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 atomosphere 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

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 $J_{9,10}$ (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 (8S,9S,10R)-trihydroxy-(7R)-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 (7R, 8R, 9S, 10R)-8,9,10-tribenzyloxy-7-benzyloxymethyl-6-oxa-1,5-pentamethylenetetrazole 10¹⁴ in 62 % yield. The photolysis of 9 gave 10 and its 10S 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.



References and Notes

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- 4. 2: ¹H-NMR (400 MHz, CDCl₃): δ 3.86 (d, 2H, CH₂OBn, $J_{7,CH2OBn} = 2.93$ Hz), 3.99 (dd, 1H, H-9, $J_{9,10} = 4.58$ Hz, $J_{8,9} = 1.28$ Hz), 4.15 (dd, 1H, H-8, $J_{8,9} = 1.28$ Hz, $J_{7,8} = 10.26$ Hz), 4.24 (d, 2H, CH₂Ph, $J_{gem} = 12.27$ Hz), 4.31 (d, 2H, CH₂Ph, $J_{gem} = 12.28$ Hz), 4.41 (d, 2H, CH₂Ph, $J_{gem} = 11.54$ Hz), 4.46 (d, 2H, CH₂Ph, $J_{gem} = 11.54$ Hz), 4.58 (d, 2H, CH₂Ph, $J_{gem} = 12.09$ Hz), 4.66 (d, 2H, CH₂Ph, $J_{gem} = 12.28$ Hz), 4.67 (d, 2H, CH₂Ph, $J_{gem} = 12.09$ Hz), 4.83 (d, 2H, CH₂Ph, $J_{gem} = 12.27$ Hz), 4.96 (dd, 1H, H-7, $J_{7,8} = 10.26$ Hz, $J_{7,CH2OBn} = 2.93$ Hz), 5.83 (d, 1H, H-10, $J_{9,10} = 4.58$ Hz), 7.00-7.02 (m, 2H, Ph), 7.20-7.37 (m, 18H, Ph). ¹³C-NMR (100.40 MHz, CDCl₃): δ 68.7 (CH₂OBn), 71.5, 72.1, 72.8, 73.7 (PhCH₂ × 4), 76.9, 77.4, 83.6, 84.4 (C-7,8,9,10), 127.8-128.6 (Ph), 135.5, 136.2, 137.1, 137.7 (ipso C of Ph × 4), 162.4 (C-5) IR (neat) 3000 (Ph), 2850 cm⁻¹ (CH); MS m/z (FAB), 579 (M + 1)⁺.
- 5. 3: ¹H-NMR (500 MHz, CDCl₃): δ 3.68 (dd, 1H, CH₂OBn, $J_{7,CH2OBn} = 5.23$ Hz, $J_{gem} = 11.55$ Hz), 3.78 (dd, 1H, CH₂OBn, $J_{7,CH2OBn} = 2.75$ Hz, $J_{gem} = 11.55$ Hz), 3.91 (dd, 1H, H-8, $J_{8,9} = 6.60$ Hz, $J_{7,8} = 6.87$ Hz), 4.12 (dd, 1H, H-9, $J_{9,10} = 6.60$ Hz, $J_{8,9} = 6.60$ Hz), 4.42 (d, 2H, CH₂Ph, $J_{gem} = 11.27$ Hz), 4.49 (s, 2H, CH₂Ph), 4.57 (d, 2H, CH₂Ph, $J_{gem} = 11.27$ Hz), 4.61 (m, 1H, H-8), 4.65-4.68 (m, 6H, CH₂Ph × 3), 4.86 (d, 2H, CH₂Ph, $J_{gem} = 11.80$ Hz), 5.04 (d, 1H, H-10, $J_{9,10} = 6.60$ Hz), 7.12-7.36 (m, 20H, Ph). ¹³C-NMR (100.40 MHz, CDCl₃): δ . 60.4 (CH₂OBn), 67.4, 72.6, 73.6, 74.1 (PhCH₂ × 4), 71.5, 76.7, 78.9, 89.4 (C-7,8,9,10), 127.5-128.5 (Ph), 136.4, 137.0, 137.1, 137.2 (ipso C of Ph × 4), 146.4 (C-5). IR (neat) 3000 (Ph), 2840 cm⁻¹ (CH); MS m/z (FAB), 579 (M +1)⁺.
- 6. 1: ¹H-NMR (500 MHz, CDCl₃): δ 3.65 (d, 1H, H-2, $J_{2,3}$ = 9.34 Hz), 3.72 (ddd, 2H, H-6, J_{gem} = 11.54 Hz, $J_{5,6}$ = 1.65, 3.57 Hz), 3.73 (dd, 1H, H-4, $J_{3,4}$ = 9.08 Hz, $J_{4,5}$ = 10.17 Hz), 3.83 (dd, 1H, H-3, $J_{2,3}$ = 9.34 Hz, $J_{3,4}$ = 9.08 Hz), 3.87 (ddd, 1H, H-5, $J_{5,6}$ = 1.65, 3.57 Hz, $J_{4,5}$ = 10.17 Hz), 4.53 (d, 2H, C<u>H</u>₂Ph, J_{gem} = 12 Hz), 4.56 (d, 2H, C<u>H</u>₂Ph, J_{gem} = 11.0 Hz), 4.60 (d, 2H, C<u>H</u>₂Ph, J

gem = 12.1 Hz), 4.76 (d, 2H, CH₂Ph, J_{gem} = 11.0 Hz), 4.79 (d, 2H, CH₂Ph, J_{gem} = 11.8 Hz), 4.81 (d, 2H, CH₂Ph, J_{gem} = 11.3 Hz), 4.86 (d, 2H, CH₂Ph, J_{gem} = 10.7 Hz), 4.95 (d, 2H, CH₂Ph, J_{gem} = 10.7 Hz), 7.15-7.17 (m, 2H, Ph), 7.23-7.35 (m, 18H, Ph).

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- 9. 2: $\Delta G = -9.9421 \text{ kcal / mol for } 6.7 \text{TB}_{1,5}$; $\Delta G = -9.1930 \text{ kcal / mol for } ^8\text{C}_{1,5}$. 3: $\Delta G = -10.4622 \text{ kcal / mol for } ^6.7 \text{TB}_{1,5}$; $\Delta G = -8.3714 \text{ kcal / mol for } ^8\text{C}_{1,5}$.
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- 14. ¹H-NMR (500 MHz, CDCl₃): δ , 3.63 (dd, 1H, CH₂OBn, $J_{7,CH_{2}OBn} = 8.40$ Hz, $J_{gem} = 11.95$ Hz), 3.85 (dd, 1H, CH₂OBn, $J_{7,CH_{2}OBn} = 3.16$, $J_{gem} = 11.95$ 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, $J_{7,CH_{2}OBn}$ = 3.11 Hz, J_{gem} = 9.08 Hz), 3.70 (dd, 1H, CH₂OBn, $J_{7,CH_{2}Ph}$ = 5.47 Hz, J_{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_{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, $J_{7,OCH_{2}Ph}$ = 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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