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Solvent-Free Optical Resolution of N-methylamphetamine by Distillation After Partial Diastereoisomeric Salt Formation

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ABSTRACT Solvent-free optical resolution of N-methylamphetamine was developed by distillation after partial diastereoisomeric salt formation. From the 18 chiral acids tested by this method, five provide by this method resolution: O,O′-dibenzoyltartaric acid, O,O′-di-p-toluoyltartaric acid, 6-methoxy-α-methyl-2-naphthaleneacetic acid (Naproxen), the *cis*-permetrinic acid, and the 2-phenoxypropionic acid. Among them the O,O′-dibenzoyltartaric acid in water-free form provided the more effective resolution. The efficiency of this resolution S = 0.74 is in the range of the industrial-scale resolutions and not worse than the efficiency achieved by optical resolution via fractional crystallization. *Chirality 13:428–430, 2001.* © 2001 Wiley-Liss, Inc.

KEY WORDS: optical resolution; diastereoisomeric salts; solvent-free process; distillation; O,O′-dibenzoyltartaric acid; O,O′-di-p-toluoyltartaric acid; 6-methoxy-α-methyl-2-naphthaleneacetic acid; *cis*-permetrinic acid; 2-phenoxypropionic acid

Optical resolutions via diastereoisomeric salt formation are usually based on the separation of diastereoisomers by fractional crystallization.[1] The accomplishment of the fractional crystallization is usually very laborious; in most cases several recrystallization steps are required to obtain the pure diastereoisomers. Optical resolutions with 5–10 recrystallizations are common,[2] but, for example, in the case of the resolution of racemic α-chlorobutyric acid by cinchonidine the precipitated salt was recrystallized 159 times.[2] Optical resolutions with several recrystallization steps cannot be scaled up economically into industrial scale, since they require large amounts of solvents, high-volume vessels, and much time.

Our research group is looking for new resolution methodologies which can be more easily applied at the industrial scale.[3–6] In this article, we report the application of a newly developed, solvent-free resolution method. An industrially important compound, the N-methylamphetamine (**MA,** Fig. 1), a key intermediate of some chiral drugs, for example, the antiparkinson agent Jumex®, served as the model compound for the investigations.

RESULTS AND DISCUSSION

For optical resolutions without solvent the application of nonstoichiometric amounts of resolving agent seemed to be suitable. Since the **MA** is an easily distillable liquid and its salts are usually solid, we expected enantiomer separation by the Marckwald method, by applying half an equivalent of resolving agent.

The experiments were performed in a way which makes resolution as simple as possible: the liquid base was layered onto the solid resolving agent and after standing at room temperature the unreacted base was distilled off. The **MA** enantiomer which formed the more stable salt with the resolving agent remained in the residue, while the other **MA** enantiomer distilled (Fig. 1).

The tartaric acid **1** and its two O-acyl derivatives (O,O′-dibenzoyl **(2)** and O,O′-di-p-toluyl **(3)**) are equally good, highly effective resolving agents of **MA** through resolution by fractional crystallization.[8] Since tartaric acids have two carboxylic groups they can form either acidic or neutral salt with an amine. Tartaric acid forms a hydrogen tartrate with **MA** during fractional crystallizations, but with its two O-acyl derivatives neutral salts are formed. The 2:1 molar ratio corresponds to the hydrogen tartrate formation, while the 4:1 to the neutral tartrate formation, leaving half of the amine unreacted. In addition to the 2:1 and 4:1 molar ratios, the 1:1 and 3:1 ratios were also tested with the three tartaric acids.

With the 1:1 molar ratio there was distillate only in the case of tartaric acid, which indicates that with this acid there was no real salt formation. With the two O-acyl derivatives the lack of distillate proved the salt formation. The distillation experiments from the tartaric acid with 2:1 and 4:1 molar ratios resulted in larger amounts of distillate than

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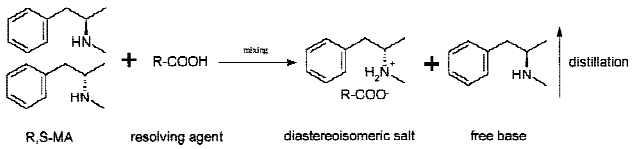

Fig. 1. Scheme of the resolution of **MA** by distillation.

could be expected from normal salt formation and the distillate showed no sign of optical activity, proving that under the applied conditions tartaric acid forms no salts with the **MA,** and without salt formation no resolution can be expected.

In contrast to the tartaric acid, its two O-acyl derivatives **2** and **3** provide optical resolution. By using the two O-acyl tartaric acids in 2:1 molar ratio, about 70% optical purity can be achieved in the distillate with about 50% yield, which means that in the residue the neutral and acidic salts should be in about the same quantity. By changing the molar ratio to 3:1, the stoichiometry of the residue does not change, while the amount of the distillate doubles, which is accompanied only by a slight decrease in optical purity. It is interesting that a further decrease in the ratio of base: acid to 4:1 does not increase, but slightly decreases the amount of the distillate (the unbound amine); the optical purity of the distillate is between the optical purity achieved by 2:1 and 3:1 ratios. The amount of the base in the residue is higher than should be expected, even assuming complete formation of neutral salt, which means that the neutral salt bonds some **MA** by complex formation too.

It seems that the chiral recognition is better in case **2** than **3,** indicated by the fact that under the same conditions and yield, **2** produces distillates with higher optical purity than **3.**

During the experiments **2** was used in its monohydrate form. We found that when it is applied in water-free form the optical purity of the distillate is close to 80% (Table 1, row 8), probably because the **MA** did not have to compete for the binding site with the water. The efficiency of the resolution is 0.74, which is in the range of industrial-scale resolutions, and not worse than the efficiency which can be achieved by optical resolution of **MA** by fractional crystallization.

The optical purity of the **MA** can be further increased by repetition of the process. For example, the redistillation of a base of 59% optical purity from **2** results in 94% optical purity **MA.**

Fifteen further chiral acids were tested as resolving agents for the **MA** by distillation with 2:1 base:acid molar ratio (Table 1, Fig. 2). Three of them were dicarboxylic acids. Aspartic acid **(4)** and glutamic acid **(6)** did not form salt with **MA,** nearly all the **MA** distilled in racemic form. The N-formyl-aspartic acid **(5)** formed salt; according to

TABLE 1. Summary of the experimental results

	Acid	Molar ratio b:a	Amount of acid g	Distillate Yield g	Y %[1]	$[\alpha]_D^{20}$ (c = 1, 1 N HCl)	OP %	S[9]
1.	2R,3R-1	1:1	3.00	1.2	80.5	0.0	0	0.0
2.	2R,3R-1	2:1	1.50	1.9	127.5	0.0	0	0.0
3.	2R,3R-1	4:1	0.75	2.1	142.0	0.0	0	0.0
4.	2R,3R-2	1:1	7.53	0.0	—	—	—	—
5.	2R,3R-2	2:1	3.76	0.6	40.3	+13.6	72	0.29
6.	2R,3R-2	3:1	2.51	1.3	87.3	+11.2	59	0.51
7.	2R,3R-2	4:1	1.88	1.2	80.5	+12.8	68	0.54
8.	2R,3R-2[2]	4:1	1.88	1.4	94.0	+14.8	78	0.74
9.	2R,3R-3	1:1	7.73	0.0	—	—	—	—
10.	2R,3R-3	2:1	3.86	0.7	47.0	+12.9	68	0.32
11.	2R,3R-3	3:1	2.58	1.3	87.3	+9.5	50	0.44
12.	2R,3R-3	4:1	1.93	1.2	80.5	+11.1	59	0.47
13.	L-4	2:1	1.33	2.7	181.2	0.0	0	0.0
14.	L-5	2:1	1.61	0.9	60.0	0.0	0	0.0
15.	L-6	2:1	1.47	2.6	174.4	0.0	0	0.0
16.	(+)-7	2:1	2.30	1.3	87.3	−1.5	8	0.07
17.	S-8	2:1	1.52	0.7	47.0	0.0	0	0.0
18.	R,R-9	2:1	3.89	1.0	67.1	0.0	0	0.0
19.	2R,3R-10	2:1	3.27	1.1	73.8	0.0	0	0.0
20.	R-11	2:1	2.21	1.1	73.8	0.0	0	0.0
21.	R-12	2:1	2.19	1.1	73.8	0.0	0	0.0
22.	R-13	2:1	2.09	0.8	53.7	0.0	0	0.0
23.	S-14	2:1	2.09	1.1	73.8	+2.9	15	0.11
24.	L-15	2:1	0.90	1.2	80.5	0.0	0	0.0
25.	1S-16	2:1	2.32	0.9	60.4	0.0	0	0.0
26.	L-17	2:1	1.76	0.9	60.4	0.0	0	0.0
27.	D-(+)-18	2:1	1.66	1.4	94.0	−2.0	11	0.10

[1]1.5 g MA = 100%.
[2]Water free; a: acid, b: base, Y: yield, OP: optical purity, S: efficiency of the resolution.

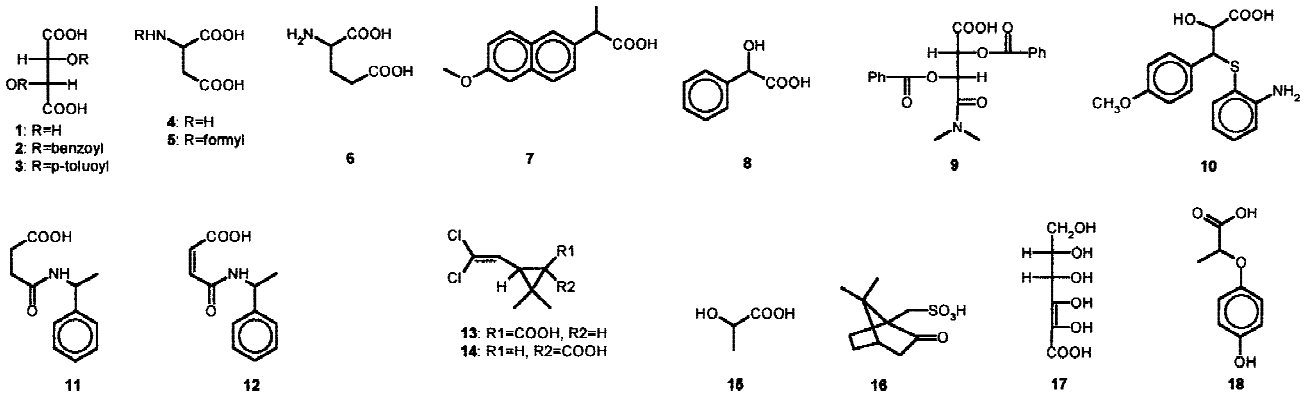

Fig. 2. Resolving agents.

the material balance the residue is a mixture of the neutral and acidic salt, but there is no optical activity in the distillate.

In the case of the 12 monocarboxylic acids the amount of distillate in most cases was less than half of all the base, which means that partial complex formation also took place, together with salt formation.

Optical resolution was achieved only in the case of three monocarboxylic acids, **7, 14,** and **18.** The yields were quite good but the optical purities were rather low. It is interesting that trans-permetrinic acid **(14)** was able to perform resolution while its *cis*-isomer **(13)** was not. There was no enantiomer separation with **9,** which is a derivative of the efficient **2.**

CONCLUSIONS

Our experiments proved that optical resolution by distillation after partial salt formation without the use of any solvent can be as effective as the conventional resolutions by fractional crystallization. Omitting the solvent eliminates several difficulties of resolutions via fractional crystallizations. The process can be scaled up at reduced cost since it is simpler, faster, and requires smaller volume. In addition, the environmental problems caused by the used solvents are eliminated.

EXPERIMENTAL

All chemicals were purchased from Merck (Darmstadt, Germany).

General procedure for the resolution experiments: 3 g (0.02 mol) **MA** was layered onto the calculated amount of resolving agent (Table 1, 4th column). After 1 h of standing at room temperature the mixture was subjected to distillation at reduced pressure to remove the free base (T = 30°C, p = 0.1 mmHg). The distillate was directed into a dry-ice/aceton-cooled trap. The optical purity of the distillate was determined by specific rotation measurements by a Perkin Elmer 241 polarimeter. The specific rotation of the optically pure (R)-N-methylamphetamine is $[\alpha]_D^{20} = -18.90$ (c = 1; 1 N HCl). The experimental results are summarized in Table 1.

LITERATURE CITED

1. Newman P. Optical resolution procedures for chemical compounds, vols. 1–3. New York: Optical Resolution Information Center, Manhattan College; 1978–84.
2. Jacques J, Collet A, Wilen SH. Enantiomers, racemates and resolutions. New York: John Wiley & Sons; 1981.
3. Ács M, Bussche Ch, Seebach D. An efficient method of preparing (R)- and (S)-4,4,4-trifluoro-3-hydroxybutanoic acid: resolution with (R)- or (S)-1-phenylethylamine. Chimica 1990;44:90–92.
4. Ács M, Kozma D, Fogassy E. Enantiomer separation via diastereoisomeric salt formation by liquid-liquid phase transition. ACH Models Chem 1995;132:475–479.
5. Fogassy E, Ács M, Szili T, Simándi B, Sawinsky J. Molecular chiral recognition in supercritical solvents. Tetrahedron Lett 1994;35:257–260.
6. Ács M, Szili T, Fogassy E. New method of optical activation for racemic bases. Tetrahedron Lett 1991;32:7325–7328.
7. Fogassy E. Ács M, Faigl F, Simon K, Rohonczy J, Ecsery Z. Pseudosymmetry and chiral discrimination in optical resolution via diastereoisomeric salt formation. The crystal structures of (R)- and (S)-N-methylamphetamine bitartarates (RMERTA and SMERTA). J Chem Soc Perkin Trans 2 1986;1881–1886.
8. Kozma D, Madarász Z, Ács M, Fogassy E. Study of mechanism of an optical resolutions via diastereoisomeric salt formation by Pope-Peachy method. Tetrahedron Asym 1994;5:193.
9. The efficiency (0 < S < 1) of the optical resolution has been defined as the product of the optical purity (0 < OP < 1) and the yield (0 < Y < 1) of the precipitated salt: S = OPxY. Fogassy E, Lopata A, Faigl F, Darvas F, Ács M, Töke L. A quantitative approach to optical resolution. Tetrahedron Lett 1980;21:647–650.