Phase Transfer Catalyzed Reactions. I. Highly Stereoselective Formation of the Thermodynamically Less Stable Manno Isomers from Nitro Sugars with Active Methylene Compounds

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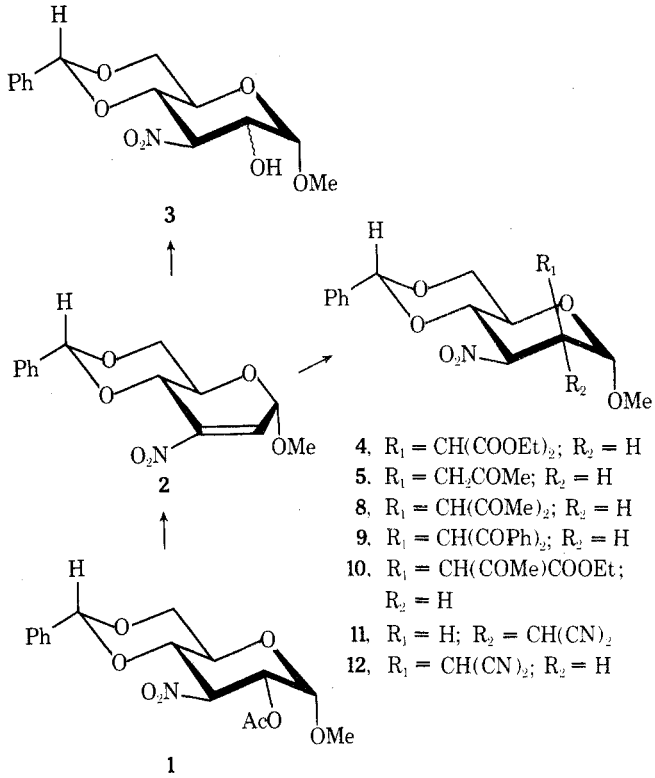
A phase transfer process was applied to the reaction of 3-nitro-2-enopyranoside (2) with some active methylene compounds to give thermodynamically less stable manno pyranosides in fairly good yields. In the case of acetylacetone deacetylation occurred to yield **5**, but under milder conditions product 8 was obtained exclusively. The reaction of 2 with malononitrile gave a mixture comprised of gluco and manno isomers (11 and 12); the latter was proved to epimerize to the former under the same conditions.

It is well known that the Michael reaction generally affords the thermodynamically more stable product because it is reversible.[1] Thus, very few examples[2] are known of stereoselective synthesis of the thermodynamically less stable isomer from nitro olefins, which are useful acceptors in the Michael reaction.

In recent years, on the other hand, great interest has developed in *phase transfer catalyzed two-phase reactions.*[3] One of the advantages of this method is that species existing in the organic phase and sensitive to hydrolysis, isomerization, etc., are more or less protected from water as well as a reagent or catalyzer in the aqueous phase.[4] This suggests such phase transfer might suppress the retro-Michael reaction to give the kinetically controlled product.[5]

We should like to report that the thermodynamically less stable manno derivatives can be prepared by the reaction of nitro sugars (**1**, **2**) with some active methylene compounds under the phase transfer conditions in fairly good yields.[6]



Results and Discussion

Reaction of **1** or **2** with ethyl malonate in benzene–0.2 *N* NaOH (excess) was not induced at room temperature even after vigorous stirring for 16 hr. When **2** was similarly treated with acetylacetone for 20 hr, almost all of **2** was recovered, but on stirring for 70 hr, half of **2** was converted into nitro alcohol **3**. These facts may be attributed to the inability of a carbanion generated in the aqueous phase and of nitro olefin remaining in the organic phase to combine. Addition of a small amount of hexadecyltributylphosphonium bromide as a phase transfer catalyst to the above two-phase reaction of **1** with ethyl malonate caused completion of the addition reaction within only 2 hr, giving methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-bis(ethoxycarbonyl)methyl-3-nitro-α-D-mannopyranoside (**4**) in over 70% yield. The manno configuration of **4** was assigned from NMR data (Table I): $J_{1,2}$ = 1.3, $J_{2,3}$ = 5.0, and $J_{3,4}$ = 10.6 Hz. The reaction doubtless proceeded via the intermediate nitro olefin **2** which arose from **1** by elimination of acetic acid and was subjected to the addition of ethyl malonate. In fact, treatment of **2** with ethyl malonate under the same conditions also afforded **4** in 74% yield. The yield of **4** was

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^8 [a]	CH_3CO	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{2,8}$
4	4.86	3.53	5.18	4.50	5.61	3.70		1.3	5.0	10.6	8.8	6.3
5	4.54	3.18–3.25	5.09	?	5.61	2.57–2.65	2.05	1.0	5.0	10.0	?	?
8	4.46	3.72	5.13	?	5.61	4.27	2.14 2.30	1.3	5.0	10.3	?	10.6
9	4.70	4.21	5.30	4.43	5.49	5.97		1.0	5.3	10.6	8.8	8.3
10	4.74	3.64	5.15	4.43	5.61	?	2.19	1.0	5.0	11.3	8.8	?
11	5.04	2.95	5.05	4.03	5.53	3.86		3.8	11.5	9.5	8.8	6.3
12	5.10	3.08	5.23	4.73	5.65	4.09		1.0	5.6	11.3	7.5	3.8

[a] H^8 means the acid methine or methylene proton(s) of a chain moiety.

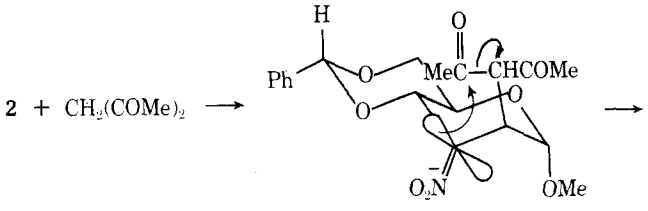
Table II
Reactions of 2 with Acetylacetone[a]

Expt	0.2 NaOH, ml	Benzene, ml	*t*-Bu-OH, ml	Catalyst, mg	Time, hr	Ratios of the products 5:8	
1	2.7	8		4	16	q[c]	*d*
2	2.7	2	1	4	1.5	q	*d*
3	2.7	2	2	4	1.5	q	*d*
4	1.0	3		6	2	1	2.2
5	0.1	3		2	2		q
6	0.1	3		2	24		q

[a] All the reactions were carried out by the use of 0.1 mmol of 2 and 0.18 mmol of acetylacetone. [b] Ratios of the products were determined by NMR spectroscopy. [c] q, quantitative or almost so. [d] Not detected by NMR spectroscopy.

improved up to 92% when the amount of sodium hydroxide was reduced to a trace.

Reaction of 2 with acetylacetone under the same conditions, on the other hand, afforded methyl 2-*C*-acetonyl-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-mannopyranoside (5). Its structure was deduced from the following data: the elemental analysis corresponded to $C_{17}H_{21}NO_7$; ir spectroscopy (KBr) showed the presence of carbonyl (1717 cm^{-1}) and nitro group (1550 cm^{-1}); NMR spectroscopy showed *C*-methyl (3 H, δ 2.05) and methylene signals (2 H, δ 2.57–2.62) as well as $J_{1,2}$ = 1.0, $J_{2,3}$ = 5.0, and $J_{3,4}$ = 10 Hz. On addition of *tert*-butyl alcohol as a proton source to the above reaction system, only 5 was formed similarly (expt 2, 3). If at the stage of nitronate ion (6) migration of an acetyl group from the newly formed diacetyl methyl moiety to C_3 is much faster than external protonation or internal proton migration from the acidic methine proton to C_3,[7] 5 should be easily formed because deacetylation from 7 probably occurs more easily than 8 owing to the stronger electron-withdrawing character of a nitro group than that of an acetyl group. When the reaction was carried



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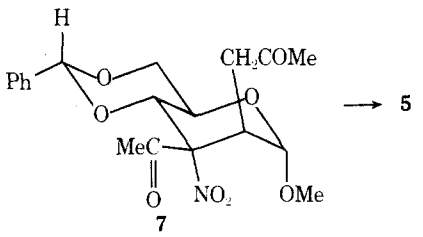

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out under milder conditions (expt 5), the intended adduct (8) was obtained exclusively in good yields. Under these conditions 8 was not affected within 2–24 hr, but it was completely converted into 5 with or without acetylacetone under conditions similar to those used for the preparation of 4. In these reactions no evidence for the simultaneous formation of both epimers of 5 and 8 was observed. These results suggest that 8 was first formed, which was subjected to deacetylation to give 5 prior to epimerization of 8. On treatment of 2 with dibenzoylmethane in the presence of a catalytic amount of alkali, manno isomer 9 was obtained in good yield.

A similar reaction of 2 with ethyl acetoacetate gave a mixture, the NMR spectrum of which suggested the manno configuration ($J_{1,2}$ = 1.0, $J_{2,3}$ = 5.0, and $J_{3,4}$ = 11.3 Hz), but which showed two signals in the acetyl region (δ 2.35 and 2.19 with the ratio of 1:2) with 3 H intensity. This mixture, therefore, may consist of two manno isomers which differ in the chirality of the ethyl acetoacetate moiety. The major product could be isolated in a crystalline form but the isolation of the minor one has not been yet achieved.

Treatment of 2 with malononitrile in the presence of a trace of alkali for 2 hr gave a mixture of gluco (11) and manno isomer (12) in the ratio of 1:1.3 (by NMR spectroscopy), which were separated by column chromatography. The ratio of 12 to 11 decreased with the reaction time: 0.3 (6 hr), and 0.1 (24 hr), and finally 12 in the mixture was completely converted into 11.[8]

These results are the first example to demonstrate the usefulness of a phase transfer catalyst in the Michael reaction. The result is a highly stereoselective formation of thermodynamically less stable isomers from nitro olefin derivative and active methylene compounds.

Experimental Section

All the melting points were determined in capillaries and are uncorrected. The ir spectra were determined in potassium bromide disks with a Hitachi 215 infrared spectrophotometer. The NMR spectra (Table I) were recorded at 100 MHz with a JNM-4H-100 (Jeol) spectrometer in chloroform-*d*, using tetramethylsilane as the internal standard. The column chromatography was carried out on silica gel (C-200, Wakogel). In this section the catalyst means hexadecyltributylphosphonium bromide.

Methyl 4,6-*O*-Benzylidene-2-*C*-bis(ethoxycarbonyl)methyl-2,3-dideoxy-3-nitro-α-D-mannopyranoside (4). A. From Nitro Acetate 1.[9] A mixture of 1 (105.9 mg, 0.3 mmol), ethyl malonate (69 mg, 0.43 mmol), benzene (24 ml), and 0.2 *N* NaOH (9.6 ml) was stirred for 2 hr 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 syrup (98 mg, 72%), which was found to contain no by-product by NMR spectroscopy. The syrup was chromatographed on a silica gel column (13 × 65 mm) with benzene: yield 88.4 mg (65%); $[\alpha]^{20}D$ −33.4° (*c* 1, $CHCl_3$); ir (KBr) 1750, 1730 (COOEt), 1560, 1370 cm^{-1} (NO_2).

Anal. Calcd for $C_{21}H_{27}NO_{10}$: C, 55.62; H, 6.00; N, 3.09. Found: C, 56.01; H, 6.32; N, 3.07.

B. From Nitro Olefin 2.[9] In the same manner as described above except for the decreased amount of 0.2 *N* NaOH to 8.1 ml, reaction between 2 and ethyl malonate gave NMR spectroscopically pure 4 (101 mg, 74%). The yield increased to 92% when the amount of 0.2 *N* NaOH was further reduced to 0.1 ml.

Methyl 2-*C*-Acetonyl-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-mannopyranoside (5). To a solution of 2 (131.9 mg, 0.45 mmol), acetylacetone (90 mg, 0.9 mmol), the catalyst (18 mg), and benzene (36 ml) was added 0.2 *N* NaOH (12 ml). The reaction mixture was stirred for 2 hr at room temperature and then washed with water (3 × 10 ml). The organic layer was evaporated in vacuo to afford a NMR spectroscopically pure solid residue (147 mg, 93%). Recrystallization from ethanol gave 134 mg (85%) of 4: mp 114–115°; $[\alpha]^{20}D$ +22.8° (*c* 1, $CHCl_3$); ir (KBr) 1717 (CO), 1550, 1370 cm^{-1} (NO_2).

Anal. Calcd for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99. Found: C, 58.33; H, 6.06; N, 4.22.

Methyl 4,6-*O*-Benzylidene-2-*C*-(diacetyl)methyl-2,3-dideoxy-3-nitro-α-D-mannopyranoside (8). To a solution of 2 (58.6 mg, 0.2 mmol), acetylacetone (36 mg, 0.36 mmol), the catalyst (4 mg), and benzene (6 ml) was added 0.2 *N* NaOH (0.2 ml). The reaction mixture was stirred for 2 hr at room temperature and then washed with water (3 × 5 ml). The benzene layer was evaporated in vacuo to give a NMR spectroscopically pure residue (74 mg, 94%), which was crystallized from ethanol to give 8 (63.5 mg, 80.8%): mp 147.5–148.5°; $[\alpha]^{20}D$ −129° (*c* 1, $CHCl_3$); ir (KBr) 1728, 1708 (CO), 1552 cm^{-1} (NO_2).

Anal. Calcd for $C_{19}H_{23}NO_8$: C, 58.01; H, 5.89; N, 3.56. Found: C, 58.07; H, 5.85; N, 3.59.

Conversion of 8 into 5. Treatment of 8 (19.7 mg, 0.05 mmol) with or without acetylacetone (9 mg, 0.09 mmol) in benzene (4 ml)–0.2 *N* NaOH (1.4 ml) solution in the presence of the catalyst

(2 mg) for 2 hr at room temperature gave **5** exclusively on the basis of its NMR spectrum.

Methyl 4,6-*O*-Benzylidene-2-*C*-(dibenzoyl)methyl-2,3-dideoxy-3-nitro-α-D-mannopyranoside (9). Treatment of **2** (58.6 mg) with dibenzoylmethane (49 mg, ca. 0.22 mmol) under the conditions used to prepare **8** gave a pure crystalline residue of **9** (88 mg, 85%). The residue (176 mg) was recrystallized from ethanol: yield 149 mg (72%); mp 214° dec; $[\alpha]^{20}D$ −262° (*c* 1, $CHCl_3$); ir (KBr) 1690 (CO), 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, 67.09; H, 5.19; N, 2.83.

Methyl 2-*C*-(Acetylethoxycarbonyl)methyl-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-mannopyranoside (10). Reaction of **2** (58.6 mg) with ethyl acetoacetate (28.6 mg, 0.22 mmol) under the conditions described above for the preparation of **8** gave a mixture (67.7 mg, 80%), which was chromatographed on silica gel (13 × 35 mm) with benzene, and the eluate was evaporated in vacuo to give a syrup of **10** (42.3 mg, 50%), which was crystallized from isopropyl ether: mp 127.5–128.5°; $[\alpha]^{20}D$ −103° (*c* 1, $CHCl_3$); ir (KBr) 1730, 1710 (CO), 1555 cm^{-1} (NO_2).

Anal. Calcd for $C_{20}H_{25}NO_9$: C, 56.73; H, 5.59; N, 3.31. Found: C, 56.78; H, 5.95; N, 3.31.

Methyl 4,6-*O*-Benzylidene-2-*C*-(dicyano)methyl-2,3-dideoxy-3-nitro-α-D-glucopyranoside (11). Treatment of **2** (58.6 mg) with malononitrile (24 mg, 0.36 mmol) under the condition described above for the preparation of **8** gave a syrup (55.3 mg, 77%) consisting of **11** and **12**, in the ratio of 1:1.3 on the basis of NMR spectrum. The syrup (11 mg) was chromatographed on silica gel (17 × 85 mm) developed slowly with benzene. The eluate was collected in 10-ml portions. Fractions 3 and 4 were combined and evaporated in vacuo to give crystals of **11**: yield 36 mg (25%); mp 163.5–164.5°; $[\alpha]^{20}D$ +110° (*c* 1, $CHCl_3$); ir (KBr) 2260 (CN), 1560 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, 56.73; H, 4.92; N, 11.79.

Methyl 4,6-*O*-Benzylidene-2-*C*-(dicyano)methyl-2,3-dideoxy-3-nitro-α-D-mannopyranoside (12). In the above chromatography, fractions 6–12 were combined and evaporated in vacuo to give a syrup (57 mg, 40.1%) of **12**: $[\alpha]^{20}D$ +21.7° (*c* 1, $CHCl_3$); ir (KBr) 2260, 2235 (CN), 1557 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, 56.93; H, 4.85; N, 11.49.

Conversion of 12 into 11. To a solution of benzene (3 ml), 0.2 *N* NaOH (0.8 ml), the catalyst (2 mg), and malononitrile (12 mg) was added a mixture (36 mg) of **12** and **11** (ratio of 1.5:1 by NMR spectroscopy). The reaction mixture was stirred for 15 hr at room temperature, and then washed with water. The benzene layer was evaporated in vacuo to give a residue, which was NMR spectroscopically pure **11**.

Registry No.—**1**, 16697-50-0; **2**, 16697-51-1; **4**, 55853-26-4; **5**, 55853-27-5; **8**, 55853-28-6; **9**, 55853-29-7; **10** isomer a, 55853-30-0; **10** isomer b, 55853-31-1; **11**, 55853-32-2; **12**, 55853-33-3; acetylacetone, 123-54-6; dibenzoylmethane, 120-46-7; ethyl acetoacetate, 141-97-9; malonitrile, 109-77-3; ethyl malonate, 105-53-3.

References and Notes

(1) For example, S. Patai and Z. Rapport, "The Chemistry of Alkenes", S. Patai, Ed., Interscience, New York, N.Y., 1964, Chapter 8.
(2) Some thermodynamically less stable isomers were prepared from nitro olefin derivatives with the following nucleophiles: hydrogen cyanide, hydrazoic acid, theophylline, and 2,6-dichloropurine, T. Sakakibara and R. Sudoh, *Chem. Commun.*, 69 (1974); hydrogen cyanide, H. Paulsen and W. Grewe, *Chem. Ber.*, **107**, 3013 (1974); *N*-bromoacetamide, H. H. Baer and W. Rank, *Can. J. Chem.*, **52**, 2257 (1974); anthranilic acid, H. H. Baer and F. Klenzle, *J. Org. Chem.*, **34**, 3848, 4204 (1969); secondary amines such as morpholine, P. Southwick and J. E. Anderson, *J. Am. Chem. Soc.*, **79**, 6222 (1957).
(3) C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971); J. Dockx, *Synthesis*, 441 (1973); E. X. Dehmlow, *Angew. Chem.*, **86**, 187 (1974); *Angew. Chem., Int. Ed. Engl.*, **13**, 170 (1974).
(4) For example, K. E. Koenig and W. P. Weker, *Tetrahedron Lett.*, 2275 (1974); M. Makosza and M. Fedorynski, *Synthesis*, 274 (1974).
(5) A phase transfer catalyst has been used in the Michael reaction but the stereochemical studies were not examined; for example, D. A. White and M. M. Baiter, *J. Chem. Soc., Perkin Trans. 1*, 2230 (1973).
(6) The facts that the thermodynamically less stable manno isomers could be isolated exclusively or predominantly by this phase transfer process prompted us to investigate the reactions of **2** with active methylene compounds under homogeneous conditions, and in some cases the manno isomers were formed also as a major product. Details are now in progress.
(7) This reaction mechanism was based on the fact that the reaction of 4-*tert*-butyl-1-cyanocyclohexene with ethyl malonate afforded ethyl 4-*tert*-butyl(e)-2-carbethoxymethyl(a)-1-cyano(a)cyclohexanecarboxylate(e); R. A. Abramovitch and D. L. Struble, *Tetrahedron*, **24**, 357 (1968).
(8) These results are in good agreement with the generalization that manno isomers are thermodynamically less stable than the gluco isomers.
(9) H. H. Baer and F. Klenzle, *Can. J. Chem.*, **45**, 983 (1967).

Synthesis of C Nucleosides. X.[1] Structural Analogs of Formycin B

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A general synthetic route to 2-substituted fused pyrimidones is described. Model reactions of benzylthioacetimidate **8** with different aminocarbethoxypyrazoles give the cyclized structures. The same condensations with glycosyl thioformimidates **10** and **14** lead to pyrazolo[4,3-*d*]pyrimidin-7-ones **11** and **15** and pyrazolol[3,4-*d*]pyrimidin-4-ones **19** and **21**. Removal of the protective ester groups is achieved with methanolic ammonia. The spectroscopic properties of anomers of the ribo and 2′-deoxyribo analogs of formycin B, **3**, **4**, **5**, and **6**, are discussed.

The biological properties of formycins[2] A (**1**) and B (**2**) have stimulated diverse studies on their total synthesis[3] or on the preparation of derivatives with modifications of the heterocycle[4,5] and of the sugar moieties.[6,7]

In pursuit of our work on the synthesis of C nucleosides we prepared isomers of formycin B and 2′-deoxyformycin B, whose sugar (ribose and 2-deoxyribose) was linked to carbon 2 of the pyrimidine cycle. We should obtain the 5-glycosylpyrazolo[4,3-*d*]pyrimidin-7-ones **3** and **4**, closely related to formycin B, or the 6-glycosylpyrazolo[3,4-*d*]pyrimidin-4-ones **5** and **6**, related to allopurinol nucleoside (Chart I).

Known methods for the preparation of 2-substituted fused pyrimidines are laborious with poor overall yield[8] or require drastic conditions.[9] A new approach, using much milder conditions, has been developed from the condensation of a thioformimidate[10] with an amino aromatic heterocycle, functionalized in the ortho position by an ester group.

Results

We start with a model reaction, using benzyl thioacetimidate (**8**) and 4-amino-3-carbethoxypyrazole (**7**), prepared by reduction of the nitro ester[11] (Scheme I). By refluxing in