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Full Papers

Development of a Practical and Reliable Synthesis of Laquinimod

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Abstract:

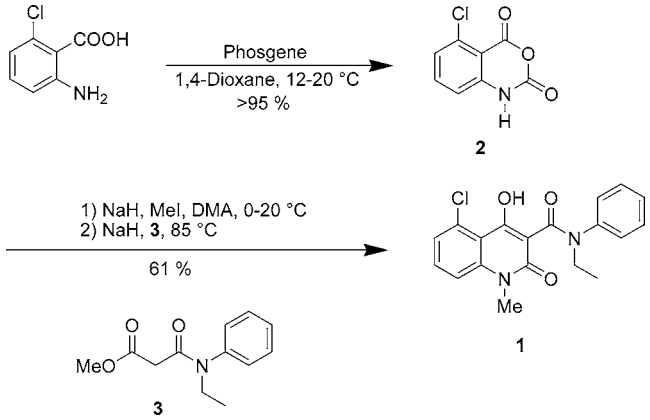
Laquinimod (5-chloro-1,2-dihydro-*N*-ethyl-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-3-quinoline carboxamide) is a drug candidate for treatment of Multiple Sclerosis. A short and industrially feasible process for the preparation of laquinimod starting from 2-amino-6-chlorobenzoic acid, in essentially four steps, is discussed. The key step is a novel reaction in which a methyl ester is converted to an amide in very high yield and with excellent purity. The present article elucidates the scale-up process along with safety aspects and the impurity profiles of the intermediates and product. Initial laboratory conditions are described as well as the changes made on transfer to pilot-plant scale.

Introduction

Multiple Sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) characterised by focal leukocyte inflammation and demyelination resulting in nerve cell dysfunction. At present β-Interferon (IFN-β) and glatiramer acetate are the major drugs used for treatment of MS. A major drawback with β-Interferon is that about 20% of the patients develop antibodies against the drug, and therefore the search for new drugs are highly desired.

Laquinimod[1] (**1**) has proven to significantly and dose-dependently inhibit disease development in Experimental Autoimmune Encephalomyelitis (EAE) which is an anti-inflammatory autoimmune disease of the CNS and an important experimental animal model for the study of MS. Laquinimod also inhibits infiltration of $CD4^+$ T cells into the CNS in EAE induced animals. In contrast to IFN-β and glatiramer acetate, laquinimod is administered orally and at very low dose levels.[2] During preclinical work and toxicology testing, the need of laquinimod was supplied via a laboratory-scale synthesis. Laquinimod will soon undergo phase III studies, and process development of a scalable synthetic route to laquinimod was essential to meet the production requirements. In this article we report a synthesis suitable for the manufacturing of **1** at large scale with a novel conversion of a methyl ester to an amide as the key step.

Scheme 1. **Medicinal chemistry route to laquinimod**



Results and Discussion

The first amounts of laquinimod used in preclinical and toxicology studies were synthesised at laboratory scale via a short three-step procedure (Scheme 1). Commercially available 2-amino-6-chlorobenzoic acid was converted to 5-chloroisatoic anhydride (**2**) with phosgene in 1,4-dioxane which after workup and drying gave **2** as a light brown powder in almost quantitative yield. Anhydride **2** was then converted to the desired compound **1** in a "one pot" two-step procedure where **2** was alkylated with NaH/MeI in dimethylacetamide followed by NaH-mediated reaction with methyl 3-(*N*-ethyl-*N*-phenylamino)-3-oxopropionate (**3**) to give **1** in 61% yield after workup and purification.

Although this synthesis seems elegant and straightforward, it has several disadvantages when applied on a larger scale. Phosgene is very poisonous and should be avoided unless special reactors and equipment are available. Also the use of sodium hydride is hazardous and should be avoided. Beyond safety aspects, the present synthesis will require synthesis of methyl 3-(*N*-ethyl-*N*-phenylamino)-3-oxopropionate (**3**) from the expensive methyl malonyl chloride which in turn will add one more step. In addition, this step requires evaporation to dryness. The workup procedure and purification in the final step are not very convenient including washings with several different solvents. Small deviations

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(1) (a) Noseworthy, J. H.; Wolinsky, J. S.; Lublin, F. D. *Neurology* **2000**, *54*, 1726. (b) Jönsson, S.; Andersson, G.; Fex, T.; Fristedt, T.; Hedlund, G.; Jansson, K.; Abramo, L.; Fritzon, I.; Pekarski, O.; Runström, A.; Sandin, H.; Thuvesson, I.; Björk, A. *J. Med. Chem.* **2004**, *47*, 2075. (c) Björk, A.; Jönsson, S.; Fex, T.; Hedlund, G. U.S. Patent 6,077,851, 2000.

(2) (a) Polman, C.; Barkhof, F.; Sandberg-Wolheim, M.; Linde, A.; Nordle, Ö.; Nederman, T. *Neurology* **2005**, *64*, 987. (b) Jansson, K. U.S. Patent 6,875,869 B2, 2005.

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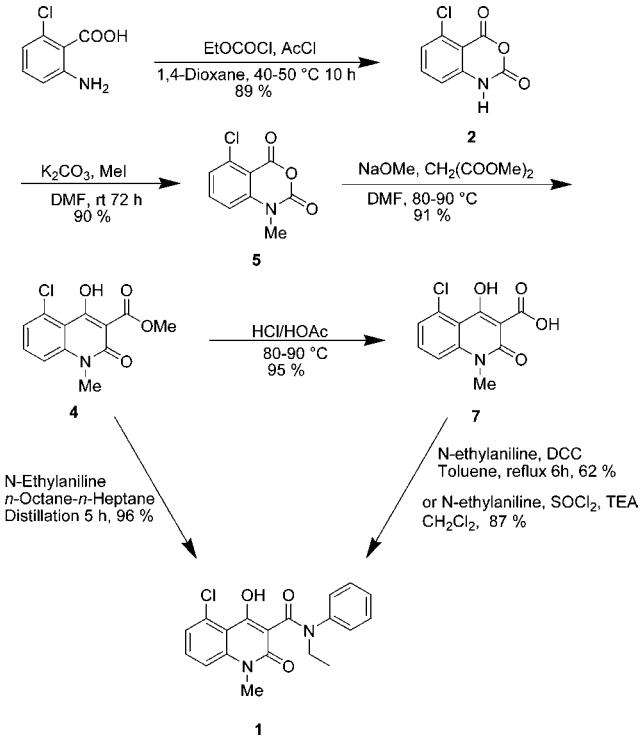
Scheme 2. **Large-scale route to laquinimod**



in the workup procedure will sometimes result in an oil, instead of crystals. The purity of laquinimod was 94−95% before and 97−98% after purification, methylester **4** (Scheme 2) being the most dominant impurity.

With this background a synthetic sequence more suitable for large scale was desirable. We have previously synthesised a similar compound, roquinimex,[3] at multi-kilogram scale, and parts of the present work are based on those experiences. Ethyl chloroformate can serve as a carbonyl equivalent instead of phosgene, and therefore the synthetic sequence, aimed at large scale synthesis, can be started as shown in Scheme 2. 2-Amino-6-chlorobenzoic acid with ethylchloroformate in 1.4-dioxane was heated at reflux temperature for 1 h after which acetyl chloride was added, followed by heating for another 6 h (Scheme 2). Small-scale experiments have revealed that approximately 60% of the carbamate intermediate **2a** (Figure 1) was formed after a few minutes according to NMR. Unreacted 2-amino-6-chlorobenzoic acid was present in a less reactive and less soluble hydrochloride form **2b** (Figure 1), but this intermediate was also transformed into the carbamate intermediate **2a** within 30 min and the mixture became clear. Addition of acetyl chloride converted the carboxylic acid to an acid chloride, which in turn underwent ring closure to the desired substance, which precipitated after formation and was isolated in 89% yield. The solubility of the product is very low in 1,4-dioxane making the isolation via centrifugation very convenient. The white product was very pure, more than 99%, and except for 0.2% free chlorides no impurities larger than 0.1% were found. NMR analysis of the 2-amino-6-chlorobenzoic acid indicated that up to 3%

(3) (a) Eriksoo, E.; Sandberg, E. B.; Stålhandske, L. J. T. U.S. Patent 4,547,511, 1985. (b) Sjovall, S.; Hansen, L.; Granquist, B. *Org. Process Res. Dev.* **2004**, *8*, 802.

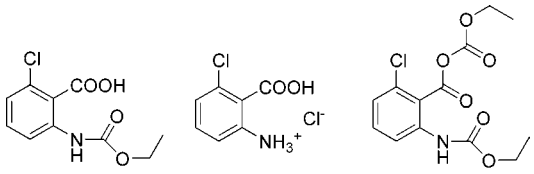


Figure 1. **Intermediates in the first step and byproduct formed in toluene.**

2-amino-6-chlorotoluene could appear in the starting material. However, this impurity, which probably originates from the manufacture of 2-amino-6-chlorobenzoic acid, or its reaction products were never seen in the product, probably due to its good solubility in the mother liquor. Scale-up from laboratory to pilot plant was straightforward for this step. However, from laboratory trials it was noticed that efficient cooling of the reflux condenser was important; otherwise loss of acetyl chloride lowered the yield due to incomplete conversion of **2a**. Other solvents such as toluene or THF gave lower yields or resulted in longer reaction times. Due to the poor salt-solvating power of toluene the conversion from hydrochloride **2b** to carbamate **2a** was extremely slow which resulted in formation of the mixed anhydride **2c** (Figure 1). **2c** seems unable to undergo cyclisation, and its formation lowers the yield of to **2**. Use of triethylamine to circumvent formation of **2b** led instead to extensive formation of **2c**. In light of these findings 1,4-dioxane seemed to be a superior solvent in this reaction despite its toxicological properties.

The next step was to alkylate the amide. At laboratory scale the reaction was performed with sodium hydride and iodomethane in dimethylacetamide. The yield and purity were both satisfying, but since sodium hydride is very hazardous, especially at large scale and in connection with solvents like DMA and DMF,[4] an alternative reagent was requested. Among tested bases potassium carbonate seemed most promising. Laboratory trials demonstrated that **5** was formed in good yield; apparently the N−H proton is acidic enough to be abstracted by potassium carbonate. When performed at large scale using iodomethane and potassium carbonate in DMF at room temperature, the reaction was complete after 72 h according to HPLC (Scheme 2). For workup the mixture was diluted with 1 M hydrochloric acid. Under these conditions the inorganic residues went into solution and the product precipitated. The product was isolated by centrifugation in 90% yield. This method was safe and convenient; however, since the reaction is heterogeneous reaction time and stirring speed were of importance. When the alkylation was performed at laboratory scale, the reaction was completed within 12 h. In this case a magnetic stirrer was used and the mixture was stirred quite vigorously (approximately 800 rpm). The stirring speed in the pilot plant reactor was much lower (approximately 50 rpm), and consequently a prolonged reaction time was required. Also in this case the assay was high, about 99%, and only two impurities at low levels (0.07 and 0.14%) were found.

(4) Buckley, J.; Webb, R. L.; Laird, T.; Ward, R. J. *Chem. Eng. News* **1982**, *60* (28), 5. De Wall, G. *Chem. Eng. News* **1982**, *60* (37), 5.

Heterogeneous reactions may behave differently on different scales.[5] Granular potassium carbonate was used, and as a consequence the reaction takes a longer time at a larger scale. However, this reaction has been run in 1 g, 10 g, 100 g, 10 kg, and 30 kg, and no significant differences have been observed except for the reaction times.

To form methyl ester **4**, compound **5** was added to the preformed enolate of dimethyl malonate at 80 °C in DMF followed by stirring overnight at room temperature (Scheme 2). The enolate was initially formed with sodium hydride, but this base was successfully replaced by sodium methoxide at pilot-plant scale. Methanol is formed during the formation of sodium dimethyl malonate and was removed together with some DMF upon distillation of 10% of the solvent amount before addition of the anhydride. If not removed, methanol may react with 5-chloro-*N*-methylisatoic anhydride to give the corresponding methyl anthranilate. The sodium dimethyl malonate attacks 5-chloro-*N*-methylisatoic anhydride in a regioselective manner. Carbon dioxide was eliminated, and the intemediate underwent cyclisation to the desired product. At the end of the reaction the product exists in the sodium salt form, which precipitates in the acidic form after addition of water and hydrochloric acid. Compound **4** was isolated by centrifugation, the yield was 91%, and the purity was almost 99%. It is also possible to carry out step 2 and 3 in one pot. This was performed at laboratory scale by alkylation of **2** with iodomethane and sodium hydride in dimethylacetamide at 5−15 °C. To avoid 3-C and 4-O alkylation in the next transformation, excess iodomethane was evaporated under reduced pressure. Additional sodium hydride and dimethyl malonate were added, while the mixture was heated to 85 °C and kept at this temperature for 5 h. Acidic workup and crystallisation from methanol afforded **4** in 71% yield. No impurities were found. Although the one-pot procedure seems convenient, it includes the use of hazardous sodium hydride and also a crystallisation step. In light of these facts the two-step procedure was the method of choice. As a matter of fact the yield in the two-step procedure is more than 10% higher (82%) than the yield in the corresponding one-pot procedure (71%).

The next transformation, in which ester **4** is converted to the carboxylic acid **7**, was more difficult to perform. Compound **7** is sensitive and seems to be prone to decarboxylate, especially under basic conditions.[6] Decarboxylation was total when **4** was heated to 80 °C in 1 M NaOH. Some observations indicate that decarboxylation under acidic conditions is favoured by high water content in the reaction mixture. When hydrolysis was carried out in a mixture of acetic acid and aqueous HCl, a large amount of decarboxylated product **6** (Figure 2) was formed. To effectuate the ester-acid transformation a rather unusual method was used.[2b] A HCl/acetic acid mixture with low water content was made by slow addition of concentrated hydrochloric acid to acetic anhydride under careful cooling (the reaction is very exothermic). This mixture was diluted with glacial acetic acid. With this method a HCl/acetic acid mixture with approximately 1.5 M HCl and 1.4% H_2O was obtained (HCl in acetic acid is commercially available but quite expensive). To this solution **4** was added, and the mixture was heated to 85 °C and kept at this temperature for 2 h (Scheme 2). The mixture was cooled and diluted with methanol to facilitate isolation. After centrifugation, washing, and drying, **7** was obtained in 95% yield. The assay was 98.5% and decarboxylation product **6** could not be detected. However, 0.1% of ester **4** was found. The present method, which releases chloromethane[7] instead of methanol as in usual hydrolysis reactions, seems to be well suited for substrates which are sensitive to decarboxylation.

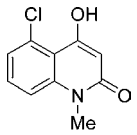


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Figure 2. **Possible impurity in the final product.**

With compound **7** in hand we were ready for the final coupling step with *N*-ethylaniline. The classical method with thionyl chloride and triethyl amine was tested at laboratory scale and gave the desired compound **1** in 88% yield and 98% purity.[2b] However the impurity profile was not promising. Single impurities were well below the specification, but numerous unknown impurities at low levels appeared as indicated by HPLC. Manufacturing a pharmaceutical product for clinical use with undefined byproducts is not very convincing, and therefore other alternatives were searched. Another common method for synthesising amides is the DCC-mediated coupling of a carboxylic acid and an amine.[8] A mixture of compound **7**, *N*-ethylaniline, and DCC in toluene was heated at 75−85 °C for 3−4 h (Scheme 2). After cooling the product was isolated by centrifugation (filtration at laboratory scale). The residue was washed with toluene and dried. To remove *N*,*N*-dicyclohexylurea the dried product was dissolved in aqueous sodium hydroxide. After adjustment of pH to 6.5 *N*,*N*-dicyclohexylurea was filtered off. Acidification of the filtrate gave a precipitate, which after isolation and drying gave the desired compound in 62% yield. The crude product was, however, contaminated with a considerable amount of **6**, but also **7** and **4** were found. To solve the problem with these impurities a purification method was developed. It was found that conversion to the crystalline sodium salt using sodium hydroxide in ethanol could significantly decrease the amounts of impurities and discolorations. This treatment yielded a product with sufficient purity, and it is possible to even increase the purity with an additional treatment. At pilot plant scale, **1** was stirred in ethanolic sodium hydroxide for 2 h and the corresponding sodium salt was isolated by filtration in 90−95% yield. The sodium salt was then dissolved in water, and **1** precipitated

(5) For examples with K_2CO_3, see: Conlon, D. A.; Drahus-Paone, A.; Ho, G.-J.; Pipik, B.; Helmy, R.; McNamara, J. M.; Shi, Y.-J.; Williams, J. M.; McDonald, D.; Deschênes, D.; Gallant, M.; Mastracchio, A.; Roy, B.; Scheigetz, J. *Org. Process Res. Dev.* **2006**, *10*, 36. Mosely, J. D.; Bansal, P.; Bowden, S. A.; Couch, A. E. M.; Hubacek, I.; Weingärtner, G. *Org. Process Res. Dev.* **2006**, *10*, 153.

(6) Jansson, K.; Fristedt, T.; Olsson, A.; Svensson, B.; Jönsson, S. *J. Org. Chem.* **2006**, *71*, 1658.

(7) Evolved chloromethane was absorbed in methanolic potassium hydroxide.

(8) Bodanszky, M. *Peptide Chemistry: A Practical Textbook*; Springer: New York, 1988.

Table 1. **Purification effect of salt conversion**[a]

byproducts[b]	**7**	**4**	**6**
impure **1**	5.0	0.3	10.0
one conversion	0.95	0.15	0.49
two conversions	0.26	0.05	0.07

[a] Impure **1** was created from pure **1** by deliberately adding **7** and **6** corresponding to a level of 5% and 10%, respectively. [b]Numbers are in %.

upon addition of HCl. To demonstrate the effectiveness of the salt−acid conversion, **1** was contaminated with 5 and 10% of **7** and **6**, respectively. This impure material was then purified *via* conversion to the sodium salt. As seen in Table 1 the purifying effect is good especially for **6**. This route, using DCC and sodium salt conversion, was used in our first manufacturing campaign of laquinimod at pilot-plant scale, but we were still not satisfied, especially with the yield in the DCC-coupling reaction.

Compounds similar to **1** have been synthesised at gram scale by heating a mixture of a quinoline carboxylic ester and an N-alkylated amine in toluene.[2b,6] Toluene and the formed alcohol are distilled off during the process, and the distillation rate greatly influences the reaction outcome. Because of a rather high solubility in toluene, the product often had to be isolated by extraction with aqueous sodium hydroxide or, if possible, precipitated with *n*-heptane. The isolated products were often contaminated with a few percent remaining ester. It occurred to us that if toluene was replaced by another solvent that had a higher boiling point, thus permitting a higher temperature and a faster reaction rate, and in which the product had a very low solubility, the yield might be increased. Our first choice was to use *trans*-decalin (*cis,trans*-decahydronaphthalene, bp 189−191 °C). By heating a mixture of methylester **4** and *N*-ethylaniline in *trans*-decalin at 100 °C and 40−50 mbar, an equilibrium between **4** and **1** is established. Methanol is formed during the reaction between **4** and *N*-ethylaniline and is removed from the reaction mixture by distillation. It is important to remove the formed methanol in order to get a high yield of **1**. This equilibrium is well shifted towards the starting materials; in fact, if **1** is heated with 1 equiv of methanol in toluene in a sealed vessel, an almost complete conversion into **4** and *N*-ethylaniline results. Similarly, if 1 equiv of water is allowed to react with **1** in a similar fashion, **7** and decarboxylated compound **6** are the products. It is important that no water, e.g., moist air, is allowed to enter the reaction mixture, since that inevitably will result in formation of **6** and **7**. It is also important that the reaction is not stopped until almost all starting material has reacted. *trans*-Decalin is promoting the reaction by allowing a high temperature at a low pressure, thus facilitating efficient and complete removal of methanol from the reaction vessel without removing extensive amounts of *trans*-decalin. *trans*-Decalin also seems to promote the reaction by providing a slightly better solvation for **4** than for **1**. The latter precipitates during the reaction. The very low solubility of **1** in *trans*-decalin may also explain the high purity of the product; as soon as it is formed it precipitates and escapes decomposition reactions. *trans*-Decalin is thus a superior medium compared

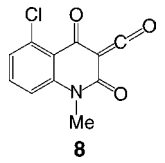

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Figure 3. **Intermediate in the amide-forming step.**

to toluene in promoting the reaction. Although the developed method seemed promising, there were still some drawbacks when applied at a larger scale. The boiling point for *trans*-decalin at 40−50 mbar is just above 100 °C, and the vacuum has to be carefully controlled to avoid sudden vigorous boiling, so that the mixture is not ejected from the reactor. A system under vacuum is sensitive to leaks; particularly this reaction is sensitive to moisture. To simplify synthesis at large scale we decided to search for a solvent with a lower boiling point in which the solubility of the product was still very low. Small-scale experiments revealed that alkanes such as *n*-heptane and *n*-octane were successful in promoting the conversion of **4** into the desired compound **1**.[6] Distillation with these solvents at atmosperic pressure gave similar results as compared to *trans*-decalin, however, with much shorter reaction times. When the reaction was performed in *n*-octane at lab scale, the reaction was completed within 2 h. A period of 6 h was required when the reaction was performed in *n*-heptane. The production at pilot-plant scale was performed with a 1:2 mixture of *n*-heptane and *n*-octane, and about one-third of the solvent was distilled off during 5 h (Scheme 2). This final method gave **1** in 96% yield, and as with the DCC-method compound **1** was converted to its sodium salt as described above. The assay in this case was as high as 99.9%. The present method is superior in all aspects. Yield and purity are excellent, and the method is simple and reliable when applied at a large scale. More aspects regarding the mechanism of this reaction, which is believed to occur via the ketene intermediate **8** (Figure 3), are reported elsewhere.[6] The purity of the *N*-ethylaniline used is important. If other *N*-alkylanilines or aniline itself are present as impurities, these will react to give compounds similar to **1** which are difficult to remove from the product. Our novel method for amide formation has been used several times to manufacture laquinimod at multi-kilogram scale as well as other substances in this class. The overall yield is 70% as compared with 43% for the route using the DCC-coupling procedure.

Conclusions

Overall, we have developed a safe, reliable, high-yielding, and robust process for the synthesis of laquinimod. The development includes a novel method for conversion of esters into amides. The current route avoids undesired chemicals like phosgene, sodium hydride, and dichloromethane. All starting materials and reagents are cheap and easily available. Isolation of intermediates and product is very convenient, and the purity and impurity profiles of products and intermediates are all very satisfying.

Experimental Section

General. HPLC analyses were performed using a Symmetry shield RP 8 (3.9 mm × 150 mm) from Waters

throughout. As mobile phase was used a gradient consisting of A: 80% TFA, 0.1 M-20% CH_3CN and B: 20% TFA, 0.1 M-80% CH_3CN except for substance **1** where an isokratic mixture of MeOH 40%, CH_3CN 10%, and TFA 0.1 M 50% was used. NMR spectra were recorded at 500.13 MHz (proton) and 125.76 MHz (carbon), respectively. Assays were determined by elemental analysis of the chlorine content in each substance. Melting points are uncorrected. Thin layer chromatography was performed on Merck precoated TLC plates, and the acquisitions were visualised with UV light or sprayed with a solution of *p*-methoxybenzaldehyde (26 mL), glacial acetic acid (11 mL), concentrated sulfuric acid (35 mL), and 95% ethanol (960 mL). Solvents and reagents were obtained from commercial sources and were used as such without any further purification. All reactors used are standard multipurpose equipment, either glass-lined or stainless steel. All reactions at pilot-plant scale are for safety reasons routinely carried out under an atmosphere of nitrogen.

5-Chloroisatoic Anhydride (2). In a glass-lined reactor, equipped with a stirrer, reflux condenser, and gas absorption, charged with 1.4-dioxane (83 kg) were added, under stirring, 2-amino-6-chlorobenzoic acid (10 kg, 58.3 mol) and ethyl chloroformate (28 kg, 258 mol) under an atmosphere of nitrogen. The mixture was heated at reflux temperature for 1 h after which it was cooled to 40 °C. Acetyl chloride (28 kg, 357 mol) was added at such a rate that the temperature did not exceed 50 °C. Stirring was continued at 45 °C for 10 h whereafter the mixture was cooled below 10 °C. The mixture was centrifuged, and the residue was washed with toluene (2 × 10 L). Drying of the residue under reduced pressure (8 mbar) at 50 °C to constant weight gave 10.2 kg (89%) of the title compound as a white solid (assay 99.3%): mp 272.5−272.9 °C; IR (KBr) 3450 (broad), 1780; ^{1}H NMR (DMSO-d_6) δ 11.85 (s, broad, 1 H), 7.65 (t, 1 H, J = 8.3 Hz), 7.31 (d, 1 H, J = 8.3 Hz), 7.09 (d, 1 H, J = 8.3 Hz); ^{13}C NMR (DMSO-d_5) δ 156.5, 146.7, 144.0, 136.5. 135.0, 125.7, 114.6, 108.1, 66.4. Anal. Calcd for $C_8H_4ClNO_3$: C, 48.63; H, 2.04; N, 7.09. Found: C, 48.80; H, 2.23; N, 7.35.

5-Chloro-*N*-methylisatoic Anhydride (5). In a stainless steel reactor, equipped with a stirrer, charged with DMF (100 L) were added, under stirring, **2** (9.5 kg, 48 mol), potassium carbonate (7.2 kg, 52 mol), and iodomethane (8.7 kg, 61 mol). The mixture was stirred for 72 h at rt after which HCl (200 L, 1 M) was added carefully (*CAUTION! gas evolution*). The mixture was stirred for an additional 30 min and was thereafter centrifuged. The residue was washed with water (2 × 10 L) and dried to constant weight at 35 °C under reduced pressure (6 mbar) which gave the title compound (8.7 kg, 90%) as a white solid (assay 98.8%): mp 217.9−218.2 °C; IR (KBr) 1780, 1725; ^{1}H NMR (DMSO-d_6) δ 7.78 (t 1 H, J = 8.6 Hz), 7.42 (m, 2 H), 3.47 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 155.5, 147.4, 144.6, 136.6, 135.4, 126.0, 114.1, 109.4, 32.4. Anal. Calcd for $C_9H_6ClNO_3$: C, 51.09; H, 2.86; N, 6.62. Found: C, 51.10; H, 2.83; N, 6.64.

5-Chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylic Acid Methyl Ester (4). In a stainless steel reactor, equipped with a stirrer and a distillation setup, charged with DMF (65 L) were added dimethyl malonate (9.1 kg, 69 mol) and sodium methoxide (3.3 kg, 61 mol) under an atmosphere of nitrogen. The mixture was heated at 85 °C for 1.5 h after which approximately 10 L of solvent were distilled off under reduced pressure (50 mbar). The temperature was adjusted to 80 °C, and **5** (8.7 kg, 41 mol) was added carefully during 10 min (*CAUTION! foaming, especially at the end of the addition*). Another 20 L of solvent were distilled off under reduced pressure (50 mbar). After cooling to 20 °C the mixture was stirred overnight at ambient temperature. Water (116 L) was added, and the mixture was stirred until the solution became clear. HCl (37%, 10.5 kg) was added slowly during 30 min until the pH was set to 1. The mixture was cooled to 10 °C and stirred for 1 h at this temperature to complete the precipitation. After centrifugation, the residue was washed with water (2 × 10 L) and dried to constant weight at 50 °C at reduced pressure (8 mbar) which gave the title compound (10.0 kg, 91%) as a white solid (assay 98.9%): mp 159.1−160.1 °C; IR (KBr) 3440 (broad), 1685; ^{1}H NMR ($CDCl_3$) δ 14.92 (s, 1 H), 7.52 (t, 1 H, J = 8.5 Hz), 7.27 (m, 2 H), 4.04 (s, 3 H), 3.66 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.4, 172.7, 158.8, 143.6, 134.6, 133.4. 126.1, 113.3, 112.5, 98.1, 53.2, 30.1. Anal. Calcd for $C_{12}H_{10}ClNO_4$: C, 53.85; H, 3.77; N, 5.23. Found: C, 53.70; H, 3.78; N, 5.40.

5-Chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylic Acid (7). A glass-lined reactor, equipped with a stirrer, reflux condenser, and gas absorption, charged with acetic anhydride (35 kg, 343 mol) was cooled to 0 °C. HCl (11.6 kg, 118 mol, 37%) was added slowly so that the temperature was kept below 20 °C (*CAUTION! The reaction is strongly exothermic*). Acetic acid (27.3 kg, 455 mol) and **4** (9.1 kg, 34 mol) were added, and the mixture was heated at 85 °C for 2 h. The mixture was cooled to 10 °C, and while it cooled, methanol (46 kg) was added at 65 °C. The mixture was centrifuged, and the residue was washed with methanol (2 × 12 kg). Drying to constant weight at 35 °C under reduced pressure (7 mbar) gave the title compound (8.2 kg, 95%) as a white solid (assay 98.5%): mp 294.9−295.1 °C; IR (KBr) 3430 (broad), 1705; ^{1}H NMR ($CDCl_3$) δ 15.78 (s, 1 H), 15.77 (s, 1 H), 7.65, (t, 1 H, J = 8.1 Hz), 7.45(d, 1 H, J = 8.1 Hz), 7.42 (d, 1 H, J = 8.1 Hz), 3.79 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.0, 172.9, 164.3, 142.1, 135.4, 134.1, 127.7, 114.0, 113.8, 95.3, 30.5. Anal. Calcd for $C_{11}H_8ClNO_4$: C, 52.09; H, 3.18; N, 5.52. Found: C, 52.00; H, 3.18; N, 5.66.

5-Chloro-1,2-dihydro-*N*-ethyl-4-hydroxy-1-methyl-2-oxo-N-phenyl-3-quinoline Carboxamide (1), DCC-Mediated from 7. To a glass-lined reactor charged with toluene (35 kg) were added **7** (6.0 kg, 23.7 mol), *N*-ethylaniline (3,0 kg, 24.8 mol), and 1.3-dicyclohexylcarbodiimide (5.2 kg, 25.2 mol) under stirring. The mixture was heated to 80 °C and kept at this temperature for 4 h under stirring. The suspension was cooled to 10−15 °C and centrifuged. The residue was washed with toluene (2 × 10 L) and dried to constant weight at 35 °C under reduced pressure (8 mbar). The dried substance was mixed with water (150 L), and aqueous 2 M NaOH was added under stirring until the pH

was between 11 and 12. The clear solution was stirred for 30 min whereafter the pH was adjusted to 6.5 with aqueous 1 M HCl followed by additional stirring for 15 min. The insoluble dicyclohexylurea was filtered off via a 3 μ filter. Aqueous 5 M HCl was added to the filtrate over 10 min so that the pH became ~1. The mixture was stirred for 15 min and was then left without stirring. After 2 h the mixture was centrifuged, and the residue was washed with water until it was free of chloride (free chloride was tested with 0.1 M $AgNO_3$ and 3 washes were usually sufficient). After drying to constant weight (35 °C, 8 mbar) the product was obtained as a white solid (5.2 kg, 62%): mp 201 (dec) °C; IR (KBr) 3450 (broad), 1640; ^{1}H NMR ($CDCl_3$) δ 12.25 (s very broad, 1 H), 7.39 (t, 1 H, J = 8.2 Hz), 7.27−7.16 (m, 7 H), 3.99 (s 2 H), 3.27 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.8, 165.7, 157.9, 142.7, 142.1, 132.8, 131.7, 128.5, 126.9, 126.7, 125.4, 113.3, 112.8, 105.1, 45.7, 29.8, 12.9; MS (ESI): *m*/*z* 222 (100). Anal. Calcd for $C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.80; N, 7.85. Found: C, 63.70; H, 4.75; N, 8.11.

5-Chloro-1,2-dihydro-*N*-ethyl-4-hydroxy-1-methyl-2-oxo-N-phenyl-3-quinoline Carboxamide (1) $SOCl_2$-mediated from 7 is described in reference 2b.

5-Chloro-1,2-dihydro-*N*-ethyl-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-3-quinoline Carboxamide (1), directly from Methylester 4. To a glass-lined reactor charged with *n*-heptane (60 L) and *n*-octane (120 L) were added N-ethylaniline (6.8 kg, 56.1 mol) and **5** (10.0 kg, 37.4 mol). The mixture was heated to reflux (112 °C) under a slow stream of nitrogen. During 5 h approximately 60 L of solvent were distilled off (temperature rises to 122 °C). The mixture was kept at 120 °C for 3 h after which it was cooled to 25 °C. *n*-Heptane (40 L) was added, and the mixture was stirred overnight at ambient temperature. After centrifugation and washing with *n*-heptane (2 × 15 L), the substance was dried to constant weight at 50 °C and reduced pressure (8 mbar). The yield of the title compound was 12.8 kg (96%), and the purity was 98.5 area%.

Conversion of 1 to Sodium Salt. To a stainless steel reactor charged with ethanol (90 L) was added **1** (12.8 kg, 35.9 mol), and the mixture was stirred for 15 min. To the mixture was added 10 M NaOH (4.0 L, 40 mol), and stirring was continued for 1.5 h. The product was centrifuged, washed with ethanol (2 × 12 L), and dried to constant weight at 35 °C under reduced pressure (7 mbar) to give the product as white crystals (12.95 kg, 95%). Assay was 99.9%.

5-Chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylic Acid Methyl Ester (4) in One Pot from 2. Compound **2** (50 g, 0.25 mol) was dissolved in dimethylacetamide (500 mL), and the solution was cooled to 5 °C under an atmosphere of nitrogen. Sodium hydride (9.6 g, 0.28 mol, 70% in mineral oil) was added, under stirring, so that the temperature was kept below 15 °C. Iodomethane (43.5 g, 0.31 mol) was added dropwise, the cooling bath was removed, and the mixture was stirred at ambient temperature for 2 h. Excess iodomethane was removed by keeping the mixture under reduced pressure (15 mbar) for 1 h. Additional sodium hydride (9.6 g, 0.28 mol, 70% in mineral oil) was added in portions followed by addition of dimethyl malonate (38.2 g, 0.29 mol) in one portion. The mixture was heated to 85 °C (gas evolution started at 40 °C) and was kept at that temperature for 5 h. The mixture was cooled and water (4 L) was added. The pH was adjusted to 1.5−2 with hydrochloric acid (1 M), and the mixture was stirred for 1 h. The mixture was filtered, and the filter cake was washed with water (200 mL) and *n*-heptane (100 mL) and dried at 50 °C under reduced pressure (5 mbar). Crystallisation from methanol gave the title compound as white crystals (48 g, 71%). No impurities were found according to NMR analysis.

5-Chloroisatoic Anhydride (2) with the Phosgene Method. To a stirred and cooled slurry of 2-amino-6-chlorobenzoic acid (100 g, 0,57 mol) in 1,4-dioxane (500 mL) was added, dropwise, phosgene (62.5 g, 0.63 mol) (*CAUTION! Very toxic*) in 1,4-dioxane (500 mL) at 12−15 °C. The mixture was stirred at 20 °C, and then after it cooled to 5 °C, sodium acetate trihydrate was added in one portion followed by a rapid addition of ice-cold water (3 L). The mixture was stirred for 2 h. The product was filtered off and washed with water (2 L), MeOH/H_2O 4:6 (1 L), and *n*-heptane (300 mL). Drying over P_2O_5 at reduced pressure (5 mbar) gave the title compound (112 g, 99%) as a light-brown powder.

Methyl 3-(*N*-Ethyl-*N*-phenylamino)-3-oxopropionate (3). To a stirred solution of *N*-ethylaniline (98 g, 0.81 mol) in acetone (900 mL) was added triethylamine (127 mL, 0.91 mol) under an atmosphere of nitrogen. The mixture was cooled to 2 °C, and methyl malonyl chloride (100 mL, 0.91 mol) was added at a rate so that the temperature did not exceed 20 °C. The mixture was stirred at rt for 2 h and thereafter concentrated under reduced pressure. The residue was dissolved in toluene (700 mL) and washed with water (700 mL), 0.5 M H_2SO_4 (700 mL), and saturated aqueous $NaHCO_3$ (3 × 700 mL). The solution was dried over $MgSO_4$ and concentrated under reduced pressure, and the residue was coevaporated twice with $CHCl_3$. Drying under reduced pressure gave the title compound (169 g, 94%) as a light brown oil; IR (film) 1745, 1700; ^{1}H NMR ($CDCl_3$) δ 7.47−7.37 (m, 3 H), 7.21 (d, 2 H, J = 7.6 Hz), 3.56 (q, 2 H, J = 10.4 Hz), 3.53, (s, 3 H), 3.17 (s, 2 H), 1.14 (t, 3 H, J = 10.4 Hz); ^{13}C NMR ($CDCl_3$) δ 168.2, 165.4, 141.7, 129.9, 128.4, 128.4, 52.3, 44.3, 41.7, 12.9. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.4; H, 6.82; N, 6.19.

5-Chloro-1,2-dihydro-*N*-ethyl-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-3-quinoline Carboxamide (1) in One Pot from 2. NaH (19.1 g, 0.56 mol. 70% in mineral oil) was washed twice with *n*-pentane and added in portions, under stirring, to a solution of **2** (101 g, 0.51 mol) in dimethylacetamide (1 L) at 4 °C under an atmosphere of nitrogen at such a rate that the temperature did not exceed 20 °C. After addition of NaH, the temperature was adjusted to 6 °C and iodomethane (38.2 mL, 0.61 mol) was added dropwise during 10 min. The cooling bath was removed, and the reaction was left stirring at rt overnight. To remove excess iodomethane the mixture was kept at reduced pressure (10 mbar) for 2 h. NMR analysis indicated that the alkylation was

complete. NaH (19.1 g, 0.56 mol. 70% in mineral oil) was washed twice with *n*-pentane and added in portions, under stirring, followed by addition of malonamide **3** (126 g, 0.56 mol). The mixture was heated to 85 °C during 2 h (gas evolution occurred at 35−40 °C), and the mixture was kept at this temperature for another 5 h. The mixture was cooled to rt and left overnight. The mixture was kept at reduced pressure (10 mbar) for 1 h after which it was cooled to 5 °C. Methanol (1 L) was added, and the temperature was adjusted to 10 °C. The cooling bath was removed, and HCl (1340 mL, 1 M) was added quickly under stirring. H_2O (7 L) was added, forming an emulsion which crystallised slowly. After 2 h of crystallisation the mixture was stirred vigorously for 1 h at rt and another 1 h at 0 °C. The product was isolated by filtration; washed with H_2O (7 L), MeOH/H_2O (1:1, 5 L), *n*-heptane (2 L), and *n*-pentane (1 L); and dried over P_2O_5 at reduced pressure. Yield 134 g (74%) and assay 94.3%.

The compound was purified as follows: The impure product was dissolved in 1 M NaOH (850 mL) and filtered through Celite and washed with CH_2Cl_2 (3 × 200 mL). The pH was adjusted to 6.5 with 2 M HCl, and the brown and turbid solution was filtered through Celite followed by acidification to pH 1.5 and stirring for 1.5 h. The precipitated product was centrifuged and washed with water (5L) and dried over P_2O_5 at reduced pressure (5 mbar). 110 g (61%) of product was obtained with an assay of 97.6%

Physical data for compound 6 can be found in ref 6.

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