Stereoselective Synthesis of Derivatives with the *manno*-Configuration from a Nitro-sugar

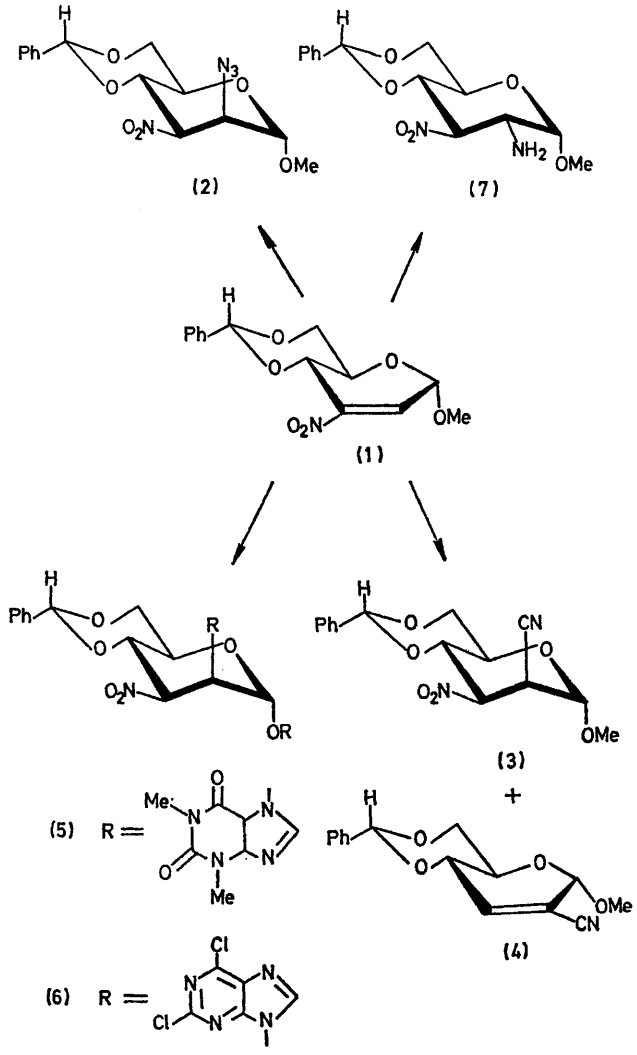
By TOHRU SAKAKIBARA* and ROKURO SUDOH

(*Department of Chemistry, Faculty of Science, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo, Japan*)

Summary Reaction of some nucleophiles with the nitro-sugar (**1**) under weakly acidic or neutral conditions results in the stereoselective synthesis of products with the thermodynamically less stable *manno*-configuration.

NUCLEOPHILIC addition to a carbon–carbon double bond activated by CO, CN, NO_2, *etc.* (Michael reaction) is important in organic syntheses, but it usually results in predominant formation of the thermodynamically more stable

isomer because it is reversible.[1] It has rarely been applied to the preparation of the thermodynamically less stable isomer.



We recently showed that the reaction of phenyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-erythro-hex-2-eno-pyranoside with hydrazoic acid involved a kinetically controlled process although it gave the thermodynamically more stable isomer.[2] This reaction could afford the kinetically controlled, thermodynamically less stable isomer under weakly acidic or neutral conditions, and we have therefore examined the reactions of the nitro-sugar (**1**) under such conditions. We find that the *manno*-isomers are indeed obtained in good yield.

Treatment of compound (**1**) with excess of hydrazoic acid in MeCN at room temperature for 6 h gave the *manno*-pyranoside (**2**) (>82%), m.p. 111—112°; $[\alpha]_D$ −18·3° (*c* 1, $CHCl_3$) together with a small amount of byproduct. The *manno*-configuration of (**2**) was assigned from n.m.r. data; $J_{1,2}$ 1·0, $J_{2,3}$ 4·0, and $J_{3,4}$ 10 Hz. Similar treatment of compound (**1**) with HCN in the presence of a catalytic amount of KCN in MeCN (8 ml)–H_2O (1 ml) at room temperature for 4 h afforded (>95% total yield) a mixture (10:1 by n.m.r. spectroscopy) of the pyranosides (**3**), m.p. 170·5—171·5°; $[\alpha]_D^{20}$ −14·7° (*c* 1, $CHCl_3$), ν_{max} (KBr) 2260 (CN) and 1560 (NO_2) cm^{-1}, and (**4**), m.p. 180·5—181·5°; $[\alpha]_D^{20}$ +168° (*c* 0·5, $CHCl_3$), which was separated by fractional cystallization from ethanol. Assignment of the *manno*-configuration to (**3**) was based on coupling constant data: $J_{1,2}$ 1·3, $J_{2,3}$ 5·0, and $J_{3,4}$ 10 Hz. The cyano-olefin structure for (**4**) was assigned on the following evidence; elemental analysis indicated a molecular formula $C_{15}H_{15}NO_4$; i.r. spectroscopy (KBr) showed no $\nu(NO_2)$, but ν(CN) at 2233 cm^{-1}; n.m.r. spectroscopy showed an olefinic proton (3-H) at δ 6·88 (1H), and only six protons from the sugar unit.

An equimolar mixture of compound (**1**) and anhydrous theophylline in anhydrous tetrahydrofuran (THF) was heated under reflux for 80 h. After evaporation and recrystallization from EtOH–Me_2CO, the *manno*-pyranoside (**5**) (>90%), m.p. 206° (decomp.); $[\alpha]_D^{20}$ + 31·6 (*c* 1, $CHCl_3$); λ_{max} (THF) 278·2 (ε 7980), was obtained.

Similarly, compound (**1**) was heated with an equimolar amount of 2,6-dichloropurine for 80 h in refluxing anhydrous THF to form the *manno*-pyranoside (**6**) (*ca.* 82%); m.p. 194° (decomp); $[\alpha]_D^{20}$ + 13·4° (*c* 1, $CHCl_3$); λ_{max} (MeOH) 273·8 nm (ε 9800). Coupling constant data for the ring protons, $J_{1',2}$ 1·2, $J_{2',3}$ 4·7, and $J_{3',4}$ 10·6 Hz, again indicate the *manno*-structure for (**5**) and (**6**). The u.v. data indicated that the sugar unit had been introduced on the purine nucleus at N-7 in (**5**) and N-9 in (**6**).

Treatment of compound (**1**) with a more basic reagent such as aqueous ammonia (*ca.* 28%) in THF at 0°, on the other hand, gave exclusively the *gluco*-product (**7**), which was identical with an authentic sample prepared by the procedure of Baer *et al.*[5]

(*Received, 5th November* 1973; *Com.* 1524.)

[1] S. Patai and Z. Rappoport in 'The Chemistry of Alkenes,' ed., S. Patai, Interscience, London, 1964, ch. 8; there have been other reports on kinetically controlled products; *e.g.*, R. A. Abramovitch and L. Struble, *Tetrahedron*, 1968, **24**, 357; W. Nagata, M. Yoshioka, and T. Terasawa, *J. Amer. Chem. Soc.*, 1972, **24**, 4672.

[2] T. Sakakibara, R. Sudoh and T. Nakagawa, *J. Org. Chem.*, 1973, **38**, 2179.

[3] The normal reaction of nitro-sugars with nucleophiles affords the thermodynamically more stable *gluco*-isomers; *e.g.*, H. H. Baer, *Adv. Carbohydrate Chem.*, 1969, **24**, 69; however, there have been two reports on the formation of the *manno*-isomers from the anomer of (**1**), but the significance of these results has not been discussed; T. Sakakibara and R. Sudoh, submitted to *Bull. Chem. Soc. Japan*; H. H. Baer and F. Kienzle, *J. Org. Chem.*, 1968, **34**, 3848.

[4] J. M. Gulland, E. R. Holiday, and T. F. Macrae, *J. Chem. Soc.*, 1934, 1639; J. M. Montgomery and H. J. Thomas, *Adv. Carbohydrate Chem.*, 1962, **17**, 304; T. Nakagawa, T. Sakakibara, and S. Kumazawa, *Tetrahedron Letters*, 1970, 1645, obtained λ_{max} (THF) 278·0 nm (ε 6980) and λ_{max} (MeOH) 273·5 nm (ε 7880) for the β-*gluco*-isomers of (**5**) and (**6**), respectively.

[5] H. H. Baer and F. Rajabalee, *Carbohydrate Res.*, 1970, **12**, 241.