boxylate anion and 1.1 equiv of 18-6 crown ether in DMF. The solution was allowed to stir overnight in order to completely dissolve the salt and was then used immediately. The 0.1 M solution of $KClO_4$ was prepared similarly.

Second-order rate constants, k_{RCOO^-}, were obtained from plots of k_{obs} vs concentration of the nucleophile. Typically five concentrations of nucleophile were used from 0.02 to 0.1 M; however, for some faster reactions lower concentrations were employed. Generally plots of k_{obs} vs nucleophile were linear with intercepts of zero; however, some plots appeared to show a small amount of upward curvature at higher nucleophile concentrations. The experimental point for the highest nucleophile concentration never deviated more than 25% from the line defined by lower concentrations of nucleophile.

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Registry No. **1a**, 18052-27-2; **1b**, 126644-72-2; **1c**, 126644-71-1; **1d**, 98525-64-5; DMF, 68-12-2; $(CH_3)_3CSi(CH_3)_2Cl$, 18162-48-6; PhOH, 108-95-2; $4\text{-}ClC_6H_4OH$, 106-48-9; $3\text{-}ClC_6H_4OH$, 108-43-0; $3\text{-}O_2NC_6H_4OH$, 554-84-7; CH_3CO_2K, 127-08-2; HCO_2K, 590-29-4; $ClCH_2CO_2K$, 7748-25-6; Cl_2CHCO_2K, 19559-59-2; F_3CCO_2K, 2923-16-2.

Separation and Stereochemical Assignment of Erythro and Threo Isomers of the *m*-Nitro Analogue of (±)-Chloramphenicol

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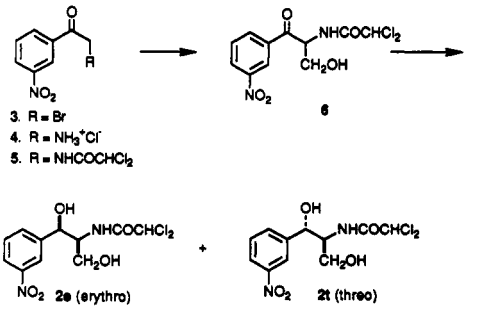
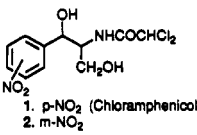
Chloramphenicol (1), the first of the broad-spectrum antibiotics, isolated from aerobic cultures of *Streptomyces venezuela* more than 30 years ago, still finds application today in human and veterinary medicine for treatment of serious staphylococcus infections and is the only dependable medication for typhoid fever and Rocky Mountain spotted fever. It has also been used in treating many diseases in food-producing animals caused by Gram-negative bacteria. Because it has serious side effects, including the rare but frequently fatal condition of aplastic anemia, however, it has not been approved for use in food animals in the U.S.[1]

Because illegal use of the antibiotic both in the U.S. and abroad is a continuing problem, sensitive and specific analytical methods for the analysis of chloramphenicol residues in animal food products are required. In 1985 Allen summarized the chromatographic methods then available.[2] The most sensitive methods use gas chromatography for chloramphenicol in tissues at <1 ppb, often with an internal standard such as thiamphenicol or resorcinol dibenzoate.[3] A radioimmunological assay which uses the *m*-nitro analogue (**2**) as a standard has been published.[4] This project was undertaken to evaluate the use of **2** as an internal GC standard, and it was consequently necessary to prepare samples of **2** of known relative configuration.

Scheme I. Synthesis of Stereoisomers of the *m*-Nitro Analogue of Chloramphenicol





Three groups have reported the synthesis of (±)-**2**, all using the sequence beginning with a nitroacetophenone originally devised by Long and Troutman[5] for chloramphenicol. All three groups isolated only a single racemic diastereomer of **2** by Meerwein–Ponndorf reduction of a keto amide intermediate and assigned it the threo configuration by analogy with the chloramphenicol synthesis. While the threo configuration of chloramphenicol is secure, there is no definitive evidence of the configuration of the *m*-nitro analogue, however, and the situation is further complicated by the disagreement in reported melting points. Buu-Hoi and Khoi[6] obtained a solid of mp 153 °C, while both Long and Jenesel[7] and Sorm et al.[8] apparently obtained a different material, mp 135–6° and 134 °C, respectively. Accordingly it became necessary to repeat the synthesis and make an unambiguous stereochemical assignment. We report that the threo and erythro isomers fortuitously have the same melting point, which is thus useless for identification, and that the assumption that the previously synthesized compound is the threo isomer is incorrect.

We chose the route of Sorm et al.[8] as the most efficient (Scheme I). *m*-Nitrophenacyl bromide (**3**) was prepared by bromination[9] of *m*-nitroacetophenone and converted to the α-amino ketone (**4**) via the hexamethylenetetramine salt, following published procedures.[10] The amine hydrochloride could be acylated directly[8,11] by heating with dichloroacetyl chloride, providing amide **5**. Condensation

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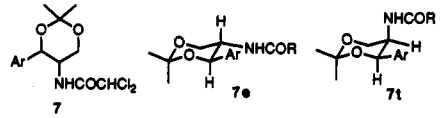
Table I. Reduction of Ketone 6 to Erythro and Threo Diols

reducing agent	% erythro	% threo
$Al(OCHMe_2)_3$	16	-
$NaBH_4$	36	36
$NaBH(OAc)_3$	52	4
$Me_4N^+BH(OAc)_3^-$	56	4
DIBALH	-	28

with formaldehyde afforded keto amide 6, the penultimate intermediate, in 30% overall yield from *m*-nitroacetophenone.

All three previous syntheses had used the Meerwein–Ponndorf procedure to reduce the ketone. The low yield of a single isolable diol reported in these reductions was an impetus to examine alternative reducing agents. Sodium borohydride gave a 1:1 mixture of two diols, inseparable by crystallization, but two modified hydrides were more selective. Sodium triacetoxyborohydride and tetramethylammonium triacetoxyborohydride, selected for their ability to reduce acyclic β-hydroxy ketones to anti diols with high stereoselectivity by intramolecular delivery of hydride from an intermediate alkoxydiacetoxyborohydride,[12] led to a 12–13:1 ratio of the two diols, the major isomer being also the major product of reduction by aluminum isopropoxide. Finally, diisobutylaluminum hydride was fairly specific in leading to the other isomer (Table I).

The identification of the isomeric diols was complicated by their identical melting points; while one crystallized from water as needles and the other as sugarlike cubes, both melted at 134–135 °C. Assignment of configuration was made in two independent ways. First, each diol was converted to its acetonide 7. The acetonide of mp 136–138 °C was assigned the erythro configuration 7e from the proton NMR spectrum, since the benzylic proton at C-4 is coupled to its neighbor by a coupling constant of 8.9 Hz, indicating an axial–axial coupling. By contrast, in the threo acetonide 7t the axial–equatorial coupling constant between the C-4 and C-5 protons is so small that the benzylic proton appears as a broad singlet. The assignments based on NMR were then confirmed by single-crystal X-ray analyses of both erythro and threo isomers.



It is interesting that Meerwein–Ponndorf reduction of ketone 6 gives, albeit in low yield, only the erythro diol 2e, in contrast to the reduction which produces the threo isomer of chloramphenicol, and the published assignment of configuration to 2 based on this presumed analogy must be reversed.

Both threo and erythro isomers, as their trimethylsilyl derivatives, proved to be useful standards in gas chromatographic analysis (electron capture detection) of chloramphenicol at 2.5 ppb in veal calf urine and muscle, and the detailed analytical method will be published in the *USDA-FSIS Chemistry Laboratory Guidebook*.

Experimental Section

Melting points were taken in open capillaries in an oil immersion apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker 270 MHz spectrometer while ^{13}C-NMR spectra were run on samples dissolved in $CDCl_3$/DMSO-d_6 on a JEOL FX-90Q instrument, using tetramethylsilane as an internal standard in both cases. Elemental analyses were determined by Atlantic Microlab, Inc., Atlanta, GA.

***m*-Nitrophenacyl Bromide (3).** A solution of bromine (2.42 g, 0.78 mL, 15 mmol) in 10 mL of $CHCl_3$ was added slowly to a solution of *m*-nitroacetophenone (2.5 g, 15 mmol) in 20 mL of $CHCl_3$ in a Pyrex vessel while irradiating the mixture with a 150-W GE sunlamp. When the addition was complete the solution was stirred an additional 20 min, washed successively with three 10-mL portions of water, aqueous sodium carbonate, and saturated brine, and then dried over sodium sulfate. Evaporation of the solvent left 2.20 g of crude product, which was recrystallized from 95% ethanol to give 1.92 g (52%), mp 90–92 °C (lit.[9] mp 96 °C). In large-scale runs yields of 58–70% were obtained.

α-Amino-*m*-nitroacetophenone Hydrochloride (4). To a mechanically stirred mixture of powdered hexamethylenetetramine (126 g, 0.899 mol) and 760 mL of $CHCl_3$ was added a solution of *m*-nitrophenacyl bromide (200 g, 0.820 mol) in 800 mL of $CHCl_3$. Another 500 mL of $CHCl_3$ was added to facilitate stirring, which was continued for 24 h. The mixture was cooled in ice and filtered, and the solid was washed immediately with 1.5 L of cold $CHCl_3$ and 1 L of cold absolute ethanol to remove the color and then dried over $CaSO_4$ in a desiccator to give 300 g (95%) of the hexamethylenetetramine salt.

With vigorous stirring, 76.8 g of this salt was added in small portions to a cold mixture of 175 mL of 95% ethanol and 85 mL of concd HCl. The salt dissolved within 30 min, and after stirring for 3 days α-amino-*m*-nitroacetophenone hydrochloride precipitated from solution. After cooling in ice the salt was filtered, recrystallized from 100 mL of water, and washed with cold absolute ethanol until colorless. Drying under vacuum afforded 39 g (90%) of the hydrochloride.

The ***N*-acetyl derivative**, prepared with acetic anhydride and sodium acetate, melted at 141–142 °C after recrystallization from ethyl acetate; lit.[7] mp 142–143 °C.

α-(Dichloroacetamido)-*m*-nitroacetophenone (5). A suspension of α-amino-*m*-nitroacetophenone hydrochloride (5.0 g, 23 mmol) in 92 mL of dry benzene was treated with dichloroacetyl chloride (3.7 g, 25 mmol), heated under reflux for 24 h, and filtered hot. The filtrate, on cooling, deposited 4.2 g (62%) of the amide, mp 106–107 °C (lit.[8] mp 106–107 °C).

α-(Dichloroacetamido)-β-hydroxy-*m*-nitropropiophenone (6). To a stirred suspension of 5 (20.0 g, 68.7 mmol) in 104 mL of absolute ethanol was added 21.2 mL (280 mmol) of a 37% formalin solution. After stirring for 5 min, $NaHCO_3$ (1.04 g) was added and the mixture was warmed at 30–35 °C for 20 min, at which time all of the solids had dissolved. TLC ($CHCl_3$, silica gel) was used to confirm the disappearance of starting material (R_f 0.66; product R_f 0.52). The mixture was diluted with cold water and cooled to 5 °C, and the precipitate was collected and dried to give 18.1 g (82%). Recrystallization from benzene gave material of mp 134–135 °C (lit.[8] mp 142 °C). ^{1}H-NMR ($CDCl_3$/DMSO-d_6): δ 7.55–8.69 (5 H, m, aromatic + NH), 6.13 (1 H, s, $CHCl_2$), 5.45 (1 H, m, CHCO), 4.65 (1 H, t, J = 6 Hz, OH), 3.90 (2 H, t, J = 6 Hz, CH_2OH). ^{13}C-NMR: δ 194.71, 163.69, 147.62, 135.98, 133.64, 129.94, 122.71, 65.55, 61.26, 57.30. Anal. Calcd for $C_{11}H_{10}N_2O_5Cl_2$: C, 41.14; H, 3.14; N, 8.72. Found: C, 41.20; H, 3.17; N, 8.74.

When this reaction was allowed to proceed for 2 h before workup, the main product, isolated in 53% yield, was the bis-formaldehyde condensation product, 2-(dichloroacetamido)-2-(*m*-nitrobenzoyl)-1,3-propanediol, mp 110–112 °C. ^{1}H-NMR ($CDCl_3$, DMSO-d_6): δ 7.30–8.91 (4 H, m, aromatic), 8.50 (1 H, s, NH), 5.93 (1 H, s, $CHCl_2$), 4.58 (2 H, br s, OH), 4.11 (4 H, AB quartet, J = 11.5 Hz, CH_2O). ^{13}C-NMR: δ 199.19, 163.47, 146.99, 137.37, 133.75, 128.88, 125.81, 122.83, 69.43, 65.87, 62.41.

2-(Dichloroacetamido)-1-(*m*-nitrophenyl)-1,3-propanediol, Erythro (2e) and Threo (2t) Isomers. (a) To a solution of tetramethylammonium triacetoxyborohydride (7.5 g, 28.5 mmol) in 23 mL of dry acetonitrile and 23 mL of glacial acetic acid (redistilled from a mixture containing 5% acetic anhydride and 2% CrO_3), kept under N_2 at −40 °C, was added a solution of 6 (1.83 g, 5.70 mmol) in 25 mL of acetonitrile over 3 min. The mixture was stirred 5 min at −40 °C and an additional 2 h at room temperature, at which time TLC showed the absence of starting material. The mixture was stirred with 50 mL of 0.5 N aqueous sodium potassium tartrate for 2 h and then extracted with eight 25-mL portions of ethyl acetate. The combined organic extracts were washed with saturated $NaHCO_3$ solution and brine, dried

(12) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* 1988, *110*, 3560.

over sodium sulfate, and concentrated to afford 1.6 g of a mixture of diols. Recrystallization from water gave 1.03 g (56%) of the erythro isomer **2e** as colorless needles, mp 134–135 °C. ^{1}H-NMR ($CDCl_3$/DMSO-d_6): δ 7.45–8.31 (4 H, m, aromatic), 8.12 (1 H, d, J = 1.0 Hz, NH), 6.08 (1 H, s, $CHCl_2$), 5.50 (1 H, d, J = 5.3 Hz, benzylic OH), 4.99 (1 H, t, J = 5.7 Hz, benzylic), 4.42 (1 H, t, J = 5.7 Hz, primary OH), 4.08 (1 H, m, CHN), 3.91–3.63 (2 H, m, CH_2). ^{13}C-NMR: δ 163.63, 147.51, 143.80, 132.37, 128.70, 121.91, 121.11, 72.25, 66.05, 60.03, 55.97. Anal. Calcd for $C_{11}H_{12}Cl_2N_2O_5$: C, 40.86; H, 3.72; N, 8.67; Found, 41.00; H, 3.74; N, 8.63.

From the mother liquors of the erythro diol was obtained 0.08 g of the threo isomer **2t** as sugarlike cubes, mp 134–135 °C. ^{1}H-NMR ($CDCl_3$/DMSO-d_6): δ 7.42–8.32 (4 H, m, aromatic), 7.69 (1 H, s, NH), 6.00 (1 H, s, $CHCl_2$), 5.45 (1 H, d, J = 4.7 Hz, sec OH), 5.24 (1 H, dd, J = 6.5, 2.5 Hz, benzylic), 4.55 (1 H, t, J = 5.8 Hz, primary OH), 4.17 (1 H, m, CHN), 3.75 (2 H, m, CH_2O). ^{13}C-NMR: δ 163.96, 147.62, 143.95, 131.94, 128.65, 121.80, 120.86, 70.33, 66.00, 61.47, 56.04. Anal. Found: C, 40.99; H, 3.76; N, 8.63.

(b) To a solution of sodium borohydride (3.0 g, 79 mmol) in 100 mL of dry acetonitrile, kept under N_2 at 0 °C, was added 115 mL of glacial acetic acid dropwise, keeping the temperature below 5 °C, over a period of 15 min. A solution of **6** (10.0 g, 31.1 mmol) in 300 mL of acetonitrile was added in one portion, and the mixture was stirred at 25 °C for 24 h, at which time TLC showed the absence of **6**. The mixture was vigorously stirred with 450 mL of 0.5 N sodium potassium tartrate for 12 h, and the organic layer was salted out and separated. Workup as in part a gave, after recrystallization from water, 5.2 g (52%) of **2e**, mp 134–135 °C, and 0.43 g (4.3%) of **2t**, mp 134–135 °C.

(c) To a solution of **6** (1.0 g, 3.1 mmol) in 25 mL of dry CH_2Cl_2 at −78 °C was added a 1.5 M solution of diisobutylaluminum hydride in toluene (4.15 mL, 6.2 mmol) over 6 min. The mixture was stirred for 20 min at −78 °C and for 3 h at 25 °C and diluted with 60 mL of cold water, and the organic layer was separated. The aqueous layer was extracted with two 20-mL portions of $CHCl_3$, and the combined organic solutions were washed with saturated brine and dried over $MgSO_4$. Evaporation of the solvents left a yellow solid (0.40 g) which was recrystallized from water to afford 0.28 g (28%) of **2t**, mp 134–135 °C.

(d) To a solution of **6** (10.0 g, 31.1 mmol) in 200 mL of methanol and 10 mL of chloroform at 30 °C was added sodium borohydride (1.5 g, 39.6 mmol) in two portions. After the vigorous reaction ceased the solution was cooled, diluted with 100 mL of water, and heated at 60 °C for 20 min. Workup as in c left a residue of 9.3 g of mixed isomers, which was recrystallized from water to give 7.3 g (73%) of a 1:1 mixture of **2e** and **2t**, mp 121–126 °C.

(e) A mixture of aluminum isopropoxide (2.3 g, 11 mmol) and 2-propanol (25 mL) was heated to 60 °C and vigorously stirred in a three-neck flask equipped with a condenser and Dean–Stark trap. Ketone **6** (2.0 g, 6.2 mmol) was added, and the mixture was heated under reflux for 10 h, removing about 6 mL of distillate from the trap every 45 min and replacing it with 6 mL of 2-propanol. After cooling to 25 °C, 12 mL of water was added and the mixture was heated to reflux for 30 min, cooled, and extracted with two 30-mL portions of ethyl acetate. The extracts were worked up as in c, and the crude yellow solid was recrystallized from water to give 0.32 g (16%) of **2e**, light yellow needles, mp 133–134 °C.

The **erythro acetonide 7e** was prepared by stirring a mixture of the diol **2e** (0.10 g, 0.31 mmol) with 2,2-dimethoxypropane (2.0 mL, 16 mmol) and a trace of *p*-toluenesulfonic acid in 2 mL of dry THF for 12 h. Removal of the solvent left a brown solid, which was taken up in $CHCl_3$ and passed through a short column of silica gel. Concentration of the eluate and recrystallization of the residue from $CHCl_3$/hexane gave 0.10 g (89%) of the acetonide, mp 136–138 °C. ^{1}H-NMR ($CDCl_3$/DMSO-d_6): δ 7.33–8.27 (5 H, m, aromatic and NH), 5.79 (1 H, s, $CHCl_2$), 5.07 (1 H, d, J = 8.9 Hz, benzylic), 3.86–3.98 (3 H, m, CH_2O and CHN), 1.55 (3 H, s, CH_3), 1.53 (s, 3 H, CH_3). ^{13}C-NMR: δ 164.16, 147.56, 140.89, 132.99, 129.13, 122.88, 122.22, 99.17, 72.71, 66.10, 61.80, 49.76, 28.66, 19.02. Anal. Calcd for $C_{14}H_{16}Cl_2N_2O_5$: C, 46.28; H, 4.41; N, 7.71. Found: C, 46.32; H, 4.46; N, 7.69.

The **threo acetonide 7t** was prepared from diol **2t** as described above; recrystallization from ethyl acetate/hexane gave the acetonide (39%), mp 182–184 °C. ^{1}H-NMR ($CDCl_3$/DMSO-d_6): δ 7.47–8.27 (5 H, m, aromatic and NH), 6.18 (1 H, s, $CHCl_2$), 5.35 (1 H, br s, benzylic), 4.39 (1 H, dd, J = 10, 2 Hz), 4.25 (1 H, dd, J = 8.0, 2.0 Hz, CHN), 3.84 (1 H, dd, J = 10, 2 Hz), 1.63 (6 H, s, CH_3). ^{13}C-NMR: δ 163.27, 147.36, 139.74, 131.59, 128.42, 121.88, 120.59, 99.30, 70.85, 65.35, 63.22, 46.58, 28.83, 18.05. Anal. Found: C, 46.11; H, 4.39; N, 7.66.

Crystallography. Crystals of **2e** and **2t** were mounted on a Syntex P3 automated diffractometer. Unit cell dimensions were determined by least-squares refinement of the best angular positions for 15 independent reflections ($2q$ > 15°) during normal alignment procedures using molybdenum radiation (I = 0.71069 Å). Data were collected at room temperature using a variable rate scan, a q–$2q$ scan mode and a scan width of 1.2° below Ka_1 and 1.2° above Ka_2 to a maximum $2q$ value of 45.0°. Backgrounds were measured at each side of the scan for a combined time equal to the total scan time. The intensities of three standard reflections were remeasured after every 97 reflections and, as the intensities of these reflections showed less than 6% variation, corrections for decomposition were deemed unnecessary. Data were corrected for Lorentz, polarization, and background effects. After removal of space group forbidden (**2e** only) and redundant data, observed data (**2e**, 1250; **2t**, 1557 points) were used for solution and refinement. The structures were solved for carbon, nitrogen, and oxygen positions using direct methods.[13] Least-squares refinement[14] converged with anisotropic thermal parameters. Hydrogen atoms (except for the hydroxyl hydrogens of **2e**) were located from a difference Fourier synthesis. These positions were included in the final refinement with isotropic thermal parameters but held invariant. A final difference Fourier revealed no electron density of interpretable level. Scattering factors were taken from Cromer and Mann.[15] The final cycle of refinement-function minimized $\Sigma(|F_o| - |F_c|)^2$, led to final agreement factor, R = 5.8% (**2e**), 5.2% (**2t**); $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| \times 100$. Unit weights were used until the final cycles of refinement, when weights equal to $1/sF$ were introduced. R_w = 7.6% (**2e**), 7.1% (**2t**).

Acknowledgment. We thank the USDA for financial support.

Registry No. 2e, 138125-71-0; **2t**, 138125-72-1; **3**, 2227-64-7; **4**, 36765-84-1; **4** acetyl deriv., 89260-48-0; **5**, 137965-23-2; **6**, 137965-24-3; **7e**, 137965-26-5; **7t**, 137965-27-6; *m*-nitroacetophenone, 121-89-1; 1-(*m*-nitrophenyl)-3,5,7-triaza-1-azoniaadamantane bromide, 7478-10-6; 2-(dichloroacetamido)-2-(*m*-nitrobenzoyl)-1,3-propanediol, 137965-25-4.

Supplementary Material Available: X-ray crystallographic data for diols **2e** and **2t**, including bond angles and distances, positional parameters, atomic thermal parameters, and ORTEP drawings (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Enantioselective Synthesis of PsiAβ, a Sporogenic Metabolite of *Aspergillus nidulans*

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Two novel hydroxy unsaturated C-18 fatty acids, psiAα (**1**) and psiAβ (**2**), have recently been identified as en-

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