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Attempted Resolution of Citalopram Using (−)-*O*,*O*′-Di-*p*-toluoyl-(*R*,*R*)-tartaric Acid, and Reflections on an Alkylation Reaction; Comment on an Article by Elati et al.

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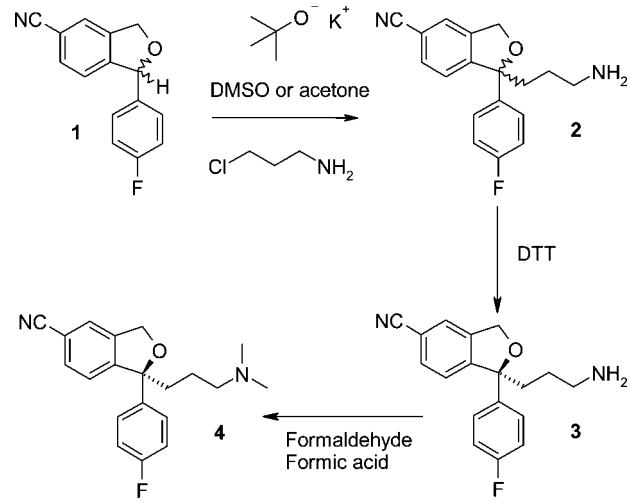
Abstract:

A recent article by Elati et al. (Elati, C. R.; Kolla, N.; Vankawala, P. J.; Gangula, S.; Chalamala, S.; Sundaram, V.; Bhattacharya, A.; Vurimidi, H.; Mathad, V. T. *Org. Process Res. Dev.* 2007, *11*, 289−292) describes the synthesis of escitalopram by means of a three-step process: (i) an alkylation reaction to provide didesmethylcitalopram, (ii) resolution of didesmethylcitalopram by classical resolution using (−)-*O*-*O*′-di-*p*-toluoyl-(*R*,*R*)-tartaric acid (DTT) as the chiral acid, and (iii) dimethylation of the resolved product to give escitalopram. However, they also mention resolution of citalopram itself by classical resolution, again using DTT as the chiral acid. We have been unable to reproduce their resolution of citalopram, obtaining only racemic or nearly racemic material. In order to better understand the system, we constructed two ternary solubility diagrams from solubility data at different temperatures. The resultant isotherms show the presence of a solid solution across the majority of the diagram in the temperature range 0−25 °C. This finding was in agreement with data from X-ray diffractograms. In addition, the solubility of the desired (*S*)-citalopram·DTT salt was found to be a factor of 5 higher than that of the corresponding *R*/*S* double addition salt. Furthermore, kinetics studies have indicated that the formation/crystal growth of the *R*/*S* double addition salt is preferred/faster than that of the desired (*S*)-citalopram·DTT salt. Taken as a whole, our findings show that resolution is not possible in any practical sense in the system described by Elati et al. Furthermore, we believe that detailed examination of their alkylation procedures casts doubt on their reproducibility.

Introduction

A recent article by Elati et al.[1] describes the synthesis of escitalopram by means of a three-step process: (i) an alkylation reaction to provide didesmethylcitalopram **(2)**, (ii) resolution of didesmethylcitalopram by classical resolution using (−)-*O*-*O*′-di-*p*-toluoyl-(*R*,*R*)-tartaric acid (DTT) as the chiral acid, and (iii) dimethylation of the resolved product to give escitalopram (**4**) (Scheme 1).[1] However, they also mention (and provide experimental details for) a resolution of citalopram itself by classical resolution, again using DTT as the chiral acid, albeit in low yield (36 %, calculated relative to theoretical, which is half racemate) and after multiple recrystallizations (Scheme 2). This latter finding was of particular interest to us, as we have attempted many resolutions of citalopram using DTT in the past without success, and were both surprised and interested in their report. We describe herein our efforts to repeat the reported process. In addition, we would like to comment on the alkylation reaction which is the first step in their reported synthesis of escitalopram. Although alkylation reactions on such phthalanes are well-known, there are elements of the reported reaction that we believe give cause for closer inspection and concern.

Scheme 1. **Alkylation of phthalane (1)[a] to give racemic didesmethylcitalopram (2), followed by classical resolution using DTT to give (*S*)-didesmethylcitalopram (3), with subsequent dimethylation to give escitalopram (4)**



[a] This alkylation reaction was not described in detail in the paper by Elati et al.[1] but was instead described in a patent referred to in Elati et al.[1] There are three examples cited in the patent. In two examples DMSO was used as solvent, and in the other example acetone was used as solvent.

The following manuscript is therefore divided into two sections. The first deals with our attempts to repeat the reported resolution of citalopram, and the second discusses certain aspects of the reported alkylation reaction.

Attempted Resolution of Citalopram: Background and Initial Experiments. According to the procedure of Elati et al.,[1] acetonitrile solutions of citalopram and DTT (as the monohydrate) were mixed and heated to 70−75 °C, whereupon methanol was added in order to give a clear solution, and the

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(1) Elati, C. R.; Kolla, N.; Vankawala, P. J.; Gangula, S.; Chalamala, S.; Sundaram, V.; Bhattacharya, A.; Vurimidi, H.; Mathad, V. T. *Org. Process Res. Dev.* **2007**, *11*, 289.

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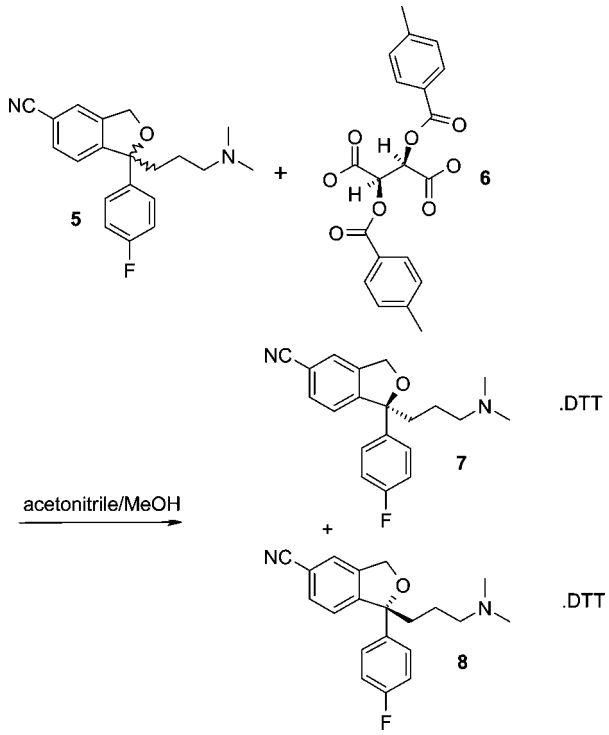
Scheme 2. **Resolution of citalopram (5) using DTT (6) to give the diastereomeric salts (7) ((*S*)·DTT) and (8) ((*R*)·DTT) according to Elati et al.**[1]



solution was cooled first to room temperature, and then to 0−5 °C. After 1−1.5 h this slurry was filtered to give a solid. According to their procedure, this recrystallization/crystallization was repeated two more times in order to give a yield (calculated relative to theoretical, which is half of the starting racemate) of 36% (*i.e.* 18 % yield relative to starting racemic citalopram), with an "optical purity" of the free base of 98.4% (corresponding to an ee of 98.4 % or 96.8 %, depending on the definition of "optical purity"). It should be emphasized here that the yield obtained by Elati et al.[1] in grams and percent implies that the citalopram·DTT salt was formed in a molar ratio of 1:1, which is consistent with the stoichiometry implied in the formula in the Experimental Section. There was no mention of solvates, so the assumption was that it was not present as a solvate. In our hands, working on precisely the same scale (and using DTT as the monohydrate), the ratio between the two citalopram isomers after the first crystallization was approximately 54.4: 45.6, and after this crystallization procedure was repeated two more times (after their procedure), we obtained a yield (calculated in the same manner as used by Elati et al.,[1] *i.e.* calculated relative to theoretical, which is half of the starting racemate) of approximately 120 % (*i.e.* 60 % yield relative to starting racemate), with the (*S*)- and (*R*)-isomers of citalopram present in a ratio of ∼56:44 (ratios for the first, second, and third crystallizations thereby approximately 54.4:45.6, 55.7:44.3, and 56.2:43.8, respectively, corresponding to ee values of 8.8, 11.4, and 12.4 %, respectively). This demonstrates both that a single crystallization was not effective and that a number of subsequent crystallizations did not lead to a dramatic improvement.

We attempted also a number of single crystallizations where the hot solutions were seeded with either (*S*)-citalopram·DTT (**7**, (*S*)·DTT) or (*R*)-citalopram·DTT (**8**, (*R*)·DTT). For these experiments, seed crystals (also present in a stoichiometry of 1:1, and were not solvates, as determined by ^{1}H NMR) were first produced from pure (*S*)-citalopram and (*R*)-citalopram, which in turn had been obtained using other methods. In the seeding experiments, the hot acetonitrile/methanol solutions were allowed to cool slowly, with heavy seeding with every drop in temperature of 5 °C until it was apparent that solid remained in the flasks. No significant differences were observed between the experiments with and without seeding (the highest isomeric ratios observed were ∼55:45). ^{1}H NMR analysis of all of the samples (both of the seed crystals and products of the crystallizations) indicated that the salts were formed with 1:1 stoichiometries between citalopram isomers:DTT, and were not present as solvates.

Physicochemical Characterization of the Resolution System. With such a dramatic difference between the reported findings and our own experiments, we initiated a more detailed physicochemical characterization of the crystallization process. First, we prepared a sample containing racemic citalopram and DTT in a ratio of 1:1 ((*rac*)·DTT). For this we dissolved equimolar amounts of racemic citalopram and DTT in isopropanol at reflux, and then allowed the solution to cool. A heavy precipitation occurred. The solution was evaporated under reduced pressure to dryness and dried under vacuum. ^{1}H NMR analysis of this solid salt indicated that it, too, was present in a 1:1 stoichiometry and that it was not a solvate.

X-ray powder diffractograms were then acquired for the (*S*)·DTT, (*R*)·DTT, and (*rac*)·DTT samples (Figure 1). These indicated clearly that the (*rac*)·DTT sample was *not* simply a physical mixture of (*S*)·DTT and (*R*)·DTT but rather appeared to be isostructural with (*R*)·DTT.[2] This indicates strongly that in this crystallization process, the (*S*)·DTT and (*R*)·DTT exist as a double salt or solid solution.

The solubilities of these three salts were measured in the acetonitrile/methanol solvent mixture used for these "resolutions" as described in Elati et al.[1] The measured solubilities were 101 mg/mL for (*S*)·DTT, 103 mg/mL for (*R*)·DTT, and 18 mg/mL for (*rac*)·DTT (Table 1). This clearly demonstrates that in such a crystallization process, the (*rac*)·DTT salt will precipitate out much earlier than the other two salts, and thus gives an explanation for the failure of this resolution process.

However, we were intrigued by the apparent similarity in the crystal structures of (*rac*)·DTT and (*R*)·DTT, so we performed a further set of solubility experiments over a range of different ratios of (*S*)- and (*R*)-citalopram (*S*:*R* 90:10, 75:25,

(2) That (*rac*)·DTT and (*R*)·DTT can be isostructural is because that, although the (*S*)- and (*R*)-citalopram enantiomers are quite distinct structurally, significant overlap of gross structural features is possible. As an illustration of this point, it has been observed that the single-crystal X-ray structures of (racemic) citalopram oxalate and (*S*)-citalopram oxalate are extremely similar (isostructural). Examination of the racemic structure reveals that the (*S*)- and (*R*)-isomers are symmetrically placed around the oxalate. Comparison with the (*S*)-citalopram structure reveals that the overall structure is essentially the same, but with the (*R*)-citalopram molecules replaced by rotated (*S*)-citalopram molecules. More specifically, the fluorophenyl group of one isomer is mapped onto the isobenzofuran aromatic ring of the other isomer, but the isobenzofuran oxygen atoms and the basic nitrogen atoms are situated more or less in the same positions in the two enantiomers. (Lopez de Diego, H. et al., manuscript in preparation). Comparison of these findings to the current case of resolution of citalopram may offer a deeper explanation as to why the resolution is not effective.

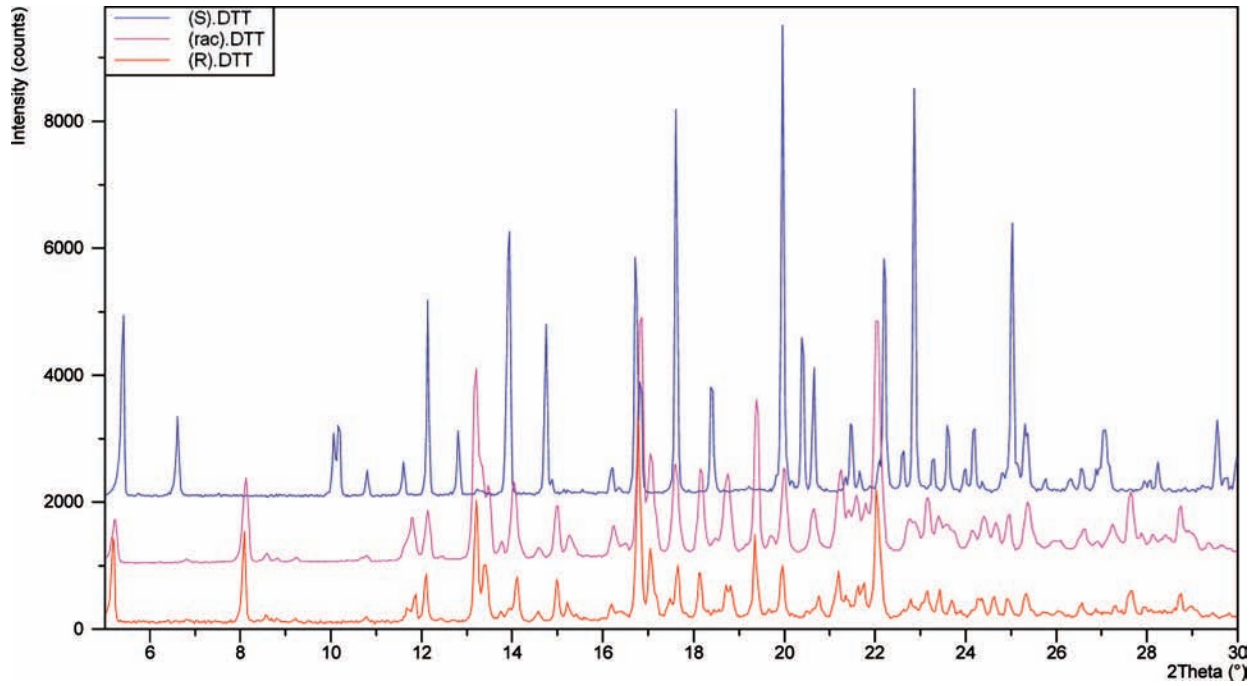


Figure 1. **X-ray diffractographs of the salts 7 ((*S*)·DTT), (*rac*)·DTT, and 8 ((*R*)·DTT). (*rac*)·DTT and 8 ((*R*)·DTT) appear to be isostuctural, whereas 7 ((*S*)·DTT) is distinctly different.**

Table 1. **Solubilities of salts formed between citalopram and enantiomers with DTT in acetonitrile/methanol (93:7 v/v)**

			solution ratio (w/w %)		
entry	salt	solubility (mg/mL)	*S*	*R*	solvent
1	(*S*)·DTT	101	12.8	0.0	87.2
2	(*rac*)·DTT	18	—	—	—
3	(*R*)·DTT	103	0.0	13.0	87.0

50:50, 25:75, 10:90). For each of these experiments, the appropriate mixture of citalopram isomers (1 g) was dissolved in a mixture of acetonitrile (9.3 mL) and methanol (0.7 mL). DTT monohydrate (1.0 equiv) was added as a solid to each solution, and the solid was dissolved. The reaction vessels were sealed tightly and were allowed to stir for 6 days at 25 °C in order to obtain thermodynamic equilibrium. After 24 h, it was observed that a precipitate had formed in all of the reactions. After 6 days, stirring was stopped, and the precipitates were allowed to settle. A sample of each of the clear solutions was removed for concentration determination and *S*:*R* ratio determination. The remainder of each of the samples was filtered, and yields and *S*:*R* ratios were obtained from them. From these data (Table 2) and the solubilities of the pure diastereomeric salts, a ternary phase diagram was constructed (Figure 2).

This phase diagram illustrates a number of interesting points. First, the shape of the solubility curve shows that the eutectics are very close to the laterals of the diagram. Second, the tie-line for the (*rac*)·DTT ends so close to 50% composition that resolution is effectively impossible for the first crystallization. Finally, the five tie-lines indicate the presence of a solid solution over the vast majority of the phase diagram, which may be explained by the isostructurality between the (*rac*)·DTT and (*R*)·DTT. X-ray powder diffractograms of these five solids, as well as of the pure diastereomeric salts are displayed in Figure 3. They show that the only precipitate among the five, with content of crystalline (*S*)·DTT detectable with XRPD, is from

Table 2. **Thermodynamic partitioning of (3) ((*S*)·DTT) and (4) ((*R*)·DTT) between solid and solution for different starting ratios of (*S*)-citalopram and (*R*)-citalopram at 25 °C, using acetonitrile/methanol (93:7 v/v) as solvent**

	initial (*S*)·DTT:(*R*)·DTT ratio (w/w %)[a]		final solid ratio (w/w %)		final solution ratio (w/w %)		
entry	*S*	*R*	*S*	*R*	*S*	*R*	solvent
1	90	10	84	16	12.8	0.3	86.9
2	75	25	68	32	9.1	0.3	90.6
3	50	50	51	49	1.4	1.4	97.2
4	25	75	40	60	0.2	11.8	88.0
5	10	90	36	64	0.4	18.0	81.6

[a] In the overall composition, the solvent is 77.9 w/w %.

the initial 90:10 mixture. Even the precipitate with composition 68:32 shows no sign of crystalline (*S*)·DTT. This further substantiates the formation of solid solutions in the major part of the (*S*)·DTT−(*R*)·DTT range.

Effect of variation of other parameters. What is the origin of the enormous disparity between our results and those of Elati *et al*? It is known that the transformation of an addition compound double salt to a resolvable eutectic type salt pair can occur with a variation in temperature.[3] The phase diagram in Figure 2 was constructed from solubility data collected at 25 °C, and since the final stirring and filtration described by Elati et al.[1] was conducted at 0−5 °C, there exists the possibility that the phase diagram in Figure 2 does not accurately reflect the composition of the attempted resolution. In addition, it could be expected that the conditions of the resolution could be quite sensitive to the presence or absence of water. In order to investigate these questions, we conducted a set of six experiments, varying both filtration temperature and water content of the solvents.

(3) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Wiley: New York, 1981.

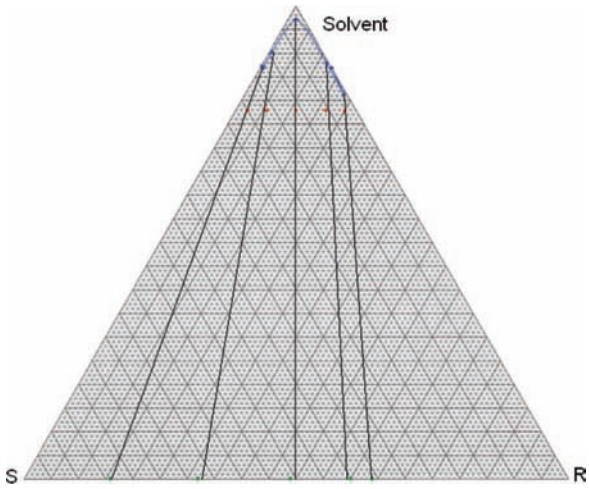


Figure 2. **Ternary phase diagram for crystallizations of citalopram and enantiomers as DTT salts from a mixture of acetonitrile and methanol (93:7 v/v) as solvent at 25 °C. The tie-lines indicate formation of solid solutions. This diagram was compiled from the data in Tables 1 and 2.**

In all experiments, dry (water content < 0.1 % v/v) acetonitrile and methanol were used, but to some experiments additional water (0.5 % v/v and 2 % v/v) was added. Anhydrous DTT was used in order to better observe differences between relatively wet and relatively dry conditions (for comparison, the use of DTT as the monohydrate in otherwise dry solvents is equivalent to ∼0.5 % v/v water). All reactions were carried out as described by Elati et al.[1] up to the point of cooling. All experiments were allowed to cool to 25 °C overnight, after which half of the experiments were filtered immediately, whereas the other half were cooled to 0−5 °C for 1−1.5 h.

The results of these experiments (Table 3) indicate that, although variations in temperature and water content gave rise to small variations in yield, the observed (negligible) resolution is essentially unchanged. In order to examine the effect of variation in filtration temperature more closely, we measured the solubilities of (*S*)·DTT, (*R*)·DTT, (*rac*)·DTT and various mixtures at 0−5 °C in a manner analogous to that used previously. The results are displayed in tabular form in Table 4, and in the form of a ternary phase diagram in Figure 4. X-ray powder diffractograms of the thus-obtained seven solids are displayed in Figure 5. None of the solids were present as solvates, as determined by TGA. The X-ray powder diffraction patterns show a number of new interesting features. The first is the emergence of a solid form of (*R*)·DTT which is distinct from (*rac*)·DTT. The other is of another solid form incorporating mostly (*S*)·DTT, but with some (*R*)·DTT, but which is still quite distinct from pure (*S*)·DTT. However, the isotherms for 25 °C and 0−5 °C are very similar (apart from the expected lower solubilities generally). Again, the tie-lines indicate that a solid solution was observed over the majority of the phase diagram, with the eutectics very close to the laterals in the diagram. These results indicate that thermodynamic resolution in the temperature range 0−5 °C is still not a practical possibility.

This does not rule out kinetic effects, although our earlier experiments using seeding with (*S*)·DTT, (*R*)·DTT, or (*rac*)·DTT did not show any significant variation with seeding method. However, there remains the possibility that other, more sensitive kinetic factors are important. To that end we examined the different time intervals involved in the crystallization experiment.

According to the experimental details in Elati et al.,[1] a clear solution is obtained after the addition of methanol at 70−75 °C. This was also consistent with our observations and implies that time intervals up to this point are not important, as at this point everything was completely in solution. There follow three distinct time periods: (a) "slow" cooling from 70−75 °C to room temperature, (b) cooling from room temperature to 0−5 °C over an undefined time, and (c) 1.0−1.5 h at 0−5 °C. The last time interval is well-defined, and although time interval (b) is not precisely defined, we believe that a reasonable reading of the text "After cooling the flask to 0−5 °C" is that the mixture was cooled relatively quickly using an ice−water bath or similar. However, the first time period, (a), is somewhat undefined. The term "slowly" will, of course, be somewhat dependant on scale (and on what scale one is used to working on). However, with a total working volume of ∼300 mL (as is the case in this example), it is probably reasonable to interpret "slowly" as being somewhere between 1−4 h. In the set of six experiments designed to probe the effect of temperature and water content (Table 3), the solutions were allowed to cool to 25 °C overnight (an effective cooling time of approximately 10 h). It is conceivable that if the cooling time is critical, then this time period could be too long. With that in mind, we performed a set of 4 experiments, where this cooling temperature was varied (using cooling times of 10 min, 45 min, 2 h, and 6 h). With all samples, the time and temperature at which precipitation occurred was noted. In all cases the mixtures were stirred at 0−5 °C for 1.5 h and then filtered cold. The monohydrate of DTT was used for these experiments. The results from this set of experiments are summarized in Table 5.

Kinetic Investigations. The principal result from this set of experiments was that the ratios between the citalopram enantiomers in the diasteromeric salts are essentially unchanged with variation in final temperature and moisture content (*i.e.* ∼*S*:*R* 55:45). However, it is also noteworthy that there was also observed a very large variation in yield (25−44 g) following no obvious trend. This indicates that under these conditions, kinetic factors have far more control over the outcome of the precipitation than purely thermodynamic factors. The maximum expected yield with stirring at 0 °C (derived from the solubility data in Table 4) would be expected to be around 51 g, so it is clear that equilibrium has not yet been established in this time frame (i.e. up to approximately 7 h). In comparison, the much longer stirring times used for the experiments shown in Table 3 (entries 1−3; approximately 15 h in total) gave higher yields (45.6−50.7 g). On the basis of this data, it appears likely that the rates of nucleation and crystal growth are also important factors determining the outcome of this precipitation. Therefore, despite the considerable differences in solubilities between (*S*)·DTT and (*rac*)·DTT, there remains the possibility that heavy seeding with (*S*)·DTT may allow preferential nucleation and growth of (*S*)·DTT over (*rac*)·DTT.

To this end, we conducted a further set of seeding experiments (again, using the monohydrate of DTT). Three portions

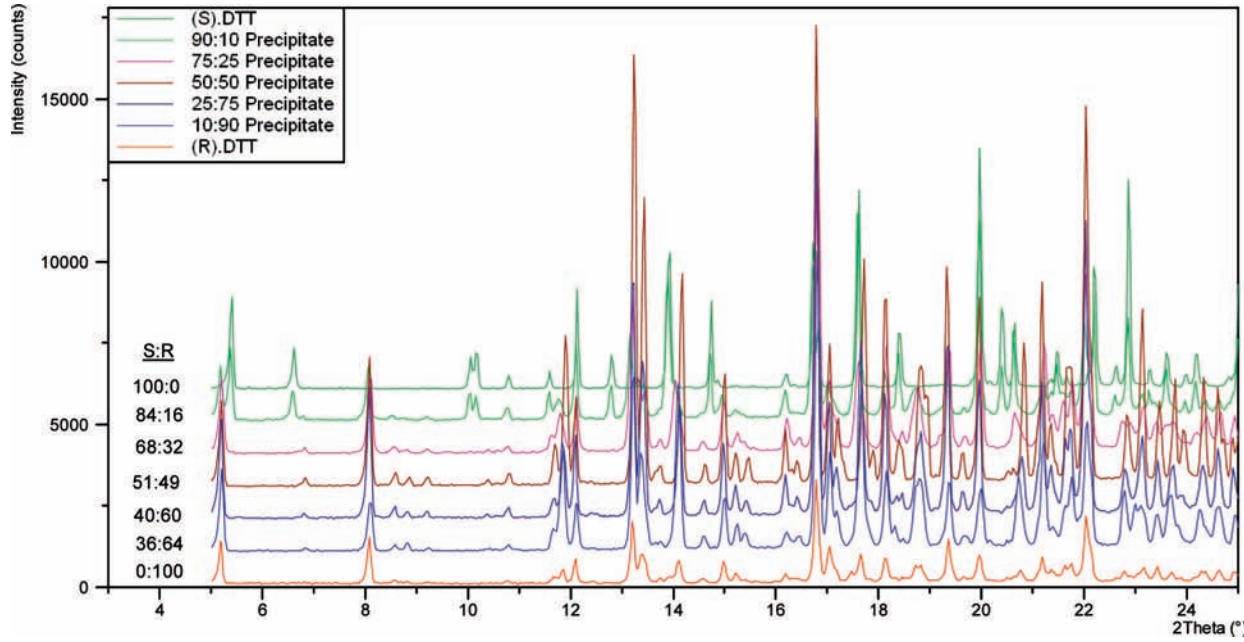


Figure 3. **X-ray diffractograms of the solids from entries 1−5 in Table 2, with (*S*)·DTT and (*R*)·DTT for comparison. It is clear that the (*R*)·DTT/(*rac*)·DTT structure pervades the majority of the diagram, and it is only in entry 1 where there is any sign of (*S*)·DTT in the formed solids.**

Table 3. **Effect of varying filtration temperature and solvent water content on the course of the resolution**

entry	water content in solvent (v/v%)	filtration temperature (°C)	yield (g)	yield (%)[a]	*S*:*R* ratio of the citalopram enantiomers in the filtered salts[b]
1	<0.1	0	50.7	180	52:48
2	0.5	0	45.6	162	52:48
3	2	0	49.0	173	52:48
4	<0.1	20	48.4	171	51:49
5	0.5	20	48.3	171	51:49
6	2	20	46.2	164	51:49

[a] Calculated relative to theoretical, which is half of the starting racemate. [b] As measured by analytical chiral HPLC.

Table 4. **Thermodynamic partitioning of (3) ((*S*)·DTT) and (4) ((*R*)·DTT) between solid and solution for different starting ratios of (*S*)-citalopram and (*R*)-citalopram at 0−5 °C, using acetonitrile/methanol (93:7 v/v) as solvent**

	initial (*S*)·DTT:(*R*)·DTT ratio (w/w %)[a]		final solid ratio (w/w %)		final solution ratio (w/w %)		
entry	*S*	*R*	*S*	*R*	*S*	*R*	solvent
1	100	0	100	0	10.5	0	89.5
2	90	10	89	11	12.9	0.4	86.7
3	75	25	68	32	7.9	0.2	91.9
4	50	50	52	48	0.6	0.5	98.9
5	25	75	30	70	0.2	4.6	95.2
6	10	90	13	87	0.2	4.6	95.2
7	0.6	99.4	0	100	0.6	8.4	91.0

[a] In the overall composition, the solvent is 77.9 w/w %.

were cooled from 70−75 °C to 25 °C over 4 h. For the first portion, seeding with (*S*)·DTT commenced at 70 °C, for the second at 40 °C, and for the third no seeding was performed at all. Although in both of the first two cases seeding was begun at a temperature where all (*S*)·DTT should dissolve (and therefore not logical from a purely thermodynamic point of view), we chose to seed aggressively so as to be sure that in both cases the predominant seed crystals available when the solution approached the metastable zone were (*S*)·DTT.

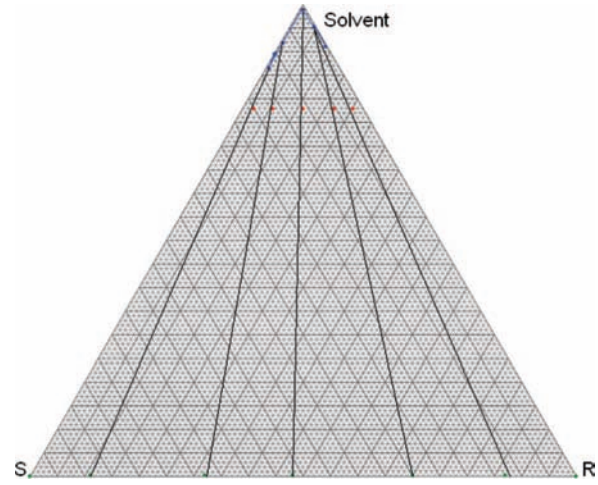


Figure 4. **Ternary phase diagram for crystallizations of citalopram and enantiomers as DTT salts from a mixture of acetonitrile and methanol (93:7 v/v) as solvent at 0−5 °C. The tie-lines indicate formation of solid solutions. This diagram was compiled from the data in Table 4.**

Therefore, in each of the first two cases, seeding was continued until precipitation began. The results are summarized in Table 6.

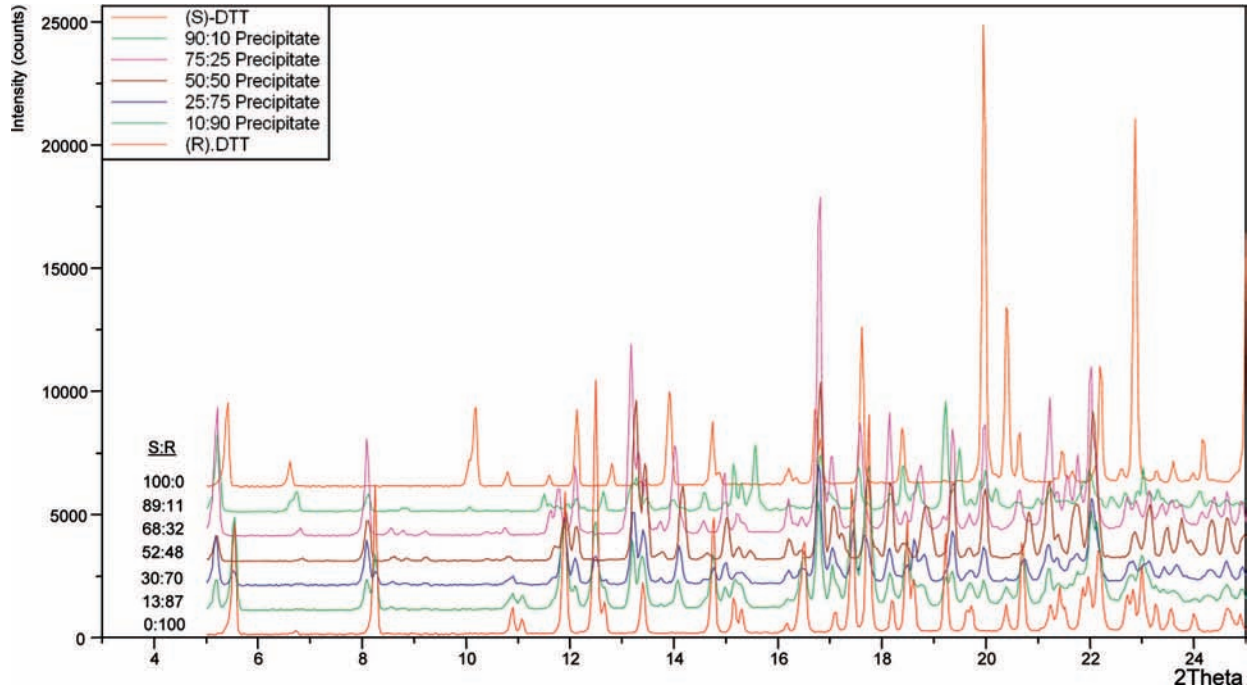


Figure 5. **X-ray diffractograms of the solids from entries 1−7 in Table 4. It is clear that the (*rac*)·DTT structure pervades the majority of the diagram.**

Table 5. **Effect of variation of cooling time (from 70 °C to 25 °C) on the course of the resolution using acetonitrile/methanol (93:7 v/v) as solvent[a]**

entry	cooling time (70 °C to 25 °C, min)	onset of crystallization[b] temperature (°C)	onset of crystallization[b] time (min)[c]	yield[d] (g)	yield (%)[e]	*S*:*R* ratio of the citalopram enantiomers in the filtered salts[f]
1	10	1	30	44	156	53:47
2	45	1	70	25	89	55:45
3	120	30	90	43	153	55:45
4	240	32	310	32	114	55:45

[a] All experiments were performed using 25 g citalopram, and DTT was used as the monohydrate. [b] After cooling to 25 °C, all experiments were cooled to 0−5 °C, and stirred at that temperature for 85 min. [c] The time is taken from the commencement of cooling from 70 °C. [d] The experiments were filtered at 1 °C and dried under vacuum. [e] Calculated relative to theoretical, which is half of the starting racemate. [f] As measured by analytical chiral HPLC.

Table 6. **Effect of variation of seeding temperatures during cooling on the course of the resolution using acetonitrile/methanol (93:7 v/v) as solvent[a]**

entry	seeding temperatures during cooling to 25 °C (°C)	onset of crystallization[b] temperature (°C)	onset of crystallization[b] time (min)[c]	yield[d] (g)	yield (%)[e]	*S*:*R* ratio of the citalopram enantiomers in the filtered salts[f]
1	70-56-41-36-33-30	30	80	40	142	54:46
2	40-36-33-30-29-27	27	113	31	110	55:45
3	not seeded	30	80	42	149	54:46

[a] All experiments were performed using 25 g citalopram, and DTT was used as the monohydrate. Solutions were cooled to 25 °C over 4 h. [b] After cooling to 25 °C, all experiments were cooled to 0−5 °C, and stirred at that temperature for 85 min. [c] The time is taken from the commencement of cooling from 70 °C. [d] The experiments were filtered at 1 °C and dried under vacuum. [e] Calculated relative to theoretical, which is half of the starting racemate. [f] As measured by analytical chiral HPLC.

The same pattern as from the previous set of experiments was observed. Although the yields varied, the ratios between the diasteromeric salts were essentially the same. This indicates that it was extremely unlikely that seeding with (*S*)·DTT was capable of having a positive effect on the resolution.

There remains the possibility that the crystallization kinetics of (*S*)·DTT, (*R*)·DTT, and (*rac*)·DTT are such that there exists a critical time window where (*S*)·DTT has begun to crystallize, but before (*R*)·DTT or (*rac*)·DTT crystallize. This would not necessarily have been detected by our previous experiments. To this end, we conducted a series of experiments monitoring the time-course of the crystallization. For these experiments, solutions were prepared at 70−75 °C as described previously. A sample of the clear solution was then removed, diluted, and analyzed by both achiral and chiral HPLC. The solution was then allowed to cool to 25 °C, and thereafter to 0−5 °C, at which temperature it was stirred for ∼1 h. Throughout the cooling process, samples of the solution phase were removed, filtered rapidly (using a small filter fitted to a syringe; both syringe and filter were pre-warmed or -cooled to approximately the same temperature as the solution), diluted, and again analyzed by both chiral and achiral HPLC. From these data it was possible to construct plots of quantities of (*S*)-citalopram

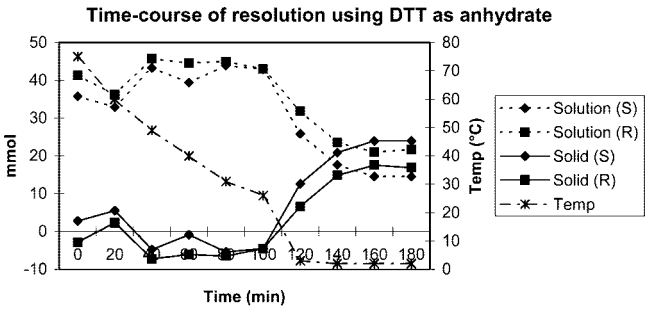


Figure 6. **Time course for crystallization using anhydrous DTT, and with cooling from 70 °C to 25 °C over 100 min.**

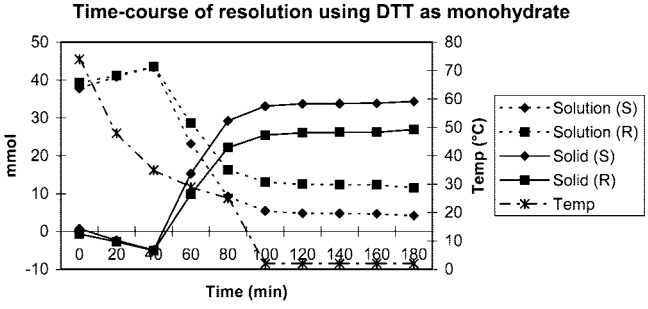


Figure 7. **Time course for crystallization using DTT as the monohydrate, and with cooling from 70 °C to 25 °C over 80 min.**

and (*R*)-citalopram in solution and, by difference, quantities of precipitated (*S*)·DTT and (*R*)·DTT.[4]

In the first experiment, DTT was used anhydrous, and the solution was cooled to 25 °C over 100 min. The solution was then cooled to 2−3 °C and was stirred at that temperature for 1 h. The results can be seen in graphical form in Figure 6. There is some noise in the signal up to 40 min (arising from the technical/practical difficulties involving removing, filtering, and diluting samples at elevated temperatures without precipitation of solids or evaporation of liquids), but otherwise the trends are clear. Precipitation begins around cooling from 25 °C to 2−3 °C, and the ratio between (*S*)-citalopram and (*R*)-citalopram in the precipitated material is fairly constant, i.e. there are no time intervals in the graph where a significant precipitation of reasonably pure (*S*)·DTT occurs. The second experiment was essentially performed in a manner identical to that of the first, with the single exception being that DTT was used as the monohydrate. The results can be seen in Figure 7. In this case, precipitation began in the temperature interval 35−29 °C, but apart from this, the results from the two experiments were extremely similar. It is also interesting to note that, despite the differences in temperature of onset of precipitation between these two experiments, the final ratios of enantiomers in the solids were very similar.

A final set of experiments was conducted in order to assess the effect of seeding on the crystallization. DTT was used as the monohydrate for all of these experiments. Three almost identical experiments were performed, one seeding with (*S*)·DTT, one with (*R*)·DTT, and one with (*rac*)·DTT. Seeding was started at 70 °C, and was continued at regular intervals until it was clear that precipitation had begun. In each case the mixtures were allowed to cool to 25 °C over 200 min. The mixtures were then cooled to 1 °C and were allowed to stir at that temperature for 1 h. The results of these experiments can

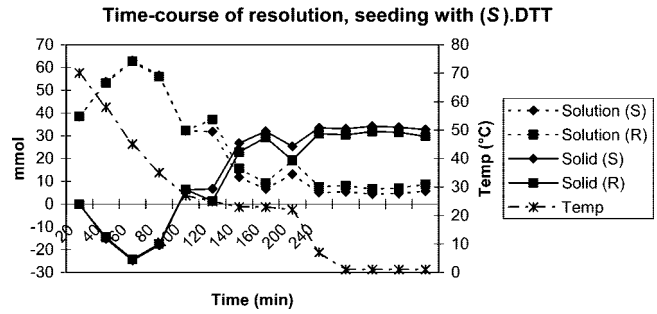


Figure 8. **Time course for crystallization using DTT as the monohydrate, seeding with (*S*)·DTT and with cooling from 70 °C to 25 °C over 200 min.**

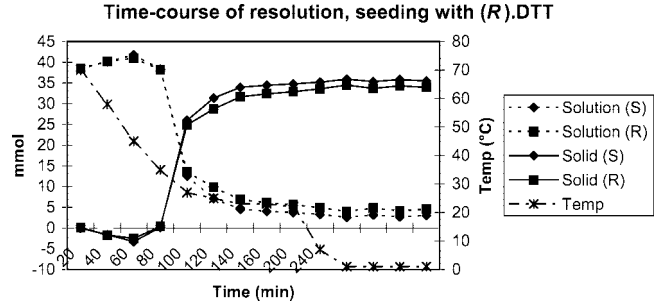


Figure 9. **Time course for crystallization using DTT as the monohydrate, seeding with (*R*)·DTT and with cooling from 70 °C to 25 °C over 200 min.**

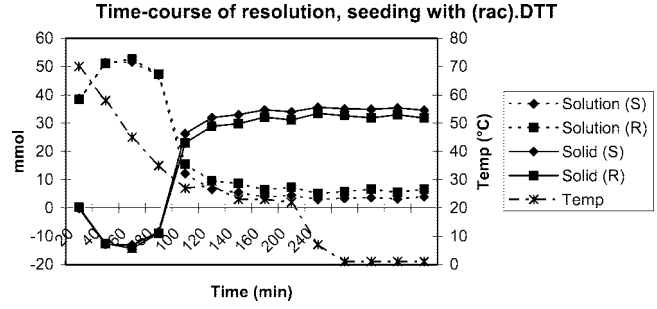


Figure 10. **Time course for crystallization using DTT as the monohydrate, seeding with (*rac*)·DTT and with cooling from 70 °C to 25 °C over 200 min.**

be seen in Figures 8, 9, and 10, for seeding with (*S*)·DTT, (*R*)·DTT and (*rac*)·DTT, respectively. All three graphs are remarkably similar in that there are no time intervals during the crystallizations where a significant precipitation of pure or mostly pure (*S*)·DTT occurs and that the products in all cases are close to racemic. However, there is a significant difference between the graphs for seeding with (*S*)·DTT on the one hand and seeding with (*R*)·DTT or (*rac*)·DTT on the other. In the case of (*S*)·DTT, the bulk (>70%) of the precipitation occured in the time interval 120−140 min (temperature 25−23 °C),

(4) It is of course not possible in this manner to distinguish between the double addition salt (*rac*)·DTT and a physical mixture containing equimolar quantities of (*S*)·DTT and (*R*)·DTT. For that matter, it would not be possible to distinguish between a solid solution containing (for example) 55 % (*S*)-citalopram and 45 % (*R*)-citalopram on the one hand, and a conglomerate containing approximately 10 % (*S*)·DTT and 90 % (*rac*)·DTT on the other. However, the purpose of the experiment was to try to detect time intervals in the precipitation process where (*S*)·DTT has precipitated out to a significant degree in a significant purity. Therefore, in this context, the precise composition of solid forms containing almost equimolar quantities of (*S*)- and (*R*)-citalopram is not relevant.

whereas in the other two cases the bulk of the precipitation occured earlier (time interval 80−100 min, temperature 35−27 °C). Given that there exist isostructural (*R*)·DTT and (*rac*)·DTT forms, it is not surprising that the curves for (*R*)·DTT and (*rac*)·DTT are essentially identical. These results therefore imply that (*rac*)·DTT was both the thermodynamic *and* kinetically favored product and that the only influence that seeding with (*S*)·DTT has on the precipitation was to slow the onset of crystallization of (*rac*)·DTT. Therefore, all of our results indicate that resolution of citalopram under the conditions described by Elati et al.[1] is not feasible (both due to thermodynamic and kinetic factors) in any meaningful, practical sense.

Discussion of the Alkylation Procedure Reported by Elati et al. Taken in perspective, it is also of interest to examine the synthesis of one of the key intermediates that this paper discusses, didesmethylcitalopram (**2**) (Scheme 1). The first mention of this compound is in a medicinal chemistry paper (Bigler et al.),[5] comparing the activities of over 50 related compounds, but apart from the statement that it was prepared via a method analogous to that of another compound, no experimental details or physical characterization was given (apart from the melting point of an oxalate salt). According to a search in Scifinder, the only published syntheses of compound **2** (up to the time of submission of the Elati et al.[1] paper) were (a) a process patent by essentially the same authors as in Elati et al.,[1] covering essentially the same subject matter as their article currently under discussion,[6] and (b) a group of other process patents using different synthetic routes.[5−8] In this context, it is perhaps surprising that the paper of Elati et al.[1] contains neither details of the synthesis of compound **2**, nor characterization of this (apparently) important intermediate (and particularly so in a journal dedicated to process research and development). Instead, they refer to their patent for experimental details.

There are three examples for this reaction step in the patent, and all deserve closer inspection. They all involve metallation of phthalane (**1**) with potassium *tert*-butoxide, with subsequent alkylation by 3-chloropropyl amine. The reaction in example 1 is performed in DMSO. A solution of potassium *tert*-butoxide (1.6 equiv) in DMSO was prepared at 60−65 °C, and then after cooling to 25−30 °C a solution of the phthalane (**1**) (1.0 equiv) is added. After 15−20 min a solution of 3-chloropropyl amine (12 g, 3.0 equiv) in DMSO (2.5 mL) was added, and the reaction proceeded. A yield of 80 % was reported. We would like to draw attention to the fact that 3-chloropropyl amine was explicitly added as the free base (and cannot be as the hydrochloride salt, as (a) there is insufficient base present to neutralize such an amount of a salt (12 g is equivalent to 2.2 equiv HCl salt, and 1.6 equiv base is added), and (b) the solubility of the hydrochloride salt is not nearly sufficient to allow the dissolution of *12 g* in *2.5 mL* of DMSO). According to a search in Scifinder, there is no published (patent or journal) procedure for the isolation of 3-chloropropyl amine *as the free base*. On the other hand, it would be expected that such a compound would be rather unstable as the free base. Indeed, the earliest report of this compound in the literature states that, although the 2- and 3-regional isomers of (diethylamino)propyl chloride could be separated by distillation (in order to analyze product distribution), "A similar separation of the addition products III and IV of allylamine and hydrogen chloride appeared hopeless, because of the instability of the chloropropylamines." (They resolved the problem of analysis through acidic hydrolysis of the hydrochloride salts.)[11] Again, in this context it is perhaps surprising that there was neither mention nor discussion of the isolation procedures for the handling of the free base of 3-chloropropyl amine in Elati et al.[1]

The second example of the alkylation reaction is particularly interesting. Whereas the first example describes subsequent metallation and alkylation of phthalane (**1**) in *DMSO*, the second example describes an almost identical procedure using *acetone* as solvent. More precisely, the first line of the procedure reads "A solution was prepared by adding 7.5 grams of potassium tertiary butoxide to acetone (40 ml) at 60−65°C under a nitrogen atmosphere." First, acetone has a boiling point of approximately 56 °C. Second, it would be expected that acetone would undergo aldol-type condensations in the presence of a strong base. Third, *Bretherick's Handbook of Reactive Chemicals*, 6th ed., cites the reaction of potassium *tert*-butoxide with acetone as hazardous.[12] Nonetheless, we attempted to repeat this example (on the same scale as reported in the patent). Upon addition of potassium *tert*-butoxide to acetone at reflux, a vigorous/violent reaction occurred, with the formation of a quantity of a white solid. Relatively little liquid remained. The phthalane (**1**) was added as described in the patent, but no sign of the intense red color typical of the metallated phthalane was observed (such a deep red color is seen clearly when DMSO is employed as solvent). When 3-aminopropyl chloride was added as a solution in dichloromethane,[13] no alkylation product was observed by HPLC although some alkylation is observed under these conditions when DMSO is used instead of acetone. A yield of 64 % is reported in the patent.

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(11) Kharasch, M. S.; Fuchs, C. F. *J. Org. Chem.* **1945**, *10*, 159–169.
(12) Urben, P. G., Ed. Pitt, M. J., Compiler. *Bretherick's Handbook of Reactive Chemical Hazards*, 6th ed.; Butterworth-Heinemann (Reed Elsevier plc group): Oxford, 1999; Vol. 1, pp 430, 551.
(13) In one of many attempts to obtain pure 3-aminopropyl chloride, we were able to extract some pure 3-aminopropyl chloride from a basic aqueous solution into dichloromethane. Attempts to remove the dichloromethane completely were unsuccessful (due to decomposition of the 3-aminopropyl chloride); however, useable (and at least transiently stable) solutions containing around 50 % w/w 3-aminopropyl chloride in dichloromethane could be isolated and used (w/w % was determined by ^{1}H NMR).

The first line of this procedure was repeated. After the vigorous reaction had subsided and the reaction mixture was allowed to cool to 25 °C, a sample of the remaining moist white solid was removed. It had an odor of higher ketones/alkenes, and analysis by NMR indicated that it was a complex mixture of products, with peaks consistent with condensation products of acetone.

The third example of alkylation in the patent (example 13) involves a two-step process. The first step describes the preparation of a toluene solution of 3-chloropropylamine via freeing the base from (apparently) the HCl salt by using a mixture of water, toluene, and sodium hydroxide (although it was stated in the example that the free base is used, it is likely that it was actually the HCl salt). A DMSO solution of the metallated phthalane was then prepared in a manner analogous to that of the first example, and then the toluene solution of the free base was added to this. It should be noted that (a) no attempt is made to dry the toluene solution prior to addition to the metallated phthalane and (b) no yields, purities, or product characteristics are reported for this example whatsoever.

Conclusions

In conclusion, in the cited article, the authors do not describe in detail the synthesis of one of the key intermediates (alkylation of phthalane (**1**) to give didesmethylcitalopram (**2**)) nor characterize the product, despite the dearth of experimental details in the published literature. Instead, the authors refer to a patent written by essentially the same authors, covering essentially the same subject matter (but still with no product characterization). This patent has three examples of this alkylation. The first example contains some serious issues of handling and safety (which are not mentioned in the article nor in the patent), the second example failed completely in our hands (we instead isolated as expected starting materials plus material consistent with condensation of acetone), and the in the third, no yields or purities were reported whatsoever.

More importantly, we have been unable to repeat the resolution of racemic citalopram (**5**) through the use of DTT (**6**) reported by Elati et al.[1] Physico−chemical analysis of the crystallization conditions they describe show the presence of a solid solution over the vast majority of the phase diagrams at both 25 °C and 0−5 °C. Variation of moisture content in the resolution solvents does not have a useful effect on the course of the resolution. Furthermore, time-course experiments indicate strongly that formation of a solid solution is preferred kinetically over formation of (*S*)·DTT. Taken together, these results show that resolution is not possible in any practical sense in the system reported by Elati et al.[1]

Experimental Section

General Methods. Acetonitrile (HPLC grade) and methanol (Anhydroscan) were purchased from LAB-Scan and were used without purification. DTT (both monohydrate and anhydrous) were purchased and were used without further purification. Chiral HPLC analyses were performed using a Chiralcel OD column (4.6 mm i.d., 250 mm) using a mixture of heptane/ethanol/diethylamine (98.4:1.5:0.1) as eluent. A flow rate of 1 mL/min was used at 30 °C with UV detection at 240 nm. Non-chiral HPLC analyses of reaction mixtures were performed using a Lichrosphere 100 RP-8e (5 μm) column (4 mm i.d., 250 mm) using a 50:50 (v/v) mixture of acetonitrile/water buffered to pH 3 with a triethylammonium phosphate buffer as mobile phase. A flow rate of 1 mL/min was used, with UV detection at 220 nm. NMR spectra were acquired on a Bruker Avance AV-500 spectrometer operating at 500.13 MHz for ^{1}H spectra and 125.77 MHz for ^{13}C spectra. Selected NMR spectra are available in the Supporting Information.

The concentrations of the saturated solutions were determined by HPLC using UV-detection at 235 nm. The solutions were diluted 500 or 1000 times and analyzed by RP-HPLC using a Xbridge C18, 3.5 μm, 4.6 mm × 150 mm column, and 25 mM phosphate buffer pH 6.0/acetonitrile (50:50) as mobile phase with column temperature of 45 °C and a flow of 1 mL/min. In this system, the citalopram top is found with retention time 2.4 min. The concentration was calculated against a standard solution of 0.1 mg/mL of the free base. The density of the solutions was determined at 0.79 g/mL, and from this value and the molar weight of the salt relative to the free base the concentration of the salt was calculated in w/w %.

X-Ray Powder Diffractograms. These were measured on a PANalytical X'Pert PRO X-Ray Diffractometer using Cu Kα_1 radiation. The samples were measured in reflection mode in the 2θ range 5−40° using an X'celerator detector.

Attempted Resolution of Citalopram with DTT after Elati *et al.* To a stirred mixture of citalopram **(5)** (25 g, 77 mmol) in acetonitrile (125 mL) was added a solution of DTT as the monohydrate (31.4 g, 77.7 mmol, 1.0 equiv) in acetonitrile (125 mL) dropwise. A homogeneous solution resulted. After 20 min a precipitate began to form. After a total of 35 min the solution was heated to 73 °C and thereafter methanol (20 mL) was added dropwise, and after a further 10 min a clear solution was obtained. The source of heating was removed and the solution was allowed to cool to 25 °C. After 1 h the mixture was cooled in an ice/water bath, and after a further 70 min the mixture was filtered, the residue was washed with acetonitrile (2 × 25 mL) and dried by suction on the filter. Analysis of a sample of the residue by chiral HPLC indicated that the citalopram enantiomers were present in a ratio of *S*:*R* 54.4:45.6. To this solid was added a mixture of acetonitrile (250 mL) and methanol (20 mL) and the mixture was heated to 73 °C. At this point all of the solid had dissolved. The solution was allowed to cool to 25 °C. After 40 min (T = 25 °C) the mixture was cooled in an ice/water bath, and after a further 60 min the mixture was filtered, and the residue was washed with acetonitrile (2 × 25 mL) and dried by suction on the filter. Analysis of a sample of the residue by chiral HPLC indicated that the citalopram enantiomers were present in a ratio of *S*:*R* 55.7:44.3. To this solid was added a mixture of acetonitrile (250 mL) and methanol (20 mL) and the mixture was heated to 74 °C. At this point all of the solid had dissolved. The solution was allowed to cool to 23 °C. After 40 min (T = 23 °C) the mixture was cooled in an ice/water bath, and held at that temperature for a further 70 min. The mixture was filtered, the residue was washed with acetonitrile (2 × 25 mL), and dried by suction on the filter. The solid was dried under vacuum to give a dry weight of 34.3 g (120 % based on maximum possible

yield of the pure diastereomeric salt) Analysis of a sample of the residue by chiral HPLC indicated that the citalopram enantiomers were present in a ratio of *S*:*R* 56.2:43.8.

Preparation of (*S*)·DTT and (*R*)·DTT. To a solution of (*S*)-citalopram (10.0 g, 30.8 mmol) in ethanol (100 mL) was added a solution of DTT as the monohydrate (11.9 g, 30.8 mmol) in ethanol (60 mL). The resultant solution was stirred for 2 h. No precipitation was observed, so the volume of the solution was reduced by evaporation under reduced pressure and was stirred overnight. A heavy precipitate occurred. Ethanol (20 mL) was added, and the mixture was filtered. The solid was dried first on the filter and then under vacuum at 40 °C to give (*S*)·DTT (19.2 g, 88 %) as a white solid.

A similar procedure was used to produce (*R*)·DTT (19.1 g, 87 %) as a white solid.

Attempted Resolution of Citalopram with DTT after Elati et al. A similar protocol to the first example above was used for the first crystallization, using citalopram (25 g, 77 mmol), DTT monohydrate (31.4 g, 77 mmol), acetonitrile (250 mL) and methanol (20 mL). Three experiments were conducted (a) no seeding upon cooling, (b) seeding with (*S*)·DTT at 68, 65, 55, 50, 45 and 40 °C during cooling after addition of methanol, and (c) the same as (b) above but with seeding with (*R*)·DTT instead. The yields and *S*:*R* ratios of the products after the first crystallizations were as follows: (a) 43 g (150 % relative to maximum yield of the pure diastereomeric salt), 55:45; (b) 49 g (170 %), 53:47; 30.6 g (94 %; some product lost in filtration), 52:48.

Preparation of (*rac*)·DTT. To a mixture of racemic citalopram (10 g, 30.8 mmol) and DTT monohydrate (11.9 g, 30.8 mmol) was added *iso*-propyl alcohol (50 mL) and the mixture was heated to reflux. The solids were completely dissolved shortly before reflux was obtained. Heating was discontinued and the resultant mixture was allowed to cool to 25 °C. The mixture was then evaporated under reduced pressure and dried under vacuum (50 °C) to give (*rac*)·DTT as a solid (21.9 g, 100 %).

Preparation of Samples (Solids and Liquids) for Solubility Measurements. Samples of citalopram enantiomers (1.0 g, 3.08 mmol; *S*:*R* 90:10, 75:25, 50:50, 25:75, 10:90) and DTT monohydrate (1.19 g, 3.08 mmol) were dissolved in a mixture of acetonitrile (9.3 mL) and methanol (0.7 mL) and stirred. All reaction tubes were sealed tightly with a septum, and a line was drawn on the outside of the tube to indicate the level of the solution. All of the samples generated a precipitate over the course of 24 h. The samples were stirred for a further 5 days. No change in the level of the solvent was detected. Stirring was stopped, and after the solutions were settled, small samples of the supernatant phases were removed for concentration determination. The remainder of the samples were then filtered, and the solids were dried under vacuum (50 °C). The yields obtained were 1.2 g, 1.4 g, 1.8 g, 1.2 g and 0.63 g respectively. The *S*:*R* ratios of the citalopram enantiomers in the solids and mother liquors were determined by chiral HPLC, and are reported in Table 2.

In a similar manner, solubilities of samples of citalopram enantiomers (*S*:*R* 100:0, 90:10, 75:25, 50:50, 25:75, 10:90, 0.6: 99.4) and DTT monohydrate were obtained for a temperature range 0−5 °C. The results are reported in Table 4.

Attempted Resolution of Citalopram with Variation in Temperature and Water Content. Six experiments were performed varying filtration temperature and water content of the solvents. Solvents were either dry (<0.1 % v/v as measured by Karl-Fisher titration), or contained 0.5 % v/v or 2 % v/v water. The general procedure is as follows. To a solution/suspension of citalopram (25 g, 77.1 mmol) in acetonitrile (125 mL) was added a solution of anhydrous DTT (31.4 g, 81.3 mmol, 1.05 eq) in acetonitrile (125 mL), and the resulting solution was stirred at 25 °C. After 10−15 min a white precipitate formed. The suspension was heated to 70 °C and methanol (20 mL) was added slowly, affording a clear solution. The solution was allowed to cool slowly to 25 °C overnight. 3 of the samples were then filtered at that temperature, whereas the other 3 were cooled to 0−5 °C for 1.5 h prior to filtration. The solids were dried under vacuum at 60 °C, and were not solvates as measured by TGA. The results are listed in Table 3.

Attempted Resolution of Citalopram with Variation in Rate of Cooling. Four experiments were performed varying the time taken to cool from 70 °C to 25 °C. The general procedure was as follows. To solutions/suspensions of citalopram (25 g, 77.1 mmol) in acetonitrile (125 mL) were added solutions of DTT monohydrate (31.4 g, 77.6 mmol, 1.01 eq) in acetonitrile (125 mL), and the resulting solutions were stirred at 25 °C. After 10−15 min white precipitates formed. The suspensions were heated to 70 °C and methanol (20 mL) was added slowly, affording clear solutions. The solutions were allowed to cool/cooled to 25 °C over either 10 min, 45 min, 2 h or 6 h. The samples were cooled to 0−5 °C for 75 min prior to filtration. The solids were dried under vacuum at 60 °C, and were not solvates as measured by TGA. The results are listed in Table 5.

Monitoring the Time Course of Precipitation. To a solution/suspension of citalopram (25 g, 77.1 mmol) in acetonitrile (125 mL) was added a solution of anhydrous DTT (31.4 g, 81.3 mmol, 1.05 equiv) in acetontrile (125 mL), and the resultant solution was stirred for 10−15 min. The resultant suspension was warmed to 70−75 °C, and methanol (20 mL) was added, giving a clear solution. A sample was removed and filtered, and than analyzed using both achiral and chiral HPLC. The solution was allowed to cool to 25 °C over 100 min, and thereafter to 2−3 °C. After 1 h the stirred suspension was filtered. From the point at which the solution was at 70−75 °C until filtration, small samples (∼500 μL) were removed, filtered, diluted, and analyzed by achiral and chiral chromatography. The results are displayed graphically in Figure 6.

The same procedure was repeated but with the use of DTT monohydrate (31.4 g, 77.1 mmol, 1.01 equiv). The results are displayed graphically in Figure 7.

Three additional similar experiments were conducted. They used a procedure similar to that used above, using DTT monohydrate (31.4 g, 77.1 mmol, 1.01 equiv), with cooling from 70 °C to 25 °C over 200 min, with subsequent cooling to 1 °C, and filtration of the stirred suspension after 1 h further. One example was seeded with (*S*)·DTT, one with (*R*)·DTT, and

one with (*rac*)·DTT. In each case, seeding was performed regularly until it was clear that precipitation was occurring. The results from these experiments are displayed graphically in Figures 8, 9, and 10, respectively.

Attempted Alkylation of Phthalane (1) in Acetone Using the Method of Example 2 from the Patent of Elati et al.[4] Acetone (40 mL) was heated to reflux. Potassium *tert*-butoxide (7.5 g, 66.9 mmol, 1.6 equiv) was added carefully portionwise. A violent/vigorous reaction ensued with the addition of each portion, and a strong odor of higher ketones/alkenes was noticed. An amount of a white solid was produced. The mixture was allowed to cool to 25 °C. A solution of phthalane **(1)** (10 g, 41.8 mmol, 1.0 equiv) in acetone (35 mL) was added dropwise over 10−15 min, and the solution was then stirred for a further 20 min. No sign of the characteristic deep red color of the phthalane anion was observed. A solution of 3-chloropropyl amine in dichloromethane (23 g of a 52 % w/w solution in dichloromethane, 125 mmol, 3.0 equiv) and acetone (2.5 mL) was added in one portion. No exotherm was observed. The temperature was increased to 45 °C, and the reaction was stirred at that temperature for 1 h. Analysis of the reaction mixture by HPLC indicated that phthalane **(1)** remained essentially unreacted, and there was no sign of the reported didesmethylcitalopram **(2)**.

The same procedure was repeated up to and including the addition of potassium *tert*-butoxide. At this point, the mixture was allowed to cool to 25 °C, and water was added. The pH was adjusted to 2 with an aqueous solution of hydrogen chloride (first 1 M, then 4 M). This water phase was extracted with diethyl ether. This organic phase was then dried over magnesium sulfate, and then the solvent was removed under reduced pressure to give an oil. NMR analysis (^{1}H, ^{13}C, COSY, HMBC, HSQC) of this oil indicated a complex mixture of products.

Supporting Information Available

Comparison of ^{1}H NMR spectra from the attempted resolution with those from standards of (*S*)·DTT, (*R*)·DTT, and (*rac*)·DTT; comparison of ^{1}H NMR spectra of the three attempted resolutions with (a) no seeding, (b) seeding with (*S*)·DTT, and (c) seeding with (*R*)·DTT; ^{1}H and APT spectra of the residue isolated after addition of potassium *tert*-butoxide to hot acetone. This material is available free of charge via the Internet at http://pubs.acs.org.

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