Organic Process Research & Development **2000**, *4*, 418–426

A Scaleable Combined Resolution and Improved Dosage Form for Etodolac with Recycle of the Off-Isomer

Martin Woods,*[,†,§] Ulrich C. Dyer,[†,||] John F. Andrews,[†,⊥] C. Neil Morfitt,[†,#] Roy Valentine,[‡] and Joanne Sanderson[‡]

Celltech-Chiroscience Ltd, Granta Park, Abington, Cambridge CB1 6GS, UK, and High Force Research Ltd., Bowburn North Industrial Estate, Bowburn, Durham, UK

Abstract:

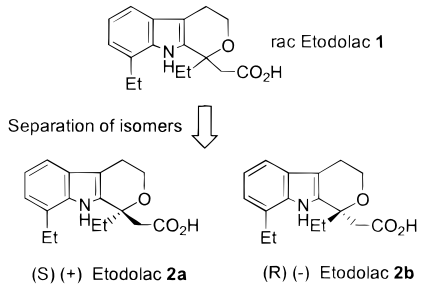
An efficient resolution process using *N*-methyl glucamine (meglumine) which directly provides (*S*)-etodolac as the meglumine salt is described. This salt is also a dosage form with improved absorption characteristics. The off-isomer is efficiently racemised via the ester, prepared by mild esterification, followed by hydrolysis affording *rac*-etodolac suitable for recycling.

Introduction

The racemic drug etodolac **1** (etodolic acid, Lodine) is a nonsteroidal antiinflammatory agent (NSAID).[1] In addition etodolac has analgesic properties and the ability to retard the progression of skeletal changes in rheumatoid arthritis. It is known that the majority of the therapeutic activity of etodolac lies in the (*S*)-(+) isomer **2a**.[2] We wished to investigate the possibility of differences in the side-effect profile between the enantiomers of the drug. In addition a more soluble salt form may be of use in reducing the onset time, which is important in post-operative pain relief (Scheme 1).

Separation of Isomers. Several procedures are known for the resolution of etodolac.[3] One of the most efficient uses cinchonine and affords the (*S*)-etodolac cinchonine salt in high yield and excellent enantiomeric purity (45% yield, 98+% enantiomeric excess).[3c] The enantiomerically pure free acid is isolated by hydrolysis of the salt and extraction into a suitable solvent. However, this procedure is limited in commercial application since it uses a relatively expensive and toxic alkaloid and is also volume inefficient requiring high dilution in methanol for optimum product quality.

Scheme 1. **Etodolac racemate and enantiomers**



Asymmetric Synthesis. Asymmetric routes to (*S*)-etodolac have been described.[4] These typically involve the use of covalently linked auxiliaries such as menthyl or bornyl esters and require lengthy synthetic sequences.

Salt Forms. The *N*-methyl glucamine (meglumine) salt of etodolac (racemate) has been proposed as a dosage form but not in conjunction with a resolution strategy.[5] Various other salt forms have been proposed for etodolac including sodium, tris-(hydroxymethyl)-aminomethane and various amino acids.[6]

Strategy and Aims. We decided to investigate a final stage resolution strategy. This approach would lead to quantities of the "off-isomer" (*R*)-(−)-etodolac that would need to be recycled to make the overall process economic. The target purity for the etodolac meglumine salt was set at a nominal 95% de, with operation up to a one kilogram scale as the initial objective.

Resolution Screen. A range of common chiral organic bases was screened for the resolution of etodolac. These included a series of *N*-alkyl glucamines and alkaloids. From the screening studies it appeared that *N*-methyl-D-glucamine (meglumine) was a good resolving agent for etodolac, affording a good yield of salt with a satisfactory diastereomeric excess. The procedure was scaled to 25 g input and performed well using a minimal input of resolving agent (Table 1).

Choice of Meglumine as Resolving Agent and Dosage Form. Meglumine is a white, odourless, crystalline powder which is available in BP/USP (low in endotoxin) grade from

[†] Celltech-Chiroscience Ltd.

[‡] High Force Research Ltd.

[§] Formerly Celltech-Chiroscience Ltd. Current address: Glaxo-Wellcome Medicines Research Centre Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK.

[||] Formerly Celltech-Chiroscience Ltd. Current address: Roche Discovery Welwyn, Broadwater Road, Welwyn Garden City, Hertfordshire AL7 3AY, UK.

[⊥] Formerly Celltech-Chiroscience Ltd. Current address: Chirotech Technology Ltd, Cambridge Science Park, Milton Rd, Cambridge CB4 0WG, UK.

[#] Formerly Celltech-Chiroscience Ltd. Current address: Tripos Receptor Research, Bude-Stratton Business Park, Bude, Cornwall EX23 8LY, UK.

(1) Review on etodolac: Humber, L. G. *Med. Res. Rev.* **1987**, *7*, (1), 1−28.

(2) Humber, L. G. *J. Med. Chem.* **1986**, *29*, 871−874.

(3) Resolution procedures (American Home Products): (a) Abraham, N. A.; Demerson, C. A. Cholesteryl aniline salt. U.S. Patent 4,501,899, 1983. (b) Demerson, C. A.; Humber, L. G. Entrainment crystallisation. U.S. Patent 4,515,961, 1983. (c) Abraham, N. A.; Demerson, C. A. Cinchonine salt. U.S. Patent 4,520,203, 1983. (d) Demerson, C. A.; Humber, L. G. Borneol esters. U.S. Patent 4,544,757, 1984.

(4) Citterio, A.; Fancelli, D.; Pesce, L. (Blaschim, SPA). Eur. Pat. Appl. 302541, 1987.

(5) Veronesi, P. A. Water soluble glucamine/meglumine salts of NSAIDs. (Therapicon). U.S. Patent 4,748,174, 1988.

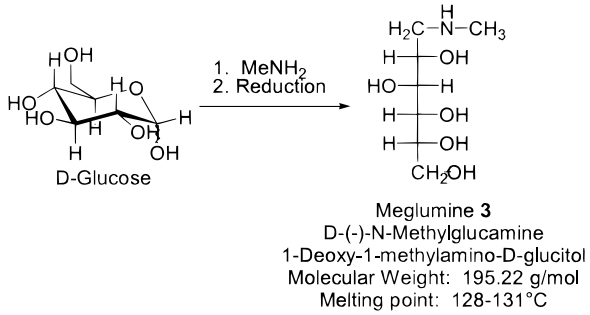
(6) a) Casero, R. Sodium salt process. (Farmaka, S.r.l.). Eur. Pat. 221032, 1985. (b) Caldwell, H. C. "Tris" salt for oral liquid compositions. (Applied Analytical Industries Inc.). U.S. Patent 5,183,829, 1991. (c) Veronesi, P. A. Arginine, lysine, and methionine salts. (Therapicon). Ital. Pat. 1,204,-954 1987.

 10.1021/op000014p CCC: $19.00 Published on Web 08/24/2000

Table 1. **Initial etodolac meglumine salt resolution results**

acid: amine ratio	input etodolac (g)	2-propanol (vols)	salt yield %th (wrt racemic acid)	% de (*S*)-etodolac meglumine salt
1: 0.6	2.0	16.5	31	80
1: 0.6	25	16	33	80
1: 0.75	2.06	18	37	75

Scheme 2. **Meglumine synthesis**



a variety of suppliers. It is readily soluble in water up to 80% w/v at 25 °C whilst the solubility in ethanol increases from 1.2% w/v at room temperature to 21% w/v at 70˚C. It is prepared by reductive amination of glucose as are the family of alkyl glucamines (Scheme 2).

Uses of Meglumine. The resolving agent meglumine is a potential base for the preparation of salts for pharmaceutical administration. A wide range of drugs have been orally administered as meglumine salts. Parenteral administration of meglumine salts has been used for X-ray contrast media and nuclear imaging agents. Meglumine has been used in cosmetic gels as a buffering agent.

Expansion of Meglumine Resolution Study. It was found that the (*S*)-etodolac meglumine salt of ∼80% de prepared initially could be recrystallised to >95% de by a single recrystallisation from 2-propanol (IPA, ∼20 vols). This achieved the target purity required for the biological testing. With this information we decided to expand the resolution study and investigated further the stoichiometry of reagents and the effect of solvent volume on the procedure, intending to isolate the (*S*)-etodolac meglumine salt directly (Table 2).

The results proved to be very variable, neither the de value nor even the isomeric outcome of the salt formation could be predicted. The resolution in 2-propanol appeared insensitive to seeding, acid:amine ratio, and concentration. The intermediate sample taken in entry 3 suggests that the initial precipitation was in fact the required (*S*)-etodolac salt, which on stir out overnight was replaced by the (*R*) salt. Repetition of three identical experiments (entries 7, 8, 9) confirmed that the outcome could not be relied upon.

The initial (*S*) salt selective results may have been due to seeding phenomena. Indeed, early attempts to prepare the pure (*R*)-etodolac meglumine salt failed to give crystalline material; hence, seeds were not present in the laboratory until a larger number of resolutions had been attempted. Seeding with the (*R*) salt in reduced volumes of IPA appeared to trigger the nonselective precipitation of all the material as

Table 2. **Etodolac meglumine salt resolution: expanded study (2-propanol)**

entry	acid: amine ratio	input etodolac (g)	2-propanol (vols)	salt yield %th (wrt racemic acid)	% de (*S*)	% de (*R*)
1	1: 0.4	4	14	35	-	54
2	1: 0.6	6.8	17	64	-	31
3	1: 0.6	2	17	50	-	20[a]
4	1: 0.75	2.1	18	37	75	-
5	1: 0.75	25	18	70	-	8
6	1: 1	2.6	21	45	62	-
7	1: 1	2	30	26	92	-
8	1: 1	2	30	47	-	26
9	1: 1	2	30	85	-	3
10	1: 1	2	10	87	-	3
11	1: 1	2	20	85	0	0

[a] 70% de (*S*) 2 h after seeding (seeded at 47 °C; sampled at 22 °C).

Table 3. **Solubility of (*R*)- and (*S*)-etodolac meglumine salts in 2-propanol**

salt	solubility in IPA at 65−70 °C (mg/mL)
(*S*)-etodolac meglumine salt	25
(*R*)-etodolac meglumine salt	20

near racemic salt (entry 11). Comparison of the relative solubilities of pure salts showed the root cause of the problem (Table 3).

These solubilities explain the capricious nature of the resolution procedure, the (*R*) salt is the thermodynamically less soluble salt and is the preferred product. Obviously in some cases seeding with the (*S*) salt can lead to its initial precipitation but this is unlikely to be controllable or reliable for scale-up. To progress the project speedily to scale-up we transferred the studies to High-Force Research Ltd. From the early studies it was apparent that accurate temperature and process control would be needed to define robust conditions for the resolution. High-Force Research Ltd have computer-controlled reactor vessels with excellent temperature and stirring control and crystallisation monitoring capability which we wished to employ in this study.

Initial Studies on Racemic Etodolac Input. The initial work concentrated on crystallisation studies of an equimolar mixture of etodolac and meglumine in ethanol and 2-propanol with and without the addition of small quantities of water. The concentrations of the solutions were varied between 5 and 30%, and crystallisations were done at isothermal temperatures between 5 and 45 °C.

Early experiments were done using controlled temperature ramping to see if a crystallisation point could be found, but this was not successful, giving mainly racemate which crystallised at low temperature. It appears that low de material is generally obtained when a low-temperature filtration is performed.

Crystallisation was also found to be slow even with seeding, and it was found that the best way to produce crops with high (*S*) or (*R*) isomer content was to seed at elevated temperatures with crystallisation slowly over a period of

hours at the elevated temperature. Since the (*R*) isomer tends to crystallise out first the approach taken has been to produce a good yield of high de (*R*) isomer salt which is filtered off, leaving a solution rich in (*S*) isomer. The (*S*) isomer-rich mother liquors are then crystallised out to give a solid with a high (*S*) content.

As temperature control is important in these crystallisations, the filtrations need to be reasonably fast to avoid further crystallisation of unwanted isomer, which would occur if the product slurry cools too much during filtration.

This approach has proved to work quite well and has been shown to be fairly reproducible. Satisfactory results were achieved using a 30% solution of the etodolac meglumine in ethanol, with crystallisation at 45 °C over 5−6 h. This typically gave a 26−28% yield of first crop material with (*R*) isomer content of 84−97%.

The ethanol mother liquors were then crystallised by seeding with pure (*S*) isomer at 35 °C to give a second crop material with (*S*) isomer content of ∼70% in 45−51% yield after overnight stir out.

It has been found that material which has an (*S*) isomer content of greater than 68% can be recrystallised to give product with a purity in the high nineties, whereas material with less than 68% (*S*) content gives disappointing results when recrystallised.

Recrystallisation of (*S*)-Rich Materials. Some satisfactory results were obtained with relatively dilute (4%) 2-propanol solutions with crystallisation at 45 °C over 3−4 h. These gave variable yields in the range 25−45% but of high (>98%) (*S*) content. Second crops of much lower purity were obtained. However, switching to ethanol allowed more concentrated solutions to be used and gave acceptable results with a purity of 98.5% (*S*) isomer in a yield of 26.6% (based on original racemate input) in 3 h from a 10% solution at 35 °C. It is preferable to use higher concentrations if possible, as more material can be obtained per crystallisation from equivalent volumes.

Out of specification, high (*S*) content (>90%), material has been recrystallised to give a de of >95% in high (>75%) yield. This indicates that a final recrystallisation should give good quality product if the results on scale-up are not quite as good as those obtained so far.

Effect of Seeding.

The effect of different purity seeds has been investigated. The recrystallisations of (*S*) rich (40% de) material in a 4% IPA solution were seeded with 84.9%, 91.7% and 99% (*S*) isomer content seeds. The salts obtained after ageing for 4 h at 50 °C were all fairly similar with de values from 95 to 98% (*S*), and thus the purity of the seed is probably not critical.

Scale-Up. Having obtained a reliable small-scale method, subsequent work was aimed at further optimisation of the process with a view to scale it up to produce 1 kg of >97% de (*S*) isomer.

Summary of Results

(a) First Crystallisation Step, Isolation of (*R*)-Rich Salt. The initial work indicated that using ethanol as solvent, the (*R*) salt was less soluble. It was found that by careful temperature control and seeding with (*R*) isomer salt, we could obtain a first crop of (*R*)-rich etodolac meglumine salt. Typically a 30% solution of racemate salt in ethanol could be crystallised out at 45 °C for 5 h after seeding with (*R*) isomer, to give 30%+ yield of material that was >90% (*R*) isomer.

(b) Second Crystallisation Step, Isolation of (*S*)-Rich Salt from Mother Liquors. The mother liquors from the filtration were then crystallised at 35 °C after seeding with (*S*) isomer, to give a second crop that was rich in (*S*) material. This crystallisation was carried out overnight for convenience in the early work, and this typically gave a yield of 45−51% of material that had an (*S*) isomer content of ∼70%.

Further work has shown that much shorter crystallisation periods have given much higher purity (*S*) material, albeit in slightly lower yield (ca 35%). This has the advantage that it is much easier to obtain pure material, using one further crystallisation step. It was found that a 2 h crystallisation produced a 35% yield of material with a purity of ∼90% (*S*) isomer. This material was further crystallised in the second crystallisation step to give material that was either in, or very close to, specification.

Third and fourth crops were also obtained from the mother liquors after filtering off the second crop, by evaporating off a portion of the solvent and crystallising at lower temperatures. This gave a further 20−25% yield of material that contained approximately equal amounts of (*R*) and (*S*) isomers. This material has been recycled with racemate so that further crops of (*R*)- and (*S*)-rich material could be obtained.

(c) Third Crystallisation Step, Recrystallisation To Give (*S*)-Rich Salt of Desired Purity. As much higher quality (*S*)-rich material can now be obtained from the second crystallisation step, it has been found that one further recrystallisation of this material from ethanol can give in specification product in one step, providing that the purity of this starting material is >90% (*S*). The use of ethanol also has the advantage that a 20% solution can be used which gives much better volume productivity than when using IPA, where a 4% solution was used. The yields are also reasonable being >50% with good quality second crops also being obtained.

When this mother liquor recrystallisation has given material which is just below spec (95% de), then one further crystallisation from a 10% ethanol solution gives very high de (*S*) product in 80% yield.

(d) Effect of Temperature Control. The early work done on a small laboratory scale showed that temperature control was a very important parameter in obtaining high purity material. The importance of accurate control of the crystallisation temperature was confirmed in the first 10 L run attempted. After heating to 65 °C, to dissolve the salt, the water bath was cooled to 45 °C to crystallise out the first crop. Unfortunately, the controller used was unable to keep the bath steady at 45 °C, and there were short temperature excursions to 55 °C. The first crop was filtered off after 5.5 h, which had been found to be about optimum for this crystallisation. It was found that a much larger first crop was

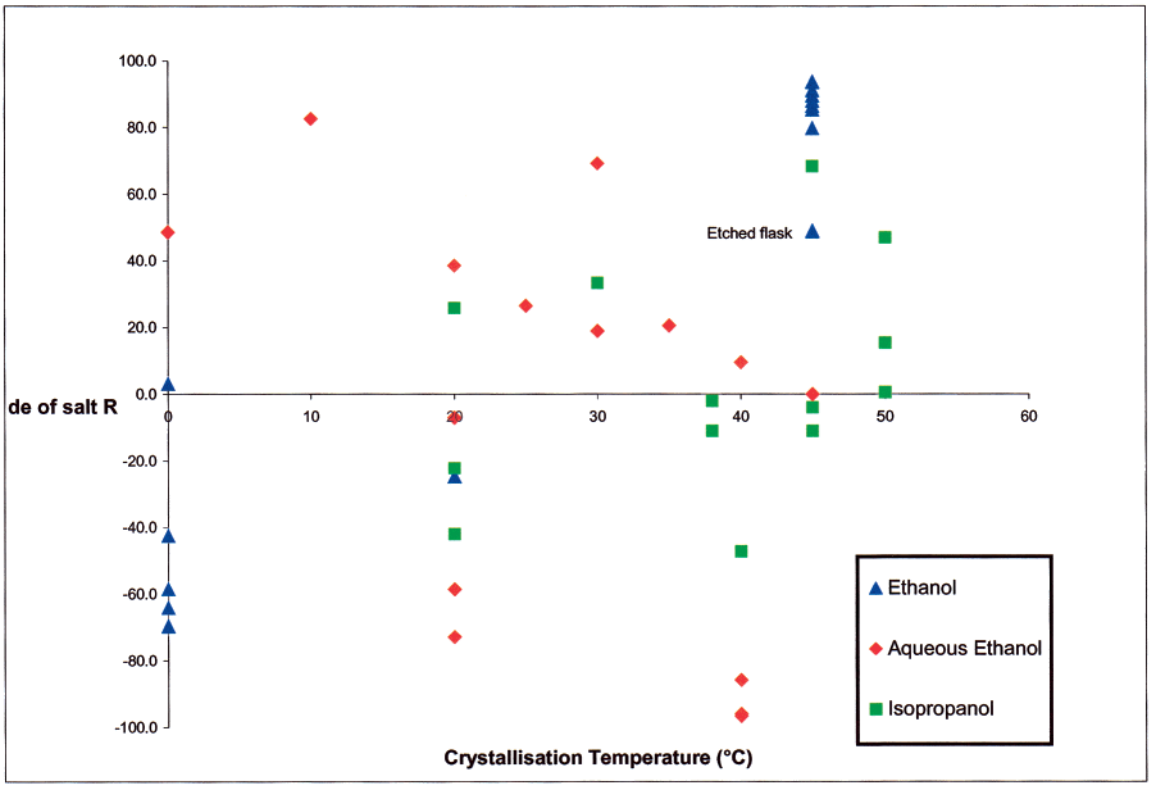


Figure 1. **Plot of de of salt (*R*) vs crystallisation temperature for EtOH, aqueous EtOH, and 2-propanol.**

obtained (57.9% cf. 30−35% for good crystallisations), but the purity was far lower than normal being 11.8% de (*R*), compared with >80% de (*R*) in well-controlled crystallisations. The corresponding second crop seeded with (*S*) isomer was of much lower yield than normal (11%) although the purity was 93% (*S*) isomer. Later crystallisations done on the same scale were much more successful, reproducing the small-scale results. This was achieved because the temperature control was much improved in these runs.

(e) Effect of Scale-Up on Crystallisations. The crystallisations scaled up remarkably well from 100 mL to 10 L, provided that good temperature control is achieved. The only time problems have been encountered was when flasks which had signs of etching or wear were used. This led to more rapid crystallisation, and lower purity product, due to uncontrolled nucleation. On further plant scale-up, the vessels used could be critical, and only vessels of high quality should be used.

f) Recycle of impure crops and mother liquors

Third and fourth crops that were obtained have been recycled successfully by the same method as with new racemate, to give good quality material. One important feature of the process is that it uses a single solvent throughout. In theory any waste stream ethanol containing etodolac meglumine salt could be directly recycled into the initial resolution. The input de levels could be adjusted by analysis and blending to provide a reliable input range for continuous use. In fact since all of the off-isomer may be racemised, the overall process has very little potential environmental impact.

(g) Filtration. The crystal form of both the (*R*)- and (*S*)-etodolac-rich salts has enabled fairly rapid filtration. This is quite important on larger scales because if filtration is slow then the unwanted isomer could crystallise out as the material cools on the filter bed. If problems are encountered on the plant scale, then it may be necessary to adapt the process further with the incorporation of constant temperature filters so that the temperature of the solution is controlled during filtration.

(h) Bulk Density of Solids. The bulk density of the in-specification material has been measured and varies between 0.3 and 0.4 g/mL. It has been indicated that higher bulk densities would be preferred, and a few experiments have been done with different solvents to see if this could be improved. The only solvents that have been found to give reasonable strength solutions of the meglumine salt are alcohols. Methanol, ethanol, propan-1-ol, 2-propanol, butan-1-ol, and *tert*-butyl alcohol have all been used, and it has been found that the solubility of the salt diminishes as the higher alcohols are used. There was not a great deal of difference between the bulk density of material crystallised from these solvents, and they were usually in the 0.3−0.4 g/mL range. Further scale-up into large plant can give a different crystal form and optimisation may be best achieved at this scale.

Graphical Representation of Data. Figures 1−4 show collected results from both the small- and large-scale experiments. All of these data relate to racemic etodolac input to form the meglumine salt in a variety of solvents. Figure 1 shows that the ethanol-based experiments display a definite trend in the relationship between de of salt and crystallisation temperature. Conversely, the aqueous ethanol and 2-propanol experiments show a certain randomness of the sense of resolution. The crystallisation time is also of importance as

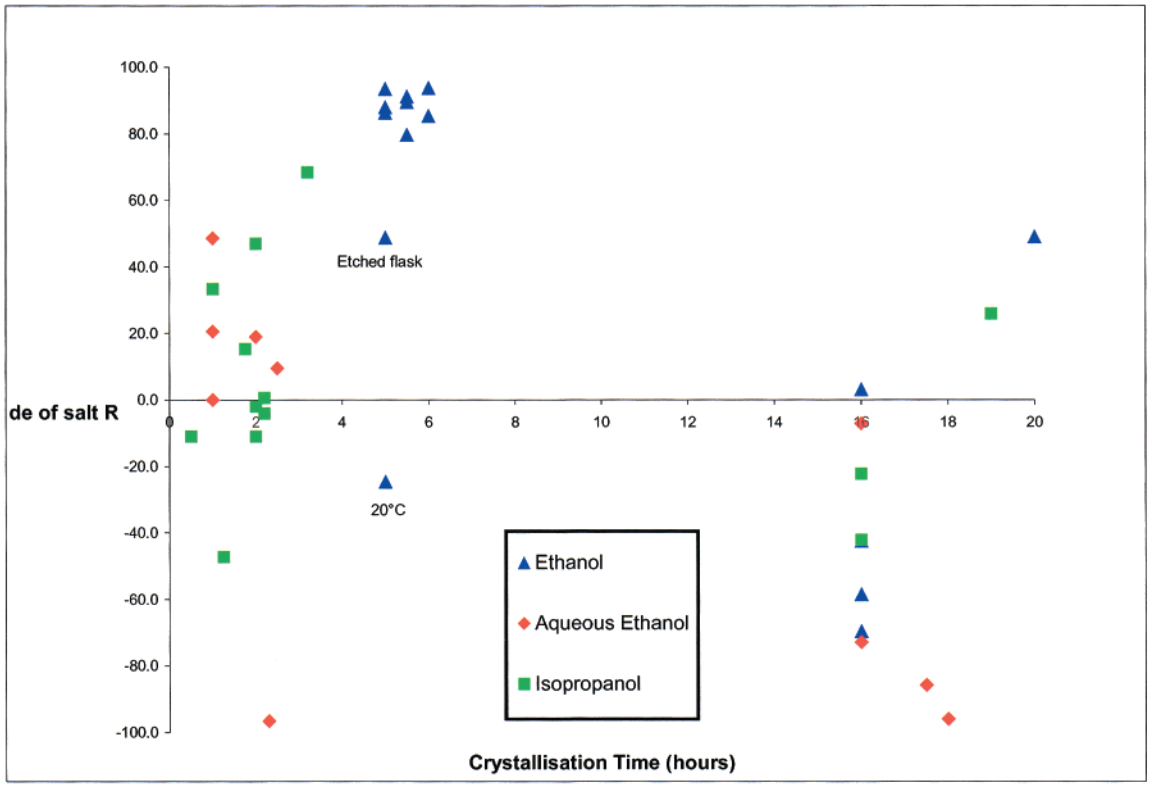


Figure 2. **Plot of de of salt (*R*) vs crystallisation time for EtOH, aqueous EtOH, and 2-propanol.**

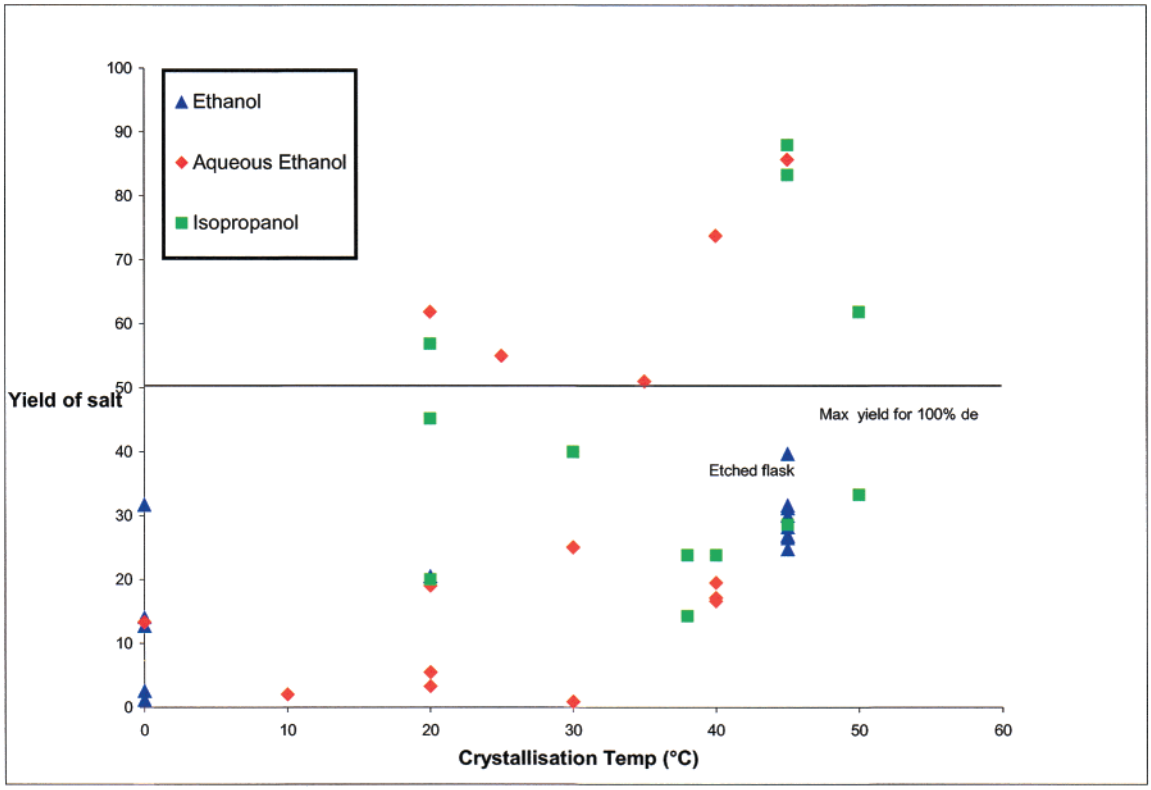


Figure 3. **Plot of yield of salt vs crystallisation temperature for EtOH, aqueous EtOH, and 2-propanol.**

can be seen from Figure 2, with 4−6 h being the optimum. In the ethanol crystallisation an extended time can lead to excessive precipitation and a consequently lower de salt. Of note is the effect of the etched flask causing a lowering of product quality.

Figures 3 and 4 show that both time and temperature also affect the yield of the process. Of course for an efficient resolution, a yield approaching 50% is the maximum possible. Again, the ethanol process has the required reproducibility although the yields are at the lower end of

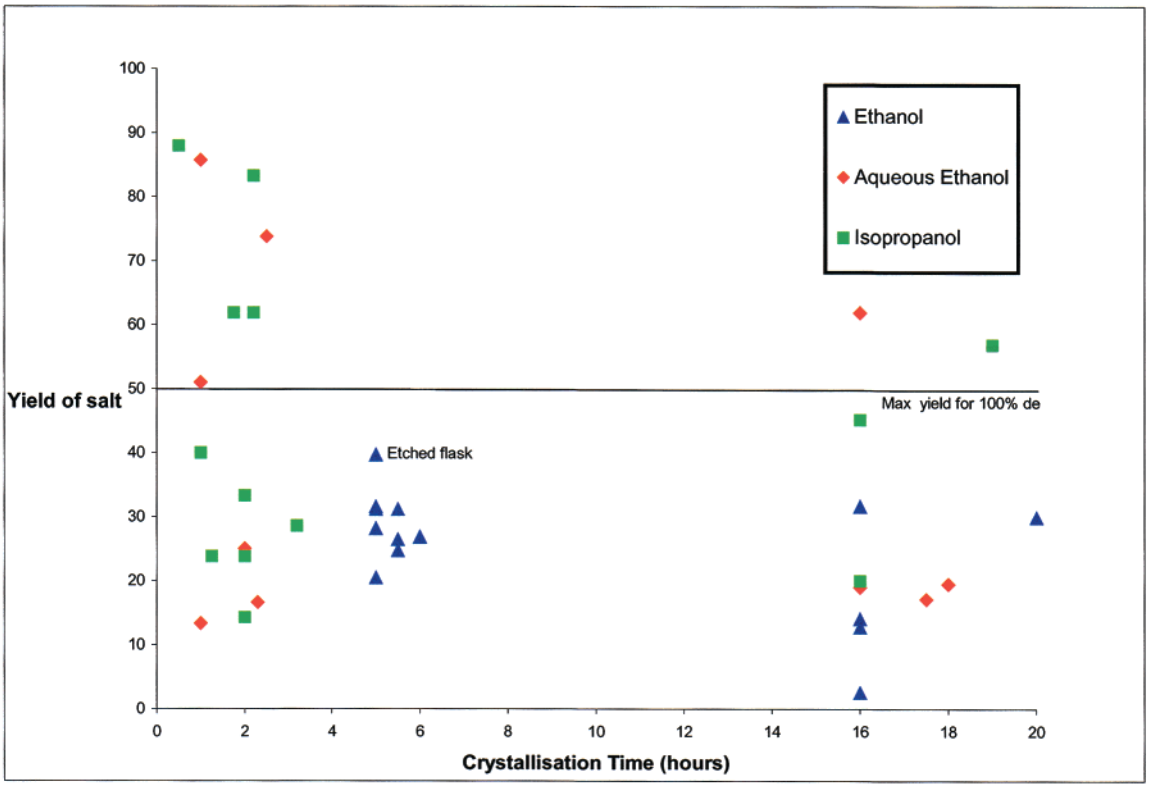


Figure 4. **Plot of yield of salt vs crystallisation time for EtOH, aqueous EtOH, and 2-propanol.**

Table 4: **Esterification of etodolac using classical conditions**

entry	conditions	yield (crude), ee
1	MeOH, 23 vols. concd H_2SO_4, 0.3 equiv, reflux 1.5 h	67% th, 49% ee (*R*)
2	MeOH, 12 vols., $CH_2(OME)_2$, 12 vols. concd H_2SO_4, 0.3 equiv, rt, 3 days	80% th, 70% ee (*R*)
3	MeOH, 23 vols., concd H_2SO_4, 0.3 equiv, rt, 3 days	69% th., 83% ee (*R*)

the desired range; again, note how the etched flask has given a higher yield at the expense of quality.

It is apparent from Figure 3 (yield versus crystallisation temperature) that the ethanol process is the more reliable. However, Figure 4 shows that even the yield of the ethanol process can also be variable with time, this obviously has consequences for the de of the salt produced.

Recycle of Etodolac Off-Isomer. It was known from a published stability study that etodolac free acid is unstable to acid degradation.[7] The mechanism for the decomposition is well understood and involves the protonation of the pyran-ring oxygen atom and the generation of a stabilised cationic intermediate. In the case of the free acid this intermediate suffers facile decarboxylation which leads to a range of decomposition products. To racemise etodolac we needed to activate the same part of the molecule that is, the β-carbon−oxygen bond. Therefore a β-elimination/reclosure mechanism should induce racemisation since the cationic intermediate is planar.

Esterification of Etodolac. We therefore reasoned that to racemise etodolac without spontaneous decarboxylation the formation of the ester was required. This should suppress the loss of the carboxylate group. Studies of the re-esterification of etodolac were undertaken using enriched material so that the extent of racemisation, if any, could be followed.

Esterification Using Classical Conditions. Etodolac free acid [~83% ee (*R*)] was treated with methanolic sulphuric acid under a variety of conditions. The esterification reactions were in general slow. Partial racemisation was noted in some cases and obviously occurred faster at higher temperatures. Results are summarised in Table 4. Of particular note is entry 3 where no racemisation occurred although the reaction is very slow.

In all three cases there were signs of some decomposition by TLC, with more polar impurities being formed. The mother liquors from a methanol-based esterification were concentrated, and the constituents purified by flash column chromatography to give three isolated fractions:

1. methyl ester plus decarboxylated product **4** (2:1 ratio, 14% th),

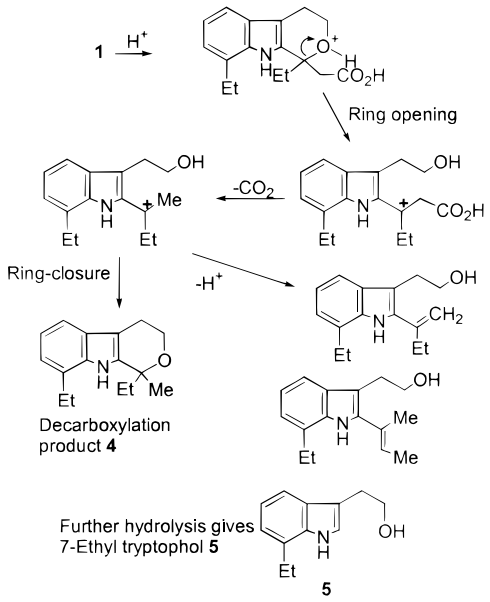
2. 7-ethyl tryptophol **5** (3% th, bright purple colour when developed with vanillin), and

3. mixed alkene decarboxylation/decomposition products (10% th).

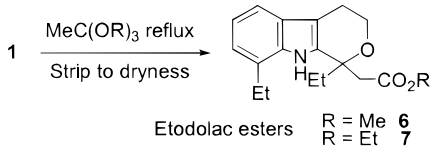
These products arise from the acid-catalyzed decomposition pathways shown in Scheme 3. This study highlighted

(7) Lee, Y. J.; Padula, J.; Lee, H. K. *J. Pharm. Sci.* **1988**, *77(1)*, 81−86.

Scheme 3. **Acid-catalysed degradation of etodolac**



Scheme 4. **Esterification of etodolac with orthoacetates**



the need for a milder esterfication procedure that did not cause extensive decomposition via decarboxylation and cleavage to tryptophol.

Initially we esterified etodolac using both neat trimethyl and triethyl orthoacetate.[8] Simply heating the substrate to reflux for 2 h affords the corresponding alkyl ester. This reagent is useful in cases where the substrate is acid-sensitive, which was to be of use in the later studies. The trialkyl orthoacetate reagents are more reactive than the commonly used orthoformates due to the electron-donating effect of the methyl group. This facilitates esterification without an added acid catalyst and generates only the corresponding alkyl acetate as a by-product (Scheme 4).

Esterification with Racemisation. Etodolac (64% ee (*R*)) was esterified by heating under reflux for 12 h in toluene and trimethyl orthoacetate (TMOA) giving (*R*)-etodolac methyl ester without racemisation. The solution was then acidified with concentrated sulphuric acid (2 mol %) and reflux continued for 5 h after which time the ee was remeasured at 64% (*R*); therefore, no racemisation had occurred. The addition of methanol followed by overnight reflux (68 °C) also failed to reduce the ee value; therefore, further concentrated sulphuric acid (10 mol %) was added, and heating continued. Samples were taken at intervals and revealed that racemisation was complete after ~7 h at reflux (see Figure 5). TLC showed that some slight decomposition was apparent. Following extractive work-up and trituration

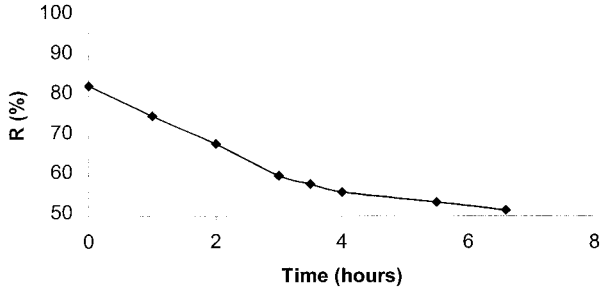
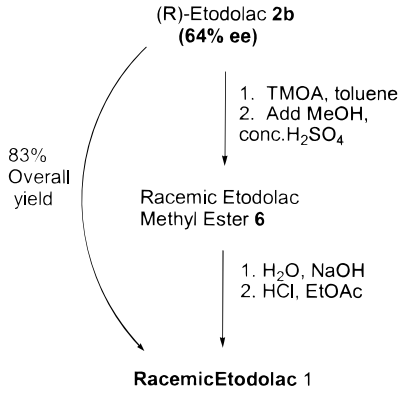


Figure 5. **Racemisation of etodolac methyl ester.**

Scheme 5. **Recycle of (*R*)-etodolac**



with methanol, etodolac methyl ester was obtained in good yield and purity (3.46 g, 66% th).

This stepwise experiment shows several important features of the esterification/racemisation process:

- once esterification is complete, the ester is quite stable to additional strong acid,
- addition of strong acid to the TMOA/toluene mixture (2 mol %) does not induce racemisation or decomposition, and
- methanol *and* a substantial acid charge are both required to support racemisation.

Therefore, for the racemisation to be supported a significant quantity of both sulphuric acid and methanol are required, but the ester must first be fully formed to avoid losses caused by acid decomposition of the free acid. An investigation of alternative acidic reagents was started but did not reveal immediately applicable improvements.

In a trial procedure (*R*)-etodolac free acid (5 g, 64% ee) was esterified with TMOA/toluene, racemised by addition of concentrated sulphuric acid and methanol, hydrolyzed and re-isolated by extractive procedures to give racemic etodolac free acid in excellent 83% overall yield (Scheme 5). The methyl ester could be isolated if desired and fed into the standard process at the penultimate stage, in this case the ester was directly hydrolyzed. This trial run represents a basis for a scalable procedure for the racemisation of etodolac free acid isomers obtained as by-products of the meglumine resolution procedure. The reagents, methods, and conditions used are compatible with general scale-up considerations.

Conclusions

A method has been established that converts racemic etodolac to pure (*S*)-etodolac meglumine salt in a maximum

(8) Trujillo, J. I.; Gopalan, A. S. *Tetrahedron Lett.* **1993**, *34*, 7355−7358.
(9) Adger, B. M.; Dyer, U. C.; Woods, M.; Andrews, J. F.; Baker, H. F. Process for the resolution of etodolac using glucamine derivatives. (Chiroscience Ltd.). U.S. Patent 5,811,558, 1996.

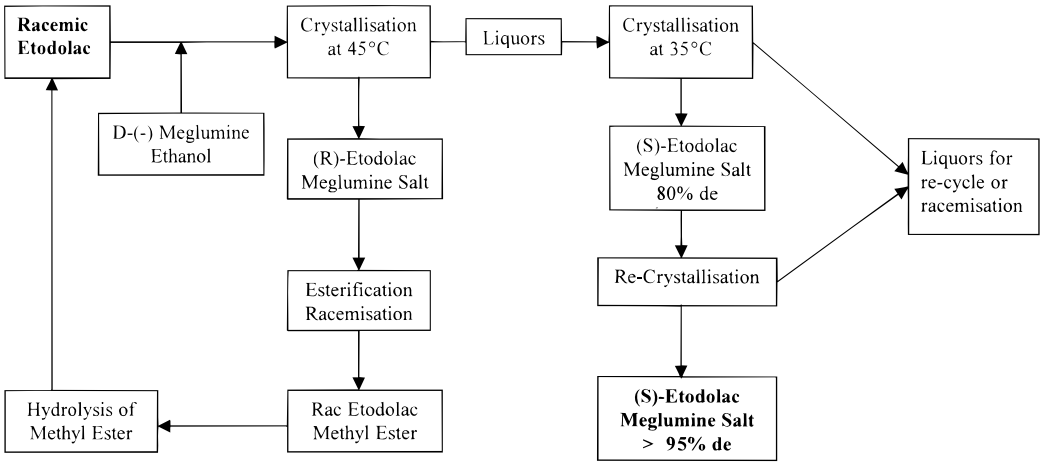


Figure 6. **Flowchart.**

of three steps using concentrated ethanolic solutions. The method has scaled up well, providing that good temperature control can be achieved, and a once through yield of 20−25% can be obtained with further, less pure crops being available for recycle. More than one kilogram of high quality material was prepared using the described process. The process uses a cheap readily available resolving agent, which is prepared from naturally occurring materials. The resolving agent is also an advantageous formulation for acidic drugs which could benefit from improved solubility. When combined with the recycle via esterification and racemisation the overall process has potential to be economically and environmentally efficient. The racemised ester may be fed into the standard production process since it is an intermediate in the commercial synthesis of etodolac (see Figure 6 for the flow chart).

Clinical Studies

Clinical studies demonstrated that good uptake rates and plasma levels of (*S*)-etodolac were achieved by oral dosing of the (*S*)-etodolac meglumine salt. The salt showed low inter-volunteer variability when compared with the racemic free acid. However, when side-effect profiles were compared, the new (*S*)-etodolac meglumine salt formulation did not provide an improved profile, and the project was consequently stopped.

General Remarks

Commercially available solvents and reagents were used without further purification. Etodolac racemate was obtained from Wilfrid Smith Limited. *N*-Methyl-D-glucamine was obtained from The Aldrich Chemical Co.

^{1}H NMR (200, 400 MHz) and ^{13}C (100.6 MHz) spectra were recorded on a Bruker AM 400/200 instruments as stated. Melting points were recorded on a Mettler Toledo DSC 12E or Buchi 510 (Oil Filled) Melting Point Apparatus and are uncorrected. The IR spectrum was determined on a Perkin-Elmer 1600 FTIR spectrometer.

Note: Etodolac is light-sensitive, and precautions should be taken to avoid UV-catalysed decomposition.

Experimental Section

Optimisation Studies for Resolution of Etodolac with Meglumine. One litre scale experiments were performed in a jacketed flask in which the temperature was computer-controlled using an external heater/cooler circulator. Larger scale (5−10 L) experiments have been done with standard flat flange flasks with temperature control from immersion in thermostatically controlled water baths.

Small-scale comparison experiments were performed in three 100 mL flasks fitted with identical stirrers and fixed speed stirrer motors. All three flasks were placed in the same water bath so that temperature control was the same in each case.

In most experiments, first, second, and in some cases third crops were obtained by filtration and they were then washed with a little fresh solvent, dried, weighed, and analysed.

The material obtained was dried in a vacuum oven at 60−70 °C under low vacuum.

Procedure for Large-Scale Crystallisation of (*S*)-(+)-Etodolac Meglumine Salt. (*S*)-(+)-1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic Acid D-(−)-Meglumine Salt [(*S*)-Etodolac Meglumine Salt]. Racemic etodolac (1148 g), D-(−)-meglumine (780.8 g) and ethanol (6.4 L) were charged to a 10 L round-bottomed flask and heated to 70 °C with stirring to dissolve the solids. When this mixture was in solution, the water bath was adjusted to 45 °C and maintained at this temperature. The solution was seeded with a small amount of pure (*R*)-etodolac meglumine salt and the mixture allowed to crystallise out over 5 h. The solid was filtered off (filtration was rapid), and the cake washed with ethanol (2 × 250 mL), filtered, and dried in a vacuum oven at 70 °C.

Yield of (*R*)-etodolac meglumine salt = 609.7 g, (86.4% de).

The mother liquors from the (*R*)-etodolac meglumine salt isolation and washes were recharged to the flask and heated back to 50 °C to dissolve solids. The bath was then cooled to 35 °C and seeded with pure (*S*)-etodolac meglumine salt. The solution soon began to crystallise and became quite thick. After 2 h at 35 °C the mixture was filtered off, and washed with ethanol (2 × 200 mL). The solid was dried in a vac oven as before.

Yield of (*S*)-etodolac meglumine salt = 689.8 g, (79.8% de).

The (*S*)-etodolac meglumine salt obtained above, was charged to a 5 L round-bottomed flask and ethanol (3.4 L) added. The mixture was heated to 60 °C to dissolve, and then the water bath was cooled to 50 °C. Pure (*S*)-etodolac meglumine salt seed was added at 55 °C; the solution stirred at 50 °C for 2 h and the mixture was then filtered, washed with ethanol (200 mL), and dried in a vac oven as before.

Yield of (*S*)-etodolac meglumine salt = 332.9 g, (96.6% de).

The mother liquors and washes from the above procedure were recharged to the flask, heated to dissolve any solids, and then stirred at 35 °C for 2.5 h after seeding with (*S*) isomer. The solid was filtered off, washed with ethanol (2 × 100 mL), and dried.

Yield of (*S*)-etodolac meglumine salt = 155.1 g, (96.1% de).

Overall yield of (*S*)-etodolac meglumine salt = 488 gms (70.7%, >96% de, 25.3% yield): mp 141−143 °C; $[\alpha]^{20}_{589}$ = + 11.3° (*c* = 1.0, H_2O); ^{1}H NMR: (D_2O, 400 MHz) δ_H = 0.66 (3H, t, *J* = 7.3, CH_3), 1.29 (3H, t, *J* = 7.6, CH_3), 2.06−2.12 (2H, m, CH_2), 2.72−2.91 (4H, m, 2 × CH_2), 2.77 (3H, s, NCH_3), 3.14−3.25 (2H, m), 3.64−3.69 (2H, m), 3.71−3.85 (2H, m), 4.04−4.13 (2H, m), 7.08−7.13 (2H, m), 7.43 (1H, dd, *J* = 7.3, 1.6). ^{13}C NMR: (D_2O, 100.6 MHz) δ_C = 7.2, 13.5, 21.5, 23.8, 30.7, 32.9, 46.3, 51.2, 60.4, 62.7, 68.2, 70.5, 70.7, 71.0, 76.8, 107.5, 115.8, 119.6, 120.2, 125.5, 127.4, 134.2, 136.6, 178.8. FTIR (KBr): 3354, 3264, 1573, 1465, 1410, 1392, 1084.

(Stripping and crystallisation of the various waste streams yielded 606 g of crystalline lower purity material (24−50% de *S*) for recycle by addition to the initial crystallisation taking account of the isomeric purity).

Procedure for Racemisation of (*R*)-Etodolac. Racemic 1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic Acid. (*R*)-Etodolac free acid (5 g, 64% ee, 17.4 mmol) was added to toluene (35 mL), giving an orange solution. Trimethyl orthoacetate (6.6 mL, 52 mmol) was added and the mixture heated to reflux for 18 h (reaction approximately 90% complete after 8 h). Concentrated sulphuric acid (180 mg, 1.74 mmol, 10 mol %) and methanol (10 mL) were added, and the mixture was heated at reflux for 16 h during which time racemisation of the ester was complete. Aqueous sodium hydroxide solution (2 M, 15 mL) was added and the mixture concentrated in vacuo to remove the organic solvents. Water (30 mL) and sodium hydroxide solution (2 M, 15 mL) were added, and the mixture was heated to reflux. Analysis showed that little saponification had occurred; therefore, methanol (10 mL) and further sodium hydroxide (48% w/w, 4 mL) were added, and reflux continued overnight. The solution was cooled to room temperature and acidified by addition of concentrated hydrochloric acid (10 mL), becoming cloudy. The product was extracted into ethyl acetate (2 × 100 mL) and the dried ($MgSO_4$) organic layer concentrated to dryness to afford racemic etodolac as a pale brown crystalline solid (4.13 g, 83% th).

^{1}H NMR: ($CDCl_3$, 200 MHz) δ_H = 0.90 (3H, t, *J* = 7.3, CH_3), 1.30 (3H, t, *J* = 7.5, CH_3), 1.96−2.28 (2H, m, CH_2), 2.73−2.89 (2H, m, CH_2), 3.00−3.17 (2H, m, CH_2), 4.00−4.20 (2H, m, CH_2), 7.00 (1H, d, *J* = 6.2), 7.08 (1H, t, *J* = 7.4), 7.37 (1H, d, *J* = 7.5), 8.81 (1H, br s).

Analytical Methods

Etodolac Enantiomers by HPLC. The etodolac enantiomers are determined by chiral HPLC on the derived anilides.

column	poly L-leucine (hi-chrom)
mobile phase	5% 2-propanol/heptane
flow rate	1 mL/min
detector	UV, 280 nm
injection volume	20 μL
typical retention times:	(*S*) 6.2 min (*R*) 9.0 min

Derivatisation Procedure. Accurately weigh approximately 30 mg of the free acid sample into a vial. Add 30 mg of 3-ethyl-1-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC·HCl) and 5 mL of dichloromethane.

Add six drops of aniline and stir for 30 min, acidifiy with dilute HCl (aq), and separate the layers. Dry the organic layer and dilute with 2-propanol, 1:100. For salts samples the free acid is released by treatment with dilute HCl and EtOAc, and the organic layer is separated and concentrated to dryness prior to derivatisation.

Etodolac Ester Enantiomers by HPLC. Procedure. Samples were dissolved in 2-propanol at approximately 0.1 mg/mL.

column	poly L-leucine (hi-chrom
mobile phase	1% 2-propanol/heptane
flow rate	1 mL/min
detector	UV, 254 nm
injection volume	20 μL
typical retention times	methyl ester (*S*) 5.5 min, (*R*) 6.8 min ethyl ester (*S*) 5.0 min, (*R*) 6.2 min

Esterification. TLC method.

plates	polygram Sil G/UV254
mobile phase	EtOAc/heptane (1:3)
visualisation	UV, vanillin (acid and esters intense purple)
R_f	etodolac ~0.2 etodolac esters ~0.7

Acknowledgment

We thank Christel Kronig for HPLC method development, Philip Gilbert for NMR studies, and Paresh Parmar for analytical services.

Received for review February 14, 2000.

OP000014P