off, the filtrate was shaken with ice (ca. 50 g) and extracted with chloroform. The extract was washed with cooled water, dried over anhydrous sodium sulfate, and then passed through a short column of silica gel using chloroform as eluent. The eluate was evaporated under reduced pressure to give the oxidation products (Table I).

Only **6k** was sensitive against silica gel and a large amount of **6k** was decomposed by column chromatography. Therefore, the reaction mixture which was obtained from the mixture of **1k** (500 mg) and TTN·3H_2O (1.2 g) was treated as follows. To the reaction mixture diluted with chloroform was added 3% hydrochloric acid (5 mL), and the mixture was additionally stirred at 0 °C for 5–10 min. The mixture was shaken with ice (ca. 50 g) and extracted with chloroform. The extract was washed with ice-cooled 0.1–0.2% hydrochloric acid and water, dried, and then concentrated. The residue was crystallized from ether–hexane and the crystal (A) and mother liquor (B) were obtained. After A was washed with a small amount of water (yellow material was removed), the crystals were treated with ether and the insoluble material was removed (**1k** was recovered, 40 mg) and recrystallized to give **6k** (120 mg). The mother liquor B was chromatographed over a silica gel column using chloroform as eluent to give **5c** (20 mg) from the second fraction.

Method B. A cooled solution (−5 to −10 °C) of TTN (1.07 g, 2.4 mmol) in methanol (25 mL) was added with stirring to a cooled solution (−5 to −10 °C) of the acetophenone or chalcone (**10**) (2 mmol) in methanol (50 mL) and the mixture was allowed to stand with stirring in an ice–salt bath. To the mixture was added a suspension of sodium hydrogen carbonate (0.8 g) in water (3–5 mL), and the mixture was additionally stirred for 5–10 min in an ice–salt bath. The separated precipitate was filtered off using a small amount of active carbon. The filtrate was concentrated to 20–25 mL under reduced pressure, diluted with chloroform, shaken with ice (ca. 50 g), and then extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure to give the quinone monoacetal (Table I).

Hydrolysis of the Quinone Monoacetals 2c, 2e, 2d, and 11. To the solution of the quinone monoacetal (ca. 50 mg) in methanol (5–10 mL) was added 5% hydrochloric acid (0.2–0.5 mL), and the mixture was allowed to stand at room temperature until the starting material disappeared (1–2 h) (in the case of the hydrolysis of **11**, the crystal of **12** was separated). The mixture was diluted with water and the product separated was collected by filtration or extraction with ether to give the desired compound in good yield. **5c**: mp 83–85 °C (from methanol); EIMS, 242 (M^+). Mixture of **5e** and **6e** (ratio, 5:1): oily material; EIMS, 272 (M^+). Mixture of **8d** and **9d** (ratio, 3:1): mp 135–136 °C dec (from EtOAc–hexane) (reaction time, 4 h). **12**: mp 138–140 °C (from methanol) (lit.[2] mp 139–140 °C); EIMS, 360 (M^+).

Hydrolysis of 2c in $H_2{}^{18}O$. To a solution of **2c** in methanol (200 μL) containing $H_2{}^{18}O$ (50 μL) was added 10% hydrochloric acid (6 μL), and the mixture was allowed to stand at room temperature for 1.5 h. The mixture was diluted with water and the crystals separated were collected to give the hydrolyzed product. EIMS (20 eV); m/z (rel intensity) M^+ 246 (33.8) [$C_{11}H_{14}O_4{}^{18}O_2$]; 244 (14.6) [$C_{11}H_{14}O_5{}^{18}O$]; 242 (2.5) [$C_{11}H_{14}O_6$].

Exchange Reaction between 5c and $H_2{}^{18}O$. **5c** was dissolved into a mixture of methanol (100 μL) and $H_2{}^{18}O$ (10 μL) and was allowed to stand at room temperature for 20 h: EIMS (20 eV); m/z (rel intensity) M^+ 244 (19.5) [$C_{11}H_{14}O_5{}^{18}O$]; 242 (1.0). The exchange reaction between **2c** and $H_2{}^{18}O$ was not observed under the same conditions.

Registry No. **1a**, 705-15-7; **1b**, 20628-06-2; **1c**, 22248-14-2; **1d**, 72424-28-3; **1e**, 3162-28-5; **1b**, 90-24-4; **1g**, 13246-14-5; **1h**, 832-58-6; **1i**, 703-23-1; **1j**, 2040-04-2; **1k**, 7507-98-4; **2b**, 138008-71-6; **2c**, 57197-14-5; **2d**, 138008-72-7; **2e**, 138008-73-8; **3b**, 138059-63-9; **5a**, 138008-69-2; **5c**, 138008-75-0; **5e**, 138008-79-4; **6a**, 138008-70-5; **6e**, 138008-77-2; **6k**, 138008-74-9; **7d**, 6172-59-4; **8d**, 138008-80-7; **9d**, 138008-81-8; **10**, 3877-67-6; **11**, 138008-76-1; **12**, 138008-78-3; thallium trinitrate, 13746-98-0.

Supplementary Material Available: Tables of ^1H NMR data for the adducts **3a** and **4a** and the time course of the oxidation of **1a** and details of the synthetic method for 4′-hydroxy-2′,6′-dimethoxyacetophenone preparation (2 pages). Ordering information is given on any current masthead page.

The Reaction of Carboxylate Nucleophiles with *tert*-Butyldimethylphenoxysilanes in Dimethylformamide

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We have examined the reaction of a series of carboxylate anions with a series of *tert*-butyldimethylphenoxysilanes (**1a–d**) in the polar aprotic solvent dimethylformamide (DMF). The reaction is an example of nucleophilic substitution at silicon (Scheme I) and is characterized by values for β_{Nuc} of 1.0 and β_{Lg} of −1.9. Scheme I depicts the reaction as involving nucleophilic attack of a carboxylate anion on a tetravalent silicon center; however, it is probable that the species actually undergoing substitution is a silicon center coordinated with a molecule of DMF.[1–7] Presumably the silicon center expands its valence shell by coordinating with a molecule of DMF; the pentavalent silicon species then undergoes reaction with the nucleophile.[1–7] It is well-known that pentavalent silicon centers are more reactive than tetravalent silicon centers.[8,9] In Scheme I any complexation with solvent is omitted for clarity.

The reaction of nucleophiles with silicon substrates cannot be studied in protic solvents. When nucleophiles and silicon substrates are allowed to react in protic solvents, the usual reaction is a general base catalyzed addition of solvent; direct substitution by the nucleophilic reagent is not observed.[10–17] The general base catalyzed addition of solvent can be avoided by examining the reaction in an aprotic solvent. DMF is a useful aprotic solvent for studying nucleophilic substitution reactions[18] since the high dielectric constant[19] (ϵ = 36.7) makes it possible to dissolve anionic nucleophiles. In addition pK_a values for many carboxylic acids and phenols have been determined in DMF,[20,21] allowing one to construct linear

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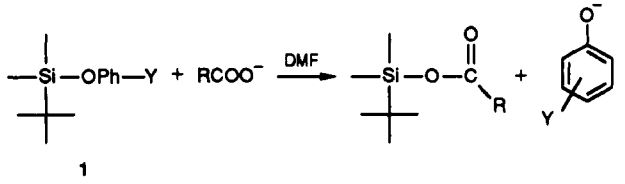
Scheme I



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a: Y = H
b: Y = 4-Cl
c: Y = 3-Cl
d: Y = 3-NO_2

Table I. Rate Constants for the Reaction of Carboxylate Nucleophiles of General Structure $RCOO^-$ Reacting with Substituted *tert*-Butyldimethylphenoxysilanes in DMF at 30 °C and Ionic Strength of 0.1 M with $KClO_4$[a]

	k_{RCOO^-} (M min), substituent Y in the phenolate leaving group			
R in $RCOO^-$	3-NO_2 (15.4)	3-Cl (16.3)	4-Cl (16.8)	H (18)[b]
CH_3 (12.5)[d]		9.2×10^2	9.1×10^1	1.7
H (11.5)[c]		8.7×10^1	1.3×10^1	2.6×10^{-1}
CH_2Cl (10.4)[d]	2.7×10^2	5.9	6.3×10^{-1}	1.2×10^{-2}
$CHCl_2$ (8.6)[d]	3.7	6.4×10^{-2}	7.5×10^{-3}	
CF_3 (7.3)[c]	1.4×10^{-1}	3.8×10^{-3}		

[a] The pK_a values of the corresponding carboxylic acids and phenols, determined in DMF, are given in parentheses, ref 20. [b] Approximate value, see ref 20. [c] Estimated by interpolation on a linear plot of pK_a vs the Taft inductive parameter as described in the text. [d] Reference 21 and adjusted to pK = 12.3 for 3-nitrophenol, see ref 20 and p 224 of ref 19.

free energy relationships such as Bronsted plots for reactions conducted in DMF. Although structure–reactivity relationships are commonly used by organic chemists in the study of reaction mechanisms, few structure–reactivity relationships have been obtained for direct nucleophilic substitution at silicon.[22]

Values for the second-order rate constants, k_{RCOO^-}, for a series of carboxylate anions reacting with **1a–d** in the presence of 18-6 crown ether are given in Table I. Also provided in Table I are the pK_a values, determined in DMF, of the corresponding carboxylic acids and phenols.[20,21] The pK_a values in DMF are not available for formic acid or for trifluoroacetic acid; the values given in Table I were obtained by interpolation on a linear plot of pK_a (determined in DMF) against the Taft inductive parameter for the substituent.[23] The line was defined using the known pK_a values of acetic acid, chloroacetic acid, and dichloroacetic acid.

Bronsted plots of log k_{RCOO^-} for reaction with **1a–d** vs the pK_a of the carboxylate nucleophiles are shown in Figure 1. The slope of these plots, β_{Nuc}, is 1.0 for all the leaving groups. The value of β_{Nuc} is a measure of the effective change in charge as seen by the substituent in the nucleophile on going from the ground state to the transition state compared to the change in charge density as seen by the substituent when the corresponding acid undergoes dissociation of a proton. Similarly a plot of log k_{RCOO^-} vs pK_a of the leaving group has a slope of β_{Lg}, which is a measure of change in effective charge as seen by the leaving group on going from the ground state to the transition state relative to that seen when a phenol undergoes dissociation of a proton. Bronsted plots of log k_{RCOO^-} vs pK_a of the leaving group for reaction with each

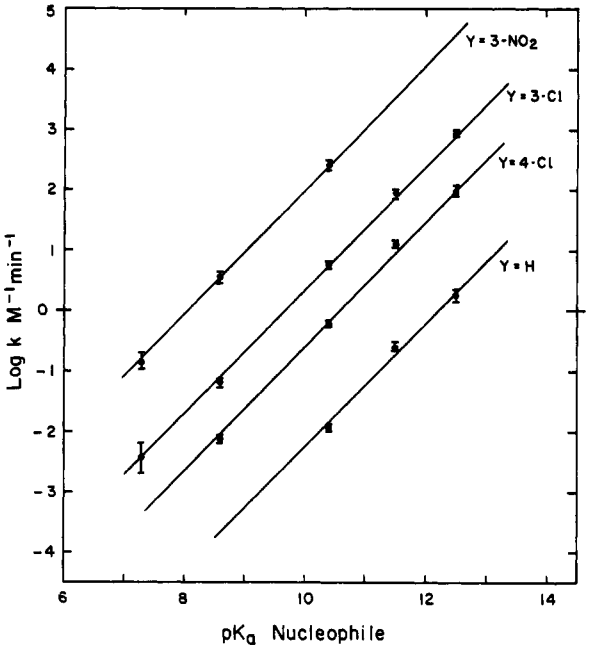

Figure 1. Bronsted plot of log k_{RCOO^-} vs the pK_a of the nucleophile for reaction of *tert*-butyldimethylphenoxysilanes with carboxylate anions of general structure $RCOO^-$ in DMF at 30 °C.

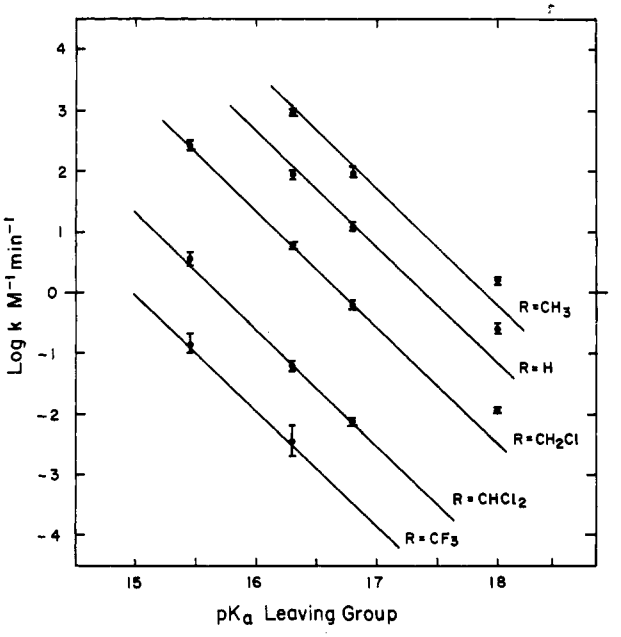

Figure 2. Bronsted plots of log k_{RCOO^-} vs the pK_a of the leaving group for reaction of *tert*-butyldimethylphenoxysilanes with carboxylate anions of general structure $RCOO^-$ in DMF at 30 °C.

nucleophile are shown in Figure 2; the slopes of these plots are all −1.9. The positive deviation in Figure 2 for the point corresponding to phenol as a leaving group is presumably due to the fact that only an approximate value of 18 is available for the pK_a of phenol. The point for phenol would fall on the line defined by the other leaving groups if it had a pK_a = 17.75, this value is in agreement with the estimated value of 18.

The above results are consistent with a mechanism where bond formation to the nucleophile has progressed about 34% and bond breaking to the leaving group is about 66% complete. This analysis is based on the assumption that the value of β_{Nuc} (β_{Lg}) is a measure of the degree of bond formation (breaking) in the transition state when calibrated by using the Bronsted β value for the overall equilibrium, β_{Eq}. The value of β_{Eq} is easily obtained from

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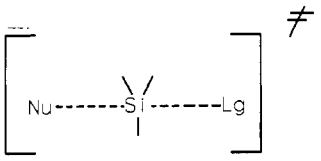

Figure 3.

the values of β_{Nuc} and β_{Lg} since $\beta_{Eq} = \beta_{Nuc} - \beta_{Lg} = 2.9$. The degree of bond formation to the nucleophile and leaving group in the transition state is then given by β_{Nuc}/β_{Eq} and β_{Lg}/β_{Eq}, respectively.[24] A transition state consistent with these results is depicted in Figure 3.

These values of β_{Nuc} and β_{Lg} suggest that the substitution reaction occurs by a one-step concerted mechanism involving a single transition state (S_N2–Si mechanism).[25] The reaction is essentially a symmetrical reaction involving the transfer of a silicon group between oxyanions. For a symmetrical transition state with a bond order to the nucleophile of ≈0.34, the bond order to the leaving group must also be ≈0.34, or ≈66% bond breaking. Since bond formation to the nucleophile is only slightly advanced and bond breaking to the leaving group is well advanced, the central silicon atom must carry some positive charge in the transition state. This is not unreasonable since the silicon atom is most likely complexed with a molecule of dimethylformamide.[1-7]

The possibility must be considered that the reaction could occur by a stepwise mechanism involving two transition states, one for formation of a pentavalent intermediate, k_1, and one for collapse of the intermediate, k_2 (S_Ni–Si mechanism).[25] For the reaction of carboxylate nucleophiles with phenoxysilanes, collapse of the intermediate (k_2) will be rate determining since phenoxides are poorer leaving groups (higher pK_a) than carboxylate anions, and bonding to the nucleophile in the transition state should be more advanced than bond breaking to the leaving group. Since this is not observed, we prefer a concerted mechanism with a single transition state to describe this reaction.

For a concerted reaction one might expect there to be an interaction between the nucleophile and leaving group leading to an increase in sensitivity toward the nucleophilic reagent (leaving group) as the leaving group (nucleophile) becomes worse.[26] The parallel lines of Figures 1 and 2 show no evidence for a change in the value of β_{Nuc} (β_{Lg}) when the pK_a of the leaving group (nucleophile) is changed. Thus there is no change in the amount of bond formation to the nucleophile or bond breaking to the leaving group as the reactants are changed. A change in the value of β_{Nuc} (β_{Lg}) due to a change in the pK_a of the leaving group (nucleophile) is described by the cross-interaction coefficient $p_{xy} = \partial\beta_{Nuc}/\partial pK_{Lg} = \partial - \beta_{Lg}/\partial pK_{Nuc}$,[26] which must be zero or close to zero for this reaction.

The β_{Lg} of −1.9 for the reaction of carboxylate nucleophiles with **1a–d** is unusually large and means that the substituent in the leaving group sees a greater change in charge density in going from the ground state to the transition state than if it were to lose a proton. For the dissociation of a proton the change in charge as seen by the substituent is from neutral oxygen (no charge) to a charge of −1. Since in the transition state of the substitution reaction the oxygen of the phenolate cannot develop a charge greater than −1, the oxygen in the ground state must have some partial positive character. The partial positive charge on the oxygen is not due to a greater electronegativity of silicon compared to hydrogen.[27] A possible explanation for the partial positive charge on oxygen in the ground state is p–d π overlap of the unpaired electrons on oxygen with vacant d orbitals on silicon. Such overlap has been suggested based on NMR experiments[28-30] and other techniques.[31,32]

Experimental Section

Materials. *tert*-Butyldimethylsilyl chloride (Aldrich) is commercially available and was used without further purification. Imidazole, potassium perchlorate, 18-6 crown ether, and all of the carboxylic acids were commercially available. Dimethylformamide was dried for several days over 4A molecular sieves, distilled, and stored under nitrogen.

The potassium salts of the carboxylic acids were prepared by adjusting the pH of an aqueous solution of the carboxylic acid to approximately 1 pH unit above the pK_a of the acid. The water was removed under vacuum, and the resulting wet solid was recrystallized from ethanol, except for trifluoroacetic acid which was recrystallized from 2-propanol. The recrystallized potassium salts were dried overnight in a vacuum desiccator. The pH of an aqueous solution of the salts was 7.

The *tert*-butyldimethylphenoxysilanes were prepared from the reaction of *tert*-butyldimethylsilyl chloride with the appropriate phenol according to a published procedure.[14] All of the phenoxysilanes gave NMR and mass spectral analyses consistent with the desired product. Mass spectral analyses were performed on a Hewlett-Packard Model 5988 GC/MS/DS operated using direct insertion in the chemical ionization mode with isobutane as the reagent gas. NMR spectra were recorded on a IBM NR/80 spectrometer.

Kinetics. Rate constants for the reaction of carboxylate anions with **1a–d** in DMF were determined at 30 °C and an ionic strength of 0.1 M with $KClO_4$ under pseudo-first-order conditions with the potassium salt of the carboxylic acid in >20-fold excess over phenoxysilane. Reactions were conducted in the presence of 1.1 equiv of 18-6 crown ether to help solubilize the potassium salts. Pseudo-first-order rate constants were determined by measuring the increase in absorbance due to the formation of the phenolate anion as a function of time using a Shimadzu UV-160 or a Gilford Response spectrophotometer equipped with a thermostated cell holder. Solutions of the nucleophile were prepared by combining known volumes of a 0.1 M stock solution of the potassium salt of the carboxylic acid with a known volume of a 0.1 M stock solution of $KClO_4$ to give a final volume of 2.0 mL. After temperature equilibration (30.0 ± 0.5 °C), 8 μL of a freshly prepared phenoxysilane solution (ca. 6 μL of phenoxysilane in 0.25 g of DMF) was added, the cuvette was shaken, and the appearance of the phenolate anion was followed as a function of time. The reactions were monitored at 282, 287.5, 286.5, and 384 nm for **1a–d**, respectively. The spectrophotometer was interfaced to a personal computer, and the pseudo-first-order rate constants, k_{obs}, were obtained by a nonlinear regression analysis of absorbance vs time data. Reactions were generally followed for more than 3 half-lives. The nonlinear regression analysis calculated the best end point. For reactions that were followed to completion, the observed end points always agreed well with the calculated end points. Good pseudo-first-order kinetics were followed, and semilog plots of $(A_\infty - A_t)$ vs time were linear. Rate constants were generally reproducible within ±10%; however, faster reactions had larger errors. The 0.1 M nucleophile solutions were prepared by dissolving an appropriate amount of the potassium salt of the car-

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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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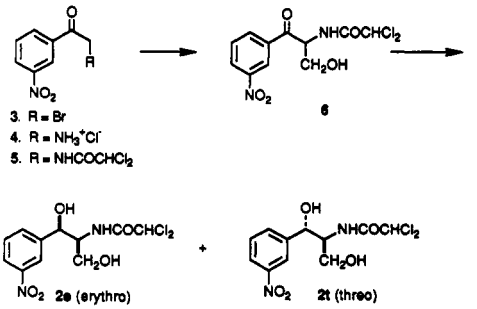
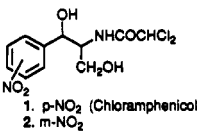
Chloramphenicol (1), the first of the broad-spectrum antibiotics, isolated from aerobic cultures of *Streptomyces venezuela* more than 30 years ago, still finds application today in human and veterinary medicine for treatment of serious staphylococcus infections and is the only dependable medication 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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