# Phase Transfer Catalyzed Reactions. II. Reactions of Methyl 3-Deoxy-3-nitro-β-D-hexopyranosides with Active Methylene Compounds

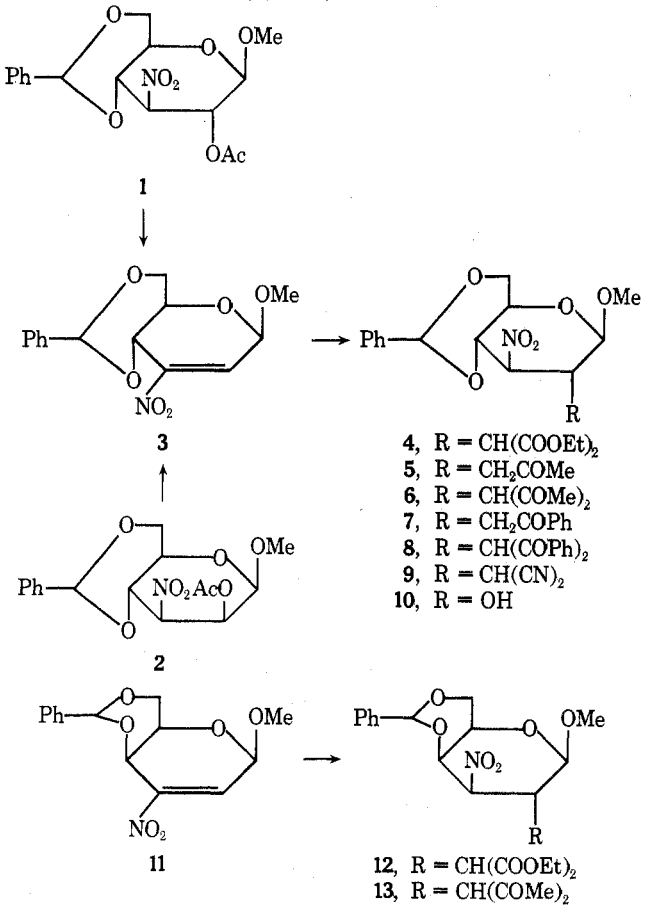
Tohru Sakakibara, Masahide Yamada, and Rokuro Sudoh*

*Department of Chemistry, Faculty of Science, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152, Japan*

*Received July 1, 1975*

In recent years a considerable number of C-branched-chain sugars have been isolated as a component of natural sources, especially in antibiotics,[1] and synthetic studies on these sugars have been developed.[2] Some nitro sugars were shown to be useful intermediates for the purpose; they react with hydrogen cyanide[3-5] or active methylene compounds[6,7] to afford the corresponding C-branched-chain nitro sugars.

In a previous paper[8] we showed the usefulness of a phase transfer process for the selective preparation of 2-C-branched-chain nitro sugars having the thermodynamically less stable manno configuration; these were obtained from methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (the anomer of **3**) on treatment with some active methylene compounds. In the present paper we wish to describe some results on application of this phase transfer process to a β series of nitro sugars **1**, **2**, **3**, and **11**.




The reaction of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (**1**) with ethyl malonate in benzene–0.2 N sodium hydroxide in the presence of hexadecyltributylphosphonium bromide as a phase transfer catalyst afforded methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-bis(ethoxycarbonyl)methyl-3-nitro-β-D-glucopyranoside (**4**) in 75% yield. Similar reactions of the 2-*O*-acetylmannopyranoside (**2**) and nitro olefin **3** also gave **4** in good yield, showing that the reactions of **1** and **2** involve the nitro olefin intermediate **3**.

A similar reaction of **3** with acetylacetone afforded the 2-*C*-acetonyl glucopyranoside (**5**) with a release of an acetyl group, but this deacetylation was suppressed under milder conditions and the 2-*C*-(diacetyl)methyl derivative (**6**) was obtained in good yield. Similar results were observed in the reaction of **3** with dibenzoylmethane; the 2-*C*-benzoylmethylglucopyranoside (**7**) was formed under stronger conditions, and under the milder conditions, the 2-*C*-(dibenzoyl)methyl derivative (**8**) was isolated. Similarly treatment of **3** with malononitrile under the milder conditions gave the 2-*C*-(dicyano)methylglucopyranoside (**9**).

On similar treatment of **3** with acetone, however, instead of an acetonyl group a hydroxyl group was introduced at the C-2 position; this result may be rationalized by assuming that the ion pair formed between the phase transfer catalyst and the carbanion derived from acetone was too weak to go to the organic layer.

Structural assignments of these compounds were based on their NMR spectra (Table I); large values of coupling constants (≥8 Hz) of $H^1$–$H^2$ indicate their β-gluco configuration.

Treatment of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*threo*-hex-2-enopyranoside (**11**) with ethyl malonate and acetylacetone, under the conditions used for the preparation of **6**, gave galacto isomers **12** and **13**, respectively. The former product (**12**) was identical with an authentic sample prepared by the procedure of Baer et al.[6] The galacto configuration of **13** was deduced from its NMR spectrum: $J_{1,2}$ = 8.8, $J_{2,3}$ = 12.2, and $J_{3,4}$ = 3.8 Hz.

## Experimental Section

All the melting points were determined in capillaries and are uncorrected. The NMR spectra were recorded at 100 MHz with a JNM-4H-100 (JEOL) spectrometer in chloroform-*d*, using tetramethylsilane as the internal standard. In this section the catalyst means hexadecyltributylphosphonium bromide.

**Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-bis(ethoxycarbonyl)methyl-3-nitro-β-D-glucopyranoside (4). A. From Nitro Acetate** 1. A mixture of **1**[9] (118 mg, 0.33 mmol), ethyl malonate (120 mg, 0.75 mmol), benzene (10 ml), and 1 N NaOH (1.25 ml) was stirred for 22 h at room temperature in the presence of the catalyst (12 mg) and then washed with water (3 × 5 ml). The benzene layer was evaporated in vacuo to give a residue (135 mg). Recrystallization from ethanol gave 113 mg (75%) of **4**, which was identi-

Table I
100-MHz NMR Spectra in $CDCl_3$ ($Me_4Si$ as an Internal Standard)

| Compd | Chemical shifts, δ | | | | | | Coupling constants, Hz | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $H^1$ | $H^2$ | $H^3$ | $H^4$ | PhCH | $H^{2'}$[a] | $J_{1,2}$ | $J_{2,3}$ | $J_{3,4}$ | $J_{4,5}$ | $J_{2,8}$ |
| **6** | 5.15 | 2.82 | 4.90 | 4.15 | 5.52 | 3.58 | 8.1 | 11.6 | 10 | 8.8 | 3.8 |
| **7** | 4.82 | 2.68 | 5.23 | 4.18 | 5.53 | 3.24<br>3.07 | 8.4 | 11.6 | 10 | 8.8 | 4.4<br>4.4 |
| **8** | 5.36 | 3.11 | 5.27 | 4.08 | 5.49 | ? | 8.1 | 11.3 | 9.7 | 8.8 | 3.4 |
| **13** | 4.87 | 3.25 | 5.04 | 4.53 | 5.51 | 3.98 | 8.8 | 12.2 | 3.8 | ≤1.5 | 3.1 |

[a] $H^{2'}$ means the acidic methine or methylene proton(s) of a chain moiety.

cal with an authentic sample prepared by the procedure of Baer et al.[6]

**B. From Nitro Acetate 2.** The same treatment of 2[10] with ethyl malonate gave **4** in 77% yield.

**C. From Nitro Olefin 3.** Under the same conditions described above except for the decreased amount of 1 N NaOH to 0.9 ml, reaction between 3[9] (98 mg) and ethyl malonate gave **4** in 77% yield. The yield was up to 87% when this reaction was carried out under the conditions described for preparation of **6**.

**Methyl 2-*C*-Acetonyl-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (5).** To a solution of **3** (98 mg, 0.33 mmol), acetylacetone (75 mg, 0.75 mmol), and the catalyst (12 mg) in benzene (10 ml) was added 1 N NaOH (0.9 ml). The mixture was stirred for 22 h and then evaporated in vacuo to afford a crystalline residue (108 mg), which was recrystallized from ethanol–acetone to afford 95 mg (81%) of **5**: mp 176–177 °C; $[\alpha]^{20}D$ −66.9° (*c* 1, MeOH); ir (KBr) 1715 (CO) and 1560 $cm^{-1}$ ($NO_2$).

Anal. Calcd for $C_{17}H_{21}NO_7$: C, 58.11, H, 6.02; N, 3.99. Found: C, 58.40; H, 6.04; N, 4.17.

The same product was also prepared in 80% yield by the similar reaction of **1** (236 mg, 0.67 mmol), acetylacetone (150 mg, 1.5 mmol), and the catalyst (60 mg) in benzene (20 ml)–0.5 N NaOH (5 ml) stirring for 23 h at room temperature.

**Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-(diacetyl)-methyl-3-nitro-β-D-glucopyranoside (6).** To a solution of **3** (29.3 mg, 0.1 mmol), acetylacetone (18 mg, 0.18 mmol), and the catalyst (2 mg) in benzene (3 ml) was added 0.2 N NaOH (0.1 ml). The mixture was stirred for 1.5 h at room temperature and then washed with water (3 × 5 ml). The organic layer was evaporated to afford a NMR spectroscopically pure syrup (35 mg, 89%). The syrup (105 mg) was crystallized from ethanol to give **6** (83%): mp 110–111 °C; $[\alpha]^{20}D$ −153° (*c* 1, $CHCl_3$); ir (KBr) 1710 (CO) and 1560 $cm^{-1}$ ($NO_2$).

Anal. Calcd for $C_{19}H_{23}NO_8$: C, 58.01; H, 5.89; N, 3.56. Found: C, 57.72; H, 6.03; N, 3.72.

**Methyl 2-*C*-Benzoylmethyl-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (7).** To a solution of **3** (87.9 mg, 0.3 mmol), dibenzoylmethane (138 mg, ca. 0.4 mmol), and the catalyst (12 mg) in benzene (24 ml) was added 0.2 N NaOH (8 ml). The mixture was stirred for 18 h at room temperature and then evaporated in vacuo to give a crystalline residue. Recrystallization from ethanol gave 102 mg (83%) of **7**: mp 172–173 °C; $[\alpha]^{20}D$ −29° (*c* 1, $CHCl_3$); ir (KBr) 1680 (CO) and 1550 $cm^{-1}$ ($NO_2$).

Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.91; H, 5.61; N, 3.39. Found: C, 64.20; H, 5.65; N, 3.39.

**Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-(dibenzoyl)-methyl-3-nitro-β-D-glucopyranoside (8).** Treatment of **3** (58.6 mg, 0.2 mmol) with dibenzoylmethane (89.6 mg, ca. 0.28 mmol) under the conditions used to prepare **6** gave a pure syrup (90 mg, 91%). The syrup was chromatographed on silica gel (C-200, Wako-gel) with benzene. The eluate was evaporated in vacuo to give a syrup, which was crystallized from *n*-propyl alcohol: yield 81%; mp 102–103 °C; $[\alpha]^{20}D$ −194° (*c* 0.5, $CHCl_3$); ir (KBr) 1680 (CO) and 1550 $cm^{-1}$ ($NO_2$).

Anal. Calcd for $C_{29}H_{27}NO_8$: C, 67.30; H, 5.26; N, 2.71. Found: C, 67.18; H, 5.38; N, 2.66.

**Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-(dicyano)-methyl-3-nitro-β-D-glucopyranoside (9).** Treatment of **3** (147 mg, 0.5 mmol) with malononitrile (36.5 mg, 0.55 mmol) under the conditions used to prepare **6** gave a NMR spectroscopically pure crystalline residue (158 mg, 87.8%), which was recrystallized from ethanol to afford 146 mg (81%) of **9**: mp 177–178 °C; $[\alpha]^{20}D$ −40.2° (*c* 1, MeOH); ir (KBr) 1565 $cm^{-1}$ ($NO_2$).

Anal. Calcd for $C_{17}H_{17}N_3O_6$: C, 56.82; H, 4.77; N, 11.70. Found: C, 56.92; H, 4.77; N, 11.58.

**Methyl 4,6-*O*-Benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (10).** Treatment of **3** (58.6 mg) with acetone (14.5 mg) under the conditions used to prepare **5** gave **10** in 73% yield, which was identical with an authentic sample.[9]

**Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-bis(ethoxycarbonyl)methyl-3-nitro-β-D-galactopyranoside (12).** Treatment of 11[10] (58.6 mg) with ethyl malonate under the conditions used to prepare **6** gave a NMR spectroscopically pure residue of **12**, which was recrystallized from ethanol, yield 82%. It was identical with an authentic sample prepared by Baer et al.[6]

**Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-(diacetyl)-methyl-3-nitro-β-D-galactopyranoside (13).** Treatment of **11** (58.6 mg) with acetylacetone under the conditions used for the preparation of **6** afforded a syrup. Its NMR spectrum showed that it consisted of **13** and unknown compound in a ratio of ca. 3:1. Crystallization from ethanol gave 21.6 mg (55%) of **13**: mp 152.5–153.5 °C; $[\alpha]^{20}D$ −53.0° (*c* 1, $CHCl_3$); ir (KBr) 1700 (CO) and 1550 $cm^{-1}$ ($NO_2$).

Anal. Calcd for $C_{19}H_{23}NO_8$: C, 58.01; H, 5.89; N, 3.56. Found: C, 57.90; H, 5.74; N, 3.71.

**Registry No.**—**1**, 18604-56-3; **2**, 3650-61-1; **3**, 25541-58-6; **4**, 20777-18-8; **5**, 29847-30-1; **6**, 57559-94-1; **7**, 57559-95-2; **8**, 57559-96-3; **9**, 29847-31-2; **10**, 25541-57-5; **11**, 3650-62-2; **12**, 20777-19-9; **13**, 57559-97-4; ethyl malonate, 105-53-3; acetylacetone, 123-54-6; dibenzoylmethane, 120-46-7; malononitrile, 109-77-3.

## References and Notes


(1) H. Grisebach and R. Schmid, *Angew. Chem.*, **84**, 192 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 159 (1972).
(2) E.g., A. A. Feast, W. G. Overend, and N. R. Williams, *J. Chem. Soc. C*, 303 (1966).
(3) T. Sakakibara and R. Sudoh, *J. Chem. Soc., Chem. Commun.*, 69 (1974).
(4) T. Sakakibara and R. Sudoh, *Bull. Chem. Soc. Jpn.*, submitted for publication.
(5) H. Paulsen and W. Greve, *Chem. Ber.*, **107**, 3013 (1974).
(6) H. H. Baer and K. S. Ong, *Can. J. Chem.*, **46**, 2511 (1968).
(7) T. Sakakibara, S. Kumazawa, and T. Nakagawa, *Bull. Chem. Soc. Jpn.*, **43**, 2655 (1970).
(8) T. Sakakibara and R. Sudoh, *J. Org. Chem.*, **40**, 2823 (1975).
(9) H. H. Baer and T. Neilson, *Can. J. Chem.*, **43**, 840 (1965).
(10) H. H. Baer, F. Kienzle and T. Neilson, *Can. J. Chem.*, **43**, 1829 (1965).


---

# Quinazolines and 1,4-Benzodiazepines. LXXII.[1] Synthesis of Benzoxazinones from Anthranilic Acids. Revision of Structures Originally Described as 1,4-Benzodiazepines

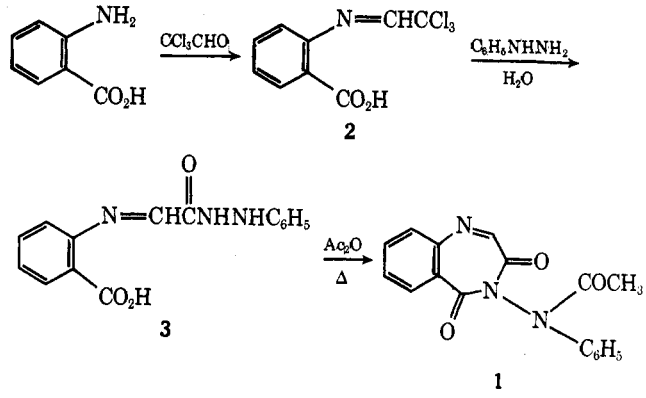

Norman W. Gilman,* John F. Blount, and R. Ian Fryer

*Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110*


*Received October 15, 1975*

A report in the chemical literature[2] in 1904 described the preparation of a compound to which the 1,4-benzodiazepine structure **1** was assigned. The mechanism for the formation of **1** from anthranilic acid was reported as outlined in Scheme I.

**Scheme I**




Owing to our continuing interest in 1,4-benzodiazepines, we have repeated the original work and found that although the reactions proceed ostensibly as described, the structures previously assigned to compounds **1**, **2**, and **3** are incorrect. The final product **1** was found to have the benzoxazinone structure **6a** rather than the 1,4-benzodiazepine structure **1**. The revised pathway for the formation of **6a** from anthranilic acid is shown in Scheme II.