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Study of the Mechanism of Optical Resolutions Via Diastereoisomeric Salt Formation Part 4. The Role of the Crystallization Temperature in Optical Resolution of Pipecolic Acid Xylidides

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STUDY OF THE MECHANISM OF OPTICAL RESOLUTIONS VIA DIASTEREOISOMERIC SALT FORMATION PART 4*
THE ROLE OF THE CRYSTALLIZATION TEMPERATURE IN OPTICAL RESOLUTION OF PIPECOLIC ACID XYLIDIDES

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Abstract The role of the crystallization temperature was investigated during the optical resolutions of some pipecolic acid xylides by 2R,3R-tartaric acid and O,O-dibenzoyl-2R,3R-tartaric acid. In 4 cases from 5 the temperature optimum of the crystallization was found between 45-50 °C, which is much higher than the usual crystallization temperature. A few trial resolutions may be enough to determine the temperature optimum of the crystallization graphically.

INTRODUCTION

The optical resolution of racemates via diastereoisomeric salt formation is the most frequent way for the production of the optically active form of a chiral molecule.[1] In spite of the growing interest of the pharmaceutical industry for this process, we still do not know much more about the resolution than in the time of Pasteur, who invented the process. The resolution processes are usually developed by trial and error method, no general rules have been recognised concerning the governing factors of the process.[2,3]

Several thousand papers have been published on optical resolutions, but unfortunately most of them describe only the preparative processes, very few of them containing detailed comparable physico-chemical data on optical resolutions or on diastereoisomeric salt pairs taking part in the resolution.[2-4]

In this series of papers we perform comparative investigations on optical resolutions, to collect a comparable data base, which hopefully may facilitate the development of optical resolutions via diastereoisomeric salt formation.

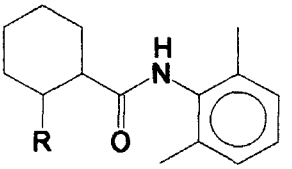
* Part 3. D.Kozma, E. Fogassy, Two Consecutive 1:X Double Salt Formation during an Optical Resolution via Diastereoisomeric Salt Formation, submitted to Mol.Cryst.Liq.Cryst.

A large number of parameters influence the resolution process, but most of them have never been investigated systematically.

The diastereoisomeric salts formed between the racemate and the resolving agent are separated by fractional crystallization. The crystallization temperature is usually selected to be as low as can be easily achieved. In most of the resolutions the precipitated salt is crystallized and filtrated from the resolution mixture between 5-20 °C.[5] In this paper we investigate the role of the temperature of the crystallization during resolutions, since in our previous practice we experienced that sometimes exceptionally high or low crystallization temperature can increase the efficiency of the resolution.

RESULTS AND DISCUSSION

The resolution of racemic 1-5 were selected for the model investigations.



	R
1	hydrogen
2	methyl
3	ethyl
4	n-propyl
5	n-butyl

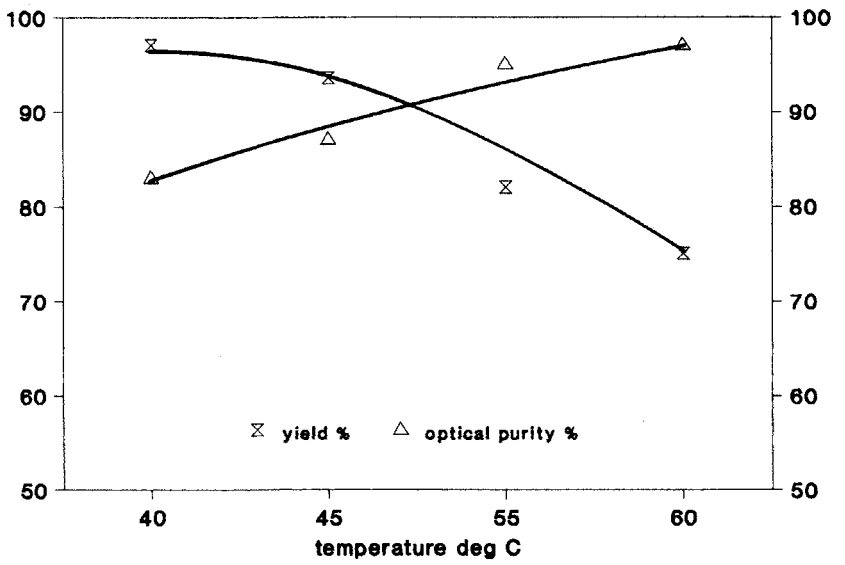
These compounds are local anaesthetics, their useful biological activity is supposed to reside in one of the enantiomer.[6,7] The homologues with shorter alkyl chain (R= H, Me, Et) can be resolved by O,O-dibenzoyl-2R,3R-tartaric acid (DBTA), while the higher homologues (R= Pr, Bu) can be resolved only by 2R,3R-tartaric acid (TA).[7-9] For the investigation of the role of the crystallization temperature, resolution experiments were performed on 3-5 different temperatures for all the five model compounds. The results are summarised in Table 1. At each temperature the yields of the precipitates were different, and the optical purity also changed. A trend can be observed: by increasing the temperature the yield of the precipitate is decreasing, while the optical purity of the precipitate is increasing. To facilitate the selection of the optimal crystallization temperature the yield and the optical purity data versus temperature data were plotted on the same diagram. Such a diagram is illustrated on Figure 1. The intersections of curves fitted to the measured points result the temperature optimum of the crystallization.

Table 1. The results of the resolution experiments at different temperatures

Racemate	Resolving agent	Temperature °C	Yield %	Optical purity %
1	DBTA	23	98	72
		25	96.5	77
		35	86	85
		52	75.5	96
	Optimum	45	83	83
2	DBTA	40	97	83
		45	93.5	87
		55	82	95
		60	75	97
	Optimum	50	91	91
3	DBTA	35	125	84
		50	64	95
		62	34	98
	Optimum	48	84	84
4	TA	20	98	63
		25	97	70
		35	95	82
		40	92	87
		60	70	98
	Optimum	50	87	87
5	TA	-10	99	52
		0	80	72
		5	67	83
		13	50	92
		18	43	96
	Optimum	5	69	69

By the comparison of the temperature optimum of the crystallization, it can be seen, that in four cases from five the temperature optimum of the crystallization is higher than 45 °C, which is much higher than the usual 5-20 °C crystallization temperature used in optical resolution experiments. The optimal crystallization temperature was under room temperature only for the resolution of racemic 5 by TA. 5 is the highest alkyl homologue of this series of compounds and the efficiency of the resolution is the lowest at this resolution. We considered the difference between the optimal crystallization temperatures unexpectedly high, for example between the resolution of 4 and 5, which model compounds differ only in the length of the alkyl chain (n-propyl, n-butyl). At the later resolution TA was used as resolving agent and iso-propanol as solvent, but they can not be responsible for the low optimal crystallization temperature, since they were used in other resolutions at which the temperature optimum of the crystallization was much higher.

Figure 1. The change of the yield and the optical purity of the precipitate in function of temperature during optical resolution of mepivacaine (2) by DBTA



CONCLUSION

As a conclusion of this study we can state that is it not worth decreasing the crystallization temperature just to increase the yield, since it may be accompanied by a substantial decrease in optical purity of the precipitate. Instead of it we can suggest to

perform some trial resolutions at different temperatures. Two or three trials may be enough to determine the optimal crystallization temperature graphically. According to our experience this simple optimization of crystallization temperature is worth while not only at industrial but in lab scale resolutions too, when for example only 5-10 g of the pure enantiomer should be prepared.

EXPERIMENTAL

The boiling solution of the racemic base was added dropwise to the boiling solution of the resolving acid. The transparent solution was left to cool back to the crystallization temperature and kept at that temperature for two hours under effective stirring. The precipitate was filtered off on a thermostated filter and dried. The optical purity of the precipitated salts was checked by the measurements of the specific rotations of bases , liberated from the salts by treatment with ammonium hydroxide.

The following specific rotation values were considered as 100 % optical purity:

1 $[\alpha]_D^{20} = 43.2$ (c: 2.3; 1N HCl)

2 $[\alpha]_D^{20} = 63.0$ (c: 5; MeOH)

3 $[\alpha]_D^{20} = 51.2$ (c: 2; EtOH)

4 $[\alpha]_D^{20} = 77.0$ (c: 5; MeOH)

5 $[\alpha]_D^{20} = 84.0$ (c: 5; MeOH)

Details of the experiments summarised in Table 2.

Table 2. Summary of the resolution experiments

Racemate	Resolving agent	Solvent	Molar ratio racemate: res. agent	Amount of Racemate g	Solvent ml	Amount Res.agent g	of Solvent ml
1	DBTA	i-PrOH	1.5 : 1	20	150	20	150
2	DBTA	abs. EtOH	1.12:1	7	25	8	10
3	DBTA	i-PrOH	2:1	5.2	30	3.6	11
4	TA	96% EtOH	1:0.9	5	10	2.5	5
5	TA	i-PrOH	1:0.95	20	50	10	50

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