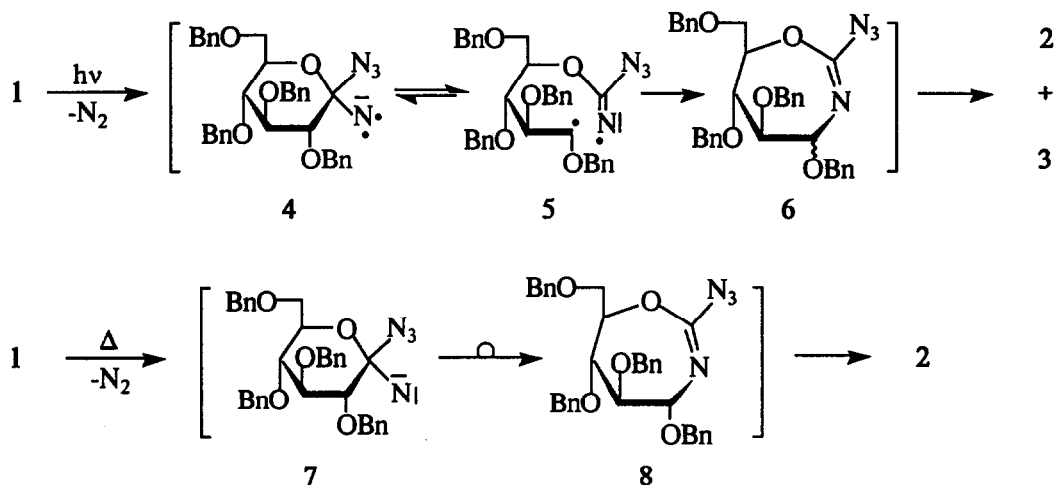
Photolysis and thermolysis of perbenzylated D-glucopyranosylidene diazide **1**² were our first method of choice, because the substrates containing the $-N=C(N_3)-$ grouping are known to cyclize to tetrazoles *via* azidonitrene.³ Thus, **1** (0.113 mmol) in dry benzene was irradiated under argon atmosphere with a high pressure Hg lamp (400 W) for 2 h using a pyrex tube to give desired (7*R*,8*S*,9*S*,10*R*)-8,9,10-tribenzyloxy-7-benzyloxymethyl-6-oxa-1,5-pentamethylenetetrazole **2** (51 %) and its 10*S* epimer **3** (20 %), together with the recovery of **1** (2 %). On the other hand, refluxing **1** in *o*-xylene for 17 h under argon atmosphere afforded only **2** as white needles in 82 % yield.



The structures of **2** and **3** were determined by ¹H-NMR (COSY and NOESY), ¹³C-NMR (DEPT), and MS (FAB): The peaks in ¹H-NMR for H-7,8,9,10 of **2**⁴ and **3**⁵ appeared at similar positions to those for H-2,3,4,5 of **1**.⁶ The big difference in ¹H-NMR between **2** and **3** was the coupling constants (*J*_{7,8}, *J*_{8,9}, and

*J*9,10) (see refs. 4 and 5). Conformations of 2 and 3 were deduced to be ^{6,7}TB_{1,5}-forms of septanoid,⁷ on the basis of the modified Karplus equation⁸ and optimized by the molecular mechanics calculations of CAChe system.⁹ Deprotection of 2 was carried out successfully by using boron trichloride¹⁰ to afford (8*S*,9*S*,10*R*)-trihydroxy-(7*R*)-hydroxymethyl-6-oxa-1,5-pentamethylenetetrazole as colorless syrup (60 %) and very soluble compound in water.

The formation of 2 and 3 is considered as follows: Photolysis of 1 gives the triplet azidonitrene 4, which exists in equilibrium with the acyclic species 5. The C-N bond formation from 5 would result in the mixture of the C-4 epimers 6 and eventually in 2 and 3. On the other hand, thermolysis of 1 gives the singlet azidonitrene 7, as is reported for simple azide,¹¹ and immediately undergoes insertion to the C₂-C₃ bond to afford the intermediate 8 and then 2 as the single product. The fact that the present reaction does not take place below 100 °C rules out a concerted migration-elimination mechanism because the thermal decomposition of *o*-nitrophenyl azide is known to occur at lower temperature (65-85 °C) than that (140-170 °C) in the unassisted decomposition of phenyl azide.¹² In the present rearrangements, the migration occurs only at the carbon atom of the pyranose ring. This coincides with the fact that the (*E*)-hydroximolactone of D-glucopyranose but not (*Z*) isomer undergoes the Beckmann rearrangement.¹³



Thermolysis of the perbenzylated D-galactopyranosyl diazide 9 synthesized by the same method² gave (7*R*,8*R*,9*S*,10*R*)-8,9,10-tribenzyloxy-7-benzyloxymethyl-6-oxa-1,5-pentamethylenetetrazole 10¹⁴ in 62 % yield. The photolysis of 9 gave 10 and its 10*S* epimer 11¹⁵ in 29 % and 13 % yields, respectively.

Since the mannopyranosyl diazides and the talopyranosyl diazides can not be prepared by the same method,² the photolysis may be useful also for the preparation of 3 and 11 even though in low yield.

- gem = 12.1 Hz), 4.76 (d, 2H, CH₂Ph, $J_{\text{gem}} = 11.0$ Hz), 4.79 (d, 2H, CH₂Ph, $J_{\text{gem}} = 11.8$ Hz), 4.81 (d, 2H, CH₂Ph, $J_{\text{gem}} = 11.3$ Hz), 4.86 (d, 2H, CH₂Ph, $J_{\text{gem}} = 10.7$ Hz), 4.95 (d, 2H, CH₂Ph, $J_{\text{gem}} = 10.7$ Hz), 7.15-7.17 (m, 2H, Ph), 7.23-7.35 (m, 18H, Ph).
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 9. 2: $\Delta G = -9.9421$ kcal/mol for ^{6,7}TB_{1,5}; $\Delta G = -9.1930$ kcal/mol for ⁸C_{1,5}. 3: $\Delta G = -10.4622$ kcal/mol for ^{6,7}TB_{1,5}; $\Delta G = -8.3714$ kcal/mol for ⁸C_{1,5}.
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 14. ¹H-NMR (500 MHz, CDCl₃): δ 3.63 (dd, 1H, CH₂OBn, $J_{7,\text{CH}_2\text{OBn}} = 8.40$ Hz, $J_{\text{gem}} = 11.95$ Hz), 3.85 (dd, 1H, CH₂OBn, $J_{7,\text{CH}_2\text{OBn}} = 3.16$, $J_{\text{gem}} = 11.95$ Hz), 4.07 (dd, 1H, H-9, $J_{9,10} = 4.67$ Hz, $J_{8,9} = 3.00$ Hz), 4.33 (dd, 1H, H-8, $J_{8,9} = 3.00$ Hz, $J_{7,8} = 4.12$ Hz), 4.43-4.73 (m, 8H, PhCH₂ × 4), 4.93 (m, 1H, H-7), 5.74 (d, 1H, H-10, $J_{9,10} = 4.67$ Hz), 7.04-7.06 (m, 2H, Ph), 7.17-7.40 (m, 18H, Ph). ¹³C-NMR (100.40 MHz, CDCl₃): δ 67.4 (CH₂OBn), 71.5, 73.0, 73.6, 73.8 (PhCH₂ × 4), 75.6, 75.7, 84.1, 84.3 (C-7,8,9,10), 127.8-128.7 (Ph), 135.1, 136.4, 137.0, 137.7 (ipso C of Ph × 4), 160.5 (C-5). IR (neat) 3000 (Ph), 2850 cm⁻¹ (CH); MS m/z (FAB), 579 (M+1)⁺.
 15. ¹H-NMR (500 MHz, CDCl₃): δ 3.32 (dd, 1H, CH₂OBn, $J_{7,\text{CH}_2\text{OBn}} = 3.11$ Hz, $J_{\text{gem}} = 9.08$ Hz), 3.70 (dd, 1H, CH₂OBn, $J_{7,\text{CH}_2\text{Ph}} = 5.47$ Hz, $J_{\text{gem}} = 9.08$ Hz), 4.19 (dd, 1H, H-9, $J_{9,8} = 6.04$ Hz, $J_{8,9} = 2.15$ Hz), 4.38 (d, 2H, CH₂Ph, $J_{\text{gem}} = 11.73$ Hz), 4.47 (dd, 1H, H-8, $J_{7,8} = 7.09$ Hz, $J_{8,9} = 2.15$ Hz), 4.51-4.63 (m, 6H, CH₂Ph × 3), 4.82 (ddd, 1H, H-7, $J_{7,8} = 7.09$ Hz, $J_{7,\text{OCH}_2\text{Ph}} = 3.11$, 5.49 Hz), 5.06 (d, 1H, H-10, $J_{9,10} = 6.04$ Hz), 7.15-7.36 (m, 20H, Ph × 4). ¹³C-NMR (100.40 MHz, CDCl₃): δ 65.0 (CH₂OBn), 67.7, 72.3, 73.6, 73.7 (PhCH₂ × 4), 76.4, 78.3, 80.2, 80.5 (C-7,8,9,10), 126.5-128.6 (Ph), 136.2, 136.9, 136.9, 137.5 (ipso C of Ph × 4), 147.4 (C-5). IR (neat) 3000 (Ph), 2840 cm⁻¹ (CH); Found: m/z (FAB), 579.2605. C₃₄H₃₅O₅N₄ (M+1)⁺ requires m/z 579.2609.

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