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The Preparation and Isolation of Chloramphenicol Palmitate in Toluene

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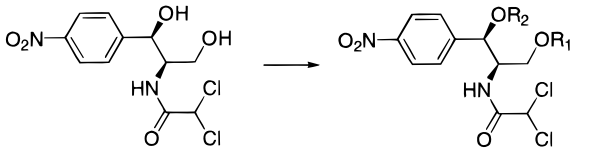
Abstract:

The development of a process for the preparation of the antibiotic chloramphenicol palmitate that did not use methylene chloride and that fit into the production plant with improved yields and product quality is described. Addition of DMF as a co-solvent allowed the use of toluene for the reaction and the isolation. The product distribution observed by competitive esterification at the primary and secondary hydroxyl groups of chloramphenicol was well modeled by simple expressions for parallel consecutive reactions and estimated a 1000-fold difference in the rate constants for the two sites. A small increase in the impurity levels found during production plant trials was traced to trans-esterification during the extended processing time required at the 1000-kg scale.

Introduction

Chloramphenicol palmitate (**2**) is an inert derivative that is hydrolyzed intestinally to the antibiotic chloramphenicol (**1**), and is used to avoid the bitter taste of chloramphenicol.[1,2] Selective esterification at the primary hydroxyl group over the secondary hydroxyl group of **1** is critical for reaction yield and product quality. The general method of preparation reported uses palmitoyl chloride and pyridine in carbon tetrachloride or dichloroethane.[3] Production of **2** at the Aventis pharmaceutical production facility in Garessio, Italy, used palmitoyl chloride with pyridine in methylene chloride. A process that avoided the use of chlorinated solvents was desired for industrial hygiene concerns. Any new process had to meet or exceed the yield, product quality, and throughput values demonstrated for the production process.



1

2: R_1=$CO(CH_2)_{14}CH_3$, R_2=H
3: R_1=H, R_2=$CO(CH_2)_{14}CH_3$
4: R_1=R_2=$CO(CH_2)_{14}CH_3$

In the production process, chloramphenicol palmitate was isolated by a series of water washes of the methylene chloride solution, and then the solvent was removed by distillation and replaced with xylene. The xylene solution was washed further with water before cooling for crystallization and centrifugation. Although it eliminated the solvent exchange, the use of xylene or toluene as the reaction solvent was limited by the low solubility of **1** (0.145 g/L of toluene at 28 °C[2]).

Table 1. **End of reaction analysis from methylene chloride, xylene, and toluene**

solvent	L/kg	mol % **1**	**2**	**3**	**4**	yield (%)
methylene chloride[a]	3 range	2.70 1.2−4.7	93.36 91.4−94.5	0.17 0.12−0.25	3.31 3.2−4.2	85
13% DMF in xylene	3 4.5	2.4 2.3	91.8 94.0	0.13 0.17	5.7 3.5	87 90
13% DMF in toluene	3 4.5	1.3 2.0	93.7 94.1	0.15 0.30	4.8 3.7	89 90

[a] Average of seven production batches.

Table 2. **Crystallization from xylene and toluene**

	mol % isolated **1**	**2**	**3**	**4**	mother liquor **4:2**
crude	0.62	85.4	0.55	13.5	
from xylene	0.36	98.2	0.15	1.3	0.772:1
from toluene	0.34	98.6	0.09	0.96	0.798:1

Results and Discussion

Addition of at least 0.4 g of DMF/g of **1** as a co-solvent increased the solubility sufficiently to give complete solution in toluene or xylene at the −10 °C reaction temperature required for the desired reaction selectivity, allowing the use of either of these solvents for the esterification. Matching the production batch size and product crystallization conditions established a maximum solvent loading of 4.5 L/kg of **1**. With the 1.15 equiv of pyridine used as the base, a concentration of 12 to 13 wt % DMF in xylene or toluene gave complete solution of **1**. Minimizing the DMF loading was important economically, as it would be removed in the water washes and difficult to recover.

Both xylene and toluene gave reaction results comparable to those of the methylene chloride process (Table 1). They also gave similar crystallization results (Table 2). Product precipitation near the end of the palmitoyl chloride addition produced a reaction mixture that, depending on the DMF loading and reaction temperature, was often difficult to stir on a laboratory scale. Reaction mixture slurries following the palmitoyl chloride addition in toluene were thinner and easier to stir at both reaction concentrations of Table 1, and

(1) Nagabhushan, T.; Miler, G. H.; Varma, K. J. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed.; John Wiley & Sons: New York, 1992; pp 961−978.
(2) *The Merck Index*, 8th ed.; Merck; Rahway, NJ, 1968; p 233.
(3) El-Shafie, S. M. M. *Chem. Age India* **1979**, *30*, 737. El-Shafie, S. M. M. *Proc. Egypt. Acad. Sci.* **1977**, *30*, 87−8.

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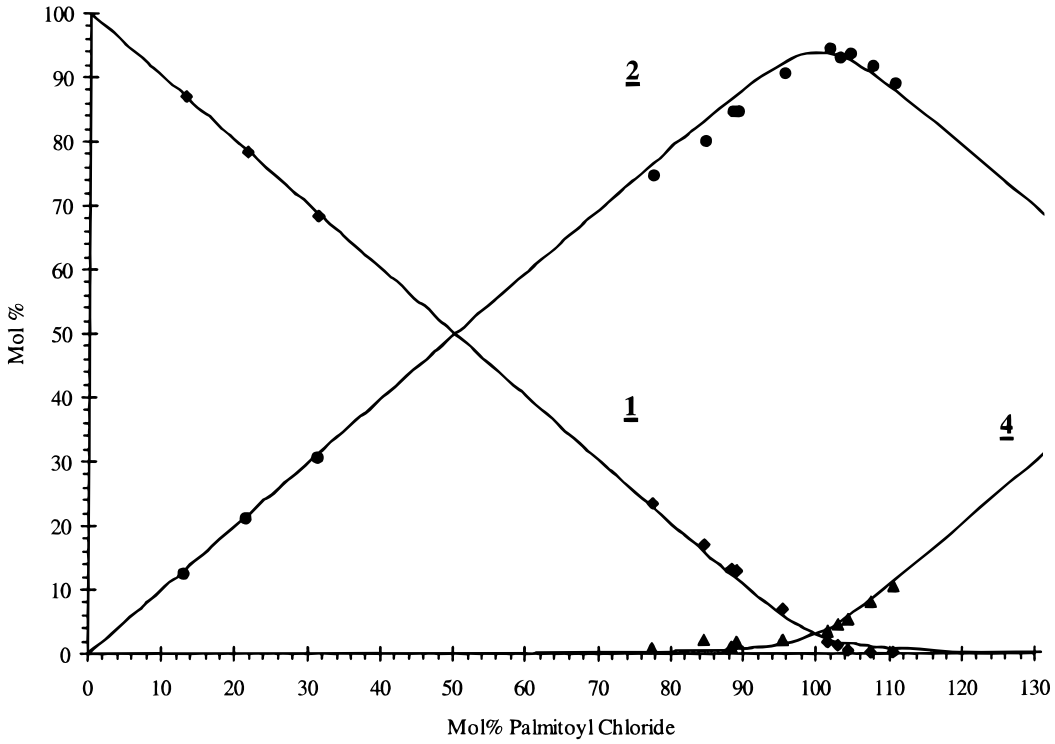

Figure 1. **Comparison of model conversion (lines) with experimental data (points).**

thus toluene was chosen as the solvent for further development. An initial reaction temperature of approximately −10 °C, near the limit of the production equipment, minimized the addition time for the exothermic acid chloride addition. A final reaction temperature of >5 °C was necessary to ensure agitation.

A simple model can be used to evaluate the product distribution for consecutive reactions at two competitive sites. The esterification reactions may be expressed as:

$$\mathbf{1} + \text{pyridine} + \text{ClCOR} \xrightarrow{k_1} \mathbf{2} + \text{pyridine·HCl}$$

$$\mathbf{1} + \text{pyridine} + \text{ClCOR} \xrightarrow{k_2} \mathbf{3} + \text{pyridine·HCl}$$

$$\mathbf{2} + \text{pyridine} + \text{ClCOR} \xrightarrow{k_3} \mathbf{4} + \text{pyridine·HCl}$$

$$\mathbf{3} + \text{pyridine} + \text{ClCOR} \xrightarrow{k_4} \mathbf{4} + \text{pyridine·HCl}$$

For parallel reactions, the ratio of product concentrations does not depend on time, but only on the corresponding rate coefficients.[4] Assuming that (a) $k_1 = k_4$ and $k_2 = k_3$, (b) all species remain in solution, and (c) the reactions are irreversible and no other side reactions occur, and setting $k_1 = xk_2$, the rate expressions may be solved by removing the time dependence on the species concentrations. Simplifying, the relative concentrations of each species in mole fraction can be calculated as the concentration of **1** decreases by:

$$[\mathbf{2}] = \frac{[x/(x+1)](100 - [\mathbf{1}])}{1 + [1/(x+1)][(100 - [\mathbf{1}])/[\mathbf{1}]]}$$

and

$$[\mathbf{3}] = \frac{[1/(x+1)](100 - [1])}{1 + [x/(x+1)][(100 - [\mathbf{1}])/[\mathbf{1}]]}$$

for various values of x.

By comparing the product distribution over the course of the palmitoyl chloride addition with the product profiles calculated with various values of x, the rate of reaction at the primary hydroxyl group was estimated to be 1000 times faster than that of the reaction at the secondary hydroxyl group (Figure 1) in either methylene chloride or toluene. This gives a maximum calculated reaction yield of 94 mol %. With $x = 100$ and 500, the maximum calculated yields were 81.9 and 91.4%, respectively. Not shown in the figure is the level of **3**. The model predicts that it reaches a steady state of 0.02 to 0.03 mol % before decreasing at the end of the reaction; experimentally, a maximum of 0.5 mol % was formed, decreasing to 0.2 mol % at the end of the reaction.

The level of **1** remaining at the end of the palmitoyl chloride addition was slightly overestimated by the simple model in toluene solvent. The model better matched the level found using methylene chloride as solvent. The difference may be due to precipitation of **2** at the end of the palmitoyl chloride addition in toluene, which lowers the relative concentration available for the formation of **4** and increases the relative concentration of **1** for the formation of **2**.

Work-up involved a number of water washes to remove DMF, pyridine hydrochloride, and residual **1** before crystallization. The pH of the wash water was adjusted to 3−3.5 to remove pyridine. GC analysis found that the DMF and pyridine were effectively removed by the third water wash. As the DMF was removed from the toluene solution, the solubility of **2** dropped, such that increasing the wash temperature to 60 °C was required to maintain a solution.[5] Water washes were continued in order to reach <0.25 mol

(4) Szabo, Z. G. In *Comprehensive Chemical Kinetics*; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: New York, 1969; Vol. 2, pp 14−24.

(5) The solubility of **2** in toluene at −5, 21, 35, 46, and 53 °C was 0.3, 1.0, 3.4, 6.4, and 23 wt %, respectively.

Table 3. **Isolated yield and purity of 2**

process	form	wt % 1	wt % 3	wt % 4	wt % others (%)	yield (%)
methylene chloride	crystalline	0.1−0.3%	0.3−1.0%	1.2−2.0%		85
	amorphous	90−110 ppm	0.4−1.0%	1.0−1.7%	0.10−0.18	99
toluene						
lab[a]	crystalline	<0.1%	<0.05%	0.23−0.52%		92−93
	amorphous	190−245 ppm	0.01−0.03%	0.24−0.59%		99
plant[a]	crystalline	505−715 ppm	0.10−0.13%	0.70−1.17%		82−92
	amorphous	100−135 ppm	0.17−0.35%	0.65−1.36%	0.07−0.08	99
	specification	<450 ppm	<2%	<2%	<0.5	

[a] Average of three batches.

% of **1**, since it was poorly rejected by crystallization of **2** (see Table 2). Following crystallization, the isolated solid was heated in water at a pH of 4−5 to a melt to convert it to an amorphous final product (non-polymorph A[6]). Levels of **1** decreased slightly during this transformation.

The toluene process was demonstrated at the 6000-L scale in the equipment used for the production of **2**. Reaction selectivity was as observed in the laboratory. As the reactor loadings were equivalent to the production process, the palmitoyl chloride addition time required to maintain the reaction temperature below 5 °C was also equivalent. Six water washes were necessary to remove the residual **1**, a decrease from the original process. Elimination of the methylene chloride solvent exchange also decreased the total processing time, increasing the throughput for the plant.

Isolated yield and purity analysis results for the crystalline and amorphous forms of **2** are listed in Table 3. The isolated yield over three 700 to 1000 kg batches averaged 87%, with a high of 92%. Yield and product quality was improved over the production process, but was lower than that obtained in the laboratory. Comparing the laboratory- and plant-scale results, the isolated yields were higher and the impurity levels were lower in the laboratory, although the reaction selectivities, as indicated by analysis at the end of the acid chloride addition, were similar. This was due to trans-esterification, especially during the methylene chloride solvent exchange, which increased the levels of **3** and **4**, and decreased the isolated yield from the process. During the work-up and solvent exchange of a methylene chloride reaction mixture in the laboratory, the level of **3** increased from 0.19 to 0.40 mol %, and the level of **4** increased from 6.46 to 7.70 mol %, decreasing the level of **2** from 92.1 to 91.3 mol %. Some degree of trans-esterification also occurred during the extended processing time in the plant-scale trial of the toluene process, as seen by the molar balance calculations of Table 4. No new impurities were found in the isolated product from the new process. All of the unidentified minor impurities detected by HPLC analysis were present in the methylene chloride production product.

Conclusions

The process for the preparation of **2** in toluene and DMF was developed and demonstrated at the production scale, with increases in isolated yield, product quality, and throughput over the process in methylene chloride. Reaction selectivity was well modeled by simple expressions derived from the rate equations for parallel consecutive reactions, which predicted the product distribution using a 1000 to 1 difference in the rate constants for reaction at the primary and secondary hydroxyl groups of **1**. Small increases in the impurity levels found upon scale-up to 1000 kg were due to trans-esterification during processing but were less than those observed during processing using methylene chloride as the solvent.

Table 4. **Molar balance of palmitates**

moles	2	3	4	total
produced	2956	3.4	115.4	3075
isolated	2817	5.4	25.0	2847
mother liquor	81.9	13.2	113.8	208.9
Δ	−57	+15.2	+23.4	−19

Experimental Section

Raw materials were obtained from the Garessio Chloramphenicol production plant. HPLC analysis was carried out at $\lambda = 254$ nm by injecting a 20 μL sample dissolved in mobile phase onto a 4.6 × 250 mm ZORBAX SIL column and eluting at 2 mL/min with 4.8 vol % 2-propanol in hexane. Molar response factors were determined using standard samples. Final product analyses were carried out by the Garessio Quality Control Laboratory using established methods.

Preparation of 2. A 1-L flask was charged with 100 g (0.3905 mol) of chloramphenicol (**1**) and 400 mL of toluene, and 50 mL of solvent was removed by vacuum distillation to remove residual water. The slurry was chilled to −4 °C, and 50 mL of toluene, 50 g of DMF, and 28.1 g (0.335 mol) of pyridine were added. Palmitoyl chloride (90.2 g, 0.328 mol) was added dropwise over 140 min. The final reaction temperature was 5 °C. After 2.5 h, the slurry was warmed to 25 °C, and a few drops of 30% hydrogen peroxide in water were added to remove the pink color. HPLC analysis found 93.7 mol % of **2**, 4.1 mol % of **4**, 0.22 mol % of **3**, and 2.0 mol % of **1**. The solution was washed with 200 mL portions of water (1 × 25 °C, 1 × 45 °C, 5 × 60 °C) at a pH of 3.5 (hydrochloric acid) to give 0.25 mol % of **1** remaining. The solution was cooled to 0 °C, and the solid

(6) Mitra, A. K.; Ghosh, L. K.; Gupta, B. K. *Drug Dev. Ind. Pharm.* **1993**, *19*, 971−80.

was isolated, washed with 100 mL of toluene, and dried at 60 °C under vacuum to give 159.7 g (0.2884 mol, 91.9% yield) of chloramphenicol palmitate (**2**; 0.38 mol % of **4**, <0.02 mol % of **3**, and <0.1 mol % of **1**).

Amorphization of 2. A 500-mL flask was charged with 30.41 g of **2** and 272 mL of water at a pH of 4 (hydrochloric acid). The slurry was heated to 95 °C to give an oil phase, then rapidly cooled to 30 °C to give a precipitate. The solid was isolated, washed with water, and dried at 60 °C under vacuum to give 30.18 g (99.2% recovery) of amorphous **2**.

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