422. *The Resolution of Chlorpheniramine and Pheniramine.*

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The resolution of the antihistaminic drugs chlorpheniramine and pheniramine with optically active di-*p*-toluoyltartaric acids is described. It has also been found that from solutions of salts of the inactive bases with an inactive acid (3,5-dinitrobenzoic acid), seeding causes preferential crystallisation of the salts of the active bases. From this observation, a method for resolving large amounts of chlorpheniramine has been developed.

SOME of the differences in pharmacological properties of the optical isomers of chlorpheniramine, (3-*p*-chlorophenyl-*NN*-dimethyl-3-2'-pyridylpropylamine), a potent antihistaminic drug,[1] were first reported by Roth and Govier [2] who used bases resolved with active phenylsuccinic acids. The details of this resolution have only recently appeared.[3] In the meantime, a communication from these laboratories reporting the pharmacological properties of the active isomers included a preliminary note on the resolution of (±)-chlorpheniramine with active di-*p*-toluoyltartaric acids and gave the physical constants of the active bases.[4]

Details of this method are now reported. It has been improved by the substitution of hydrochloric acid for half an equivalent of the active acid,[5] resulting in easier crystallisation and a cleaner separation of the less soluble diastereoisomeric salt. 30% Aqueous ethanol is the best solvent found, and when crystallisation has commenced it is important to allow the solution to cool very slowly to avoid separation of the salt in a sticky form of low optical purity.

To avoid confusion, the term (+−)-salt will be used here to describe the salt of the dextrorotatory base with the lævorotatory acid derived from (+)-tartaric acid.

At first, the two enantiomorphs of chlorpheniramine were obtained by the use of the (+)- and the (−)-acid respectively. However, since the (−)-acid is more readily available, it was desirable to find a salt of a simple acid which could be used to separate active from inactive base in partially resolved mixtures obtained from the mother-liquors after the (±)-salt had crystallised. Most salts of (±)-chlorpheniramine do not crystallise easily or well, but since the salt of the (±)-base with 3,5-dinitrobenzoic acid had already been made in these laboratories and was found to crystallise well, this acid was an obvious choice.

The 3,5-dinitrobenzoates of the active bases were found to be only about half as soluble as the inactive salt and by conversion of the total base in a partially resolved mixture into dinitrobenzoate, the salt of the active base could be recovered optically pure in very high yield.

On one occasion the mother-liquors remaining after the removal of excess of (−)-base from such a mixture were found to be slightly dextrorotatory, indicating that preferential crystallisation of a small amount of the salt of the (−)-isomer in the racemic base had occurred in addition to the separation of the salt of the free (−)-base in the mixture. It was then found that if an acetone solution of the dinitrobenzoate of the inactive base was seeded with active dinitrobenzoate, resolution occurred and gave 9% of that isomer in the inactive mixture as salt of 60% optical purity. This resolution by seeding is not limited to solutions in acetone: it also occurs in ethyl methyl ketone, methanol, propan-2-ol, ethyl acetate, and isopropyl acetate, but no resolution has been observed in benzene, ethylene dichloride, and other non-polar solvents.

If a solution of dinitrobenzoate already containing an excess of one enantiomorph is

[1] Sperber, Papa, Schwenk, Sherlock, and Fricano, *J. Amer. Chem. Soc.*, 1951, **73**, 5752.
[2] Roth and Govier, *J. Pharmacol.*, 1958, **124**, 347.
[3] B.P. 834,984.
[4] Brittain, D'Arcy, and Hunt, *Nature*, 1959, **183**, 734.
[5] Pope and Peachey, *J.*, 1899, **75**, 1066.

seeded, the amount of base resolved is increased, the increase depending to some extent on the amount of the excess. For a given concentration in a given solvent it is possible within limits to choose an excess of active base such that the first crop of dinitrobenzoate contains in addition to the salt of the excess active base an equal quantity of salt of th same enantiomorph from the inactive base. An equal amount of the other enantiomorph is left in the mother-liquor from which, after replenishment with more inactive salt, a second crop of dinitrobenzoate is obtained equal to the first but of opposite rotation. This procedure can be repeated indefinitely and provides a very successful process for resolving large quantities of (±)-chlorpheniramine. One experimental run was continued for three months during which more than 50 crops [alternately of (+)- and (−)-salt] were collected with no significant falling off in quantity or quality of the product.*

An initial excess of (+)- or (−)-base equal to 15% of the inactive base (*i.e.*, a 30% excess of that enantiomorph) has been found to be satisfactory, and ethyl methyl ketone is the best solvent found, giving least variation in amount and optical purity of successive crops of salt. It is also an advantage to limit the amount of dinitrobenzoic acid to that required to combine with the total amount of the isomer which is in excess; acetic acid may be added to complete the neutralisation but with no advantage.

The salt thus obtained, of average optical purity 85%, gives, after one recrystallisation from acetone, dinitrobenzoate of 98% optical purity in excellent yield. The factors which favour the resolution also operate in this recrystallisation.

The melting-point curve for mixtures of (+)- and (−)-chlorpheniramine dinitrobenzoates has been determined. It is of normal two-component type with one eutectic corresponding to the composition of the inactive salt, and indicates that the latter is a racemic mixture. The success of the resolution is doubtless partly due to this and also to the extreme stability of supersaturated solutions of the inactive dinitrobenzoate. A solution in acetone containing four times the amount for saturation failed to crystallise during three weeks at room temperature.

The preparation of (+)-pheniramine (*NN*-dimethyl-3-phenyl-3-2′-pyridylpropylamine) by catalytic dehalogenation of (+)-chlorpheniramine appeared in a recent patent [3] in which the resolution of (±)-pheniramine by (+)-phenylsuccinic and (+)-*p*-nitrophenylsuccinic acid is inferred although no optical constants are quoted for the base so prepared.

In the present study, (±)-pheniramine could only be partially resolved with (−)-*OO*-di-*p*-toluoyltartaric acid,† giving a base with $[\alpha]_D$ −8°. However, by repeated crystallisation of the 3,5-dinitrobenzoate of the partially resolved base, the (−)-base was obtained with $[\alpha]_D$ −36·3°. The (+)-base was obtained with $[\alpha]_D$ +37·5° in a similar way from the di-*p*-toluoyltartrate mother-liquors.

By its preparation from (+)-chlorpheniramine, (+)-pheniramine has by inference the same configuration; also in both compounds the (+)-forms have the higher antihistaminic activity. It is interesting therefore that whereas with chlorpheniramine it is the (+)-base which gives the less soluble diastereoisomeric salt with the (−)-acid, with pheniramine it is the (−)-base.

It has been found that, as with chlorpheniramine, solutions of pheniramine 3,5-dinitrobenzoate can be resolved by seeding with a crystal of an active form; also that a similar semi-continuous method of resolution can be applied, although from a limited number of experiments it appears that the method is not so satisfactory as with chlorpheniramine. This is probably due to the lesser tendency of (±)-pheniramine 3,5-dinitrobenzoate to form stable supersaturated solutions. As a result, the salt which separates

* A somewhat similar method of working has been used for " seeding " resolutions of (±)-threonine and (±)-*threo*-2-amino-1-*p*-nitrophenylpropane-1,3-diol.[6]

† It is regretted that in an earlier paper (*J.*, 1957, 1926) dextrorotatory *OO*-di-*p*-toluoyltartaric acid, referred to in the manuscript as di-*p*-toluoyl-L-tartaric acid, was changed editorially to (−)-*OO*-di-*p*-toluoyltartaric acid.

[6] B.P. 740,319, 756,042.

is of lower optical purity and is also more difficult to purify, requiring six or seven recrystallisations.

The 3,5-dinitrobenzoates of chlorpheniramine and pheniramine can be added to the few examples of inactive substances which can be resolved by preferential crystallisation of either enantiomorph.[6,7]

Experimental

Rotations were determined in a 4 dm. tube.

Resolution of Chlorpheniramine by OO-*Di*-p-*toluoyltartaric Acids.*—(±)-3-*p*-Chlorphenyl-*NN*-dimethyl-3-2′-pyridylpropylamine (24 g.) and (−)-*OO*-di-*p*-toluoyltartaric acid [8] (16·7 g., 0·5 mol.) were dissolved in warm ethanol (60 ml.), and water (80 ml.) containing N-hydrochloric acid (43·1 ml., 0·5 mol.) was added. The solution was cooled slowly until clouding commenced, held at that temperature and scratched until crystallisation began, then allowed to cool overnight to room temperature. The crystals were filtered off, washed with 30% aqueous ethanol (50 ml.), and dried. Two recrystallisations from 50% aqueous ethanol gave (+ −)-3-p-*chlorophenyl*-NN-*dimethyl*-3-2′-*pyridylpropylamine* OO-*di*-p-*toluoyltartrate monohydrate*, m. p. 135—136° (needles), $[\alpha]_D^{20}$ −57·8° (*c* 1·7 in EtOH) (Found: C, 64·0; H, 5·9; Cl, 5·0; N, 4·0. $C_{36}H_{37}ClN_2O_8,H_2O$ requires C, 63·7; H, 5·8; Cl, 5·2; N, 4·1%). The anhydrous salt obtained on drying at 60° was very hygroscopic, reverting to the hydrate after a few hours' exposure to air.

The above salt (14 g.) was suspended in water (50 ml.) and basified with N-sodium hydroxide (50 ml.). An ethereal extract of the base was dried (KOH) and evaporated and the residual oil was distilled, giving (+)-3-*p*-chlorophenyl-*NN*-dimethyl-3-2′-pyridylpropylamine, b. p. 120°/0·1 mm., n_D^{20} 1·5608, $[\alpha]_D^{21·5}$ +31·6° (*c* 1·8 in EtOH) (Found: C, 70·0; H, 7·1; Cl, 12·75; N, 10·1. Calc. for $C_{16}H_{19}ClN_2$: C, 69·9; H, 7·0; Cl, 12·9; N, 10·2%). The hydrogen maleate was prepared by adding a solution of maleic acid (1·65 g.) in isopropyl acetate (30 ml.) to a solution of the above base (3·9 g.) in isopropyl acetate (10 ml.). The salt, which crystallised on cooling, recrystallised from isopropyl acetate and then had m. p. 113—114°, $[\alpha]_D^{24}$ +23·1° (*c* 1·2 in H_2O) (Found: C, 61·4; H, 6·0; Cl, 9·3; N, 6·7. Calc. for $C_{20}H_{23}ClN_2O_4$: C, 61·4; H, 5·9; Cl, 9·1; N, 7·2%).

In a similar way, (±)-base and (+)-*OO*-di-*p*-toluoyltartaric acid [9] gave (− +)-3-p-*chlorophenyl*-NN-*dimethyl*-3-2′-*pyridylpropylamine* OO-*di*-p-*toluoyltartrate monohydrate*, m. p. 135°, $[\alpha]_D^{24}$ +57·4° (*c* 1·1 in EtOH) (Found: C, 64·3; H, 5·9; Cl, 5·7; N, 4·7%). By basifying the salt, (−)-3-*p*-chlorophenyl-*NN*-dimethyl-3-2′-pyridylpropylamine was obtained, with b. p. 121°/0·1 mm., n_D^{19} 1·5609, $[\alpha]_D^{21·5}$ −31·6° (*c* 1·8 in EtOH) (Found: C, 70·3; H, 7·1; Cl, 12·4; N, 9·9%). The hydrogen maleate had m. p. 114—115°, $[\alpha]_D^{25}$ −23·1° (*c* 1·2 in H_2O) (Found: C, 61·1; H, 5·8; Cl, 9·2; N, 7·4%).

(±)-3-p-*Chlorophenyl*-NN-*dimethyl*-3-2′-*pyridylpropylamine* 3,5-*Dinitrobenzoate.*—To a solution of (±)-3-*p*-chlorophenyl-*NN*-dimethyl-3-2′-pyridylpropylamine (249 g.) in isopropyl acetate (1 l.) was added a solution of 3,5-dinitrobenzoic acid (192 g.) in acetone (375 ml.). The salt, which was filtered off, washed with isopropyl acetate, and dried, had m. p. 132° (Found: C, 57·05; H, 4·9; Cl, 7·6; N, 11·9. $C_{23}H_{23}ClN_4O_6$ requires C, 56·7; H, 4·8; Cl, 7·3; N, 11·5%).

(+)-3-p-*Chlorophenyl*-NN-*dimethyl*-3-2′-*pyridylpropylamine* 3,5-*Dinitrobenzoate.*—(a) *From* (+)-*base.* 3,5-Dinitrobenzoic acid (7·8 g.) and (+)-base (10 g.) were dissolved in boiling acetone (180 ml.). The crystals which separated on cooling were twice recrystallised from acetone, giving the *salt* [" the (+)-dinitrobenzoate "], m. p. 146°, $[\alpha]_D$ +54·6° (*c* 2·1 in $CHCl_3$) (Found: C, 57·0; H, 4·8; Cl, 6·9; N, 11·25%).

(b) *From the dinitrobenzoate of* (±)-*base, by seeding.* 3,5-Dinitrobenzoic acid (1·93 g.) and (±)-base (2·5 g.) were dissolved in warm acetone (50 ml.), and the solution was cooled to room temperature. The supersaturated solution was seeded with a few crystals (<0·5 mg.) of " (+)-dinitrobenzoate " and was set aside overnight. The salt which separated (0·35 g.) had m. p. 144—145°, and $[\alpha]_D$ +33° (*c* 1 in $CHCl_3$), corresponding to 60·4% of the (+)-isomer. Thus a 9·5% resolution of the racemic base had occurred.

[7] Houben-Weyl, " Methoden der Organischen Chemie," 4th edn., 1955, Vol. IV, 509; Anderson and Hill, *J.*, 1928, 993; Zaugg, *J. Amer. Chem. Soc.*, 1955, **77**, 2910; Potanov, *Uspekhi Khim.*, 1957, **26**, 1152; B.P. 709,595.

[8] Stoll and Hofmann, *Helv. Chim. Acta*, 1943, **26**, 922.

[9] Hunt, *J.*, 1957, 1925.

(−)-3-p-*Chlorophenyl*-NN-*dimethyl*-3-2′-*pyridylpropylamine* 3,5-*Dinitrobenzoate*.—Partially resolved (−)-base (50 g.; $[\alpha]_D$ −15°) obtained from the mother-liquors after collection of the (+)-di-*p*-toluoyltartrate of the (+)-base} and 3,5-dinitrobenzoic acid (39 g.) were dissolved in hot acetone (200 ml.) and the mixture evaporated to dryness *in vacuo*. The hard crystalline cake which remained was digested twice for 0·25 hr. with boiling isopropyl acetate (200 ml.). The remaining solid, after two recrystallisations from isopropyl acetate (1070 ml.), had $[\alpha]_D$ −49° (44 g.). Three recrystallisations from acetone gave the pure *salt* (30 g.), m. p. 145—146°, $[\alpha]_D$ −54·6° (*c* 2·1 in $CHCl_3$) (Found: C, 56·4; H, 4·55; Cl, 7·5; N, 11·75%).

Resolution of (±)-3-p-*Chlorophenyl*-NN-*dimethyl*-3-2′-*pyridylpropylamine* 3,5-*Dinitrobenzoate*.—(±)-Base (100 g.), 3,5-dinitrobenzoic acid (38·6 g., 0·5 equiv.), and " (+)-3,5-dinitrobenzoate " [26·6 g., providing a 30% excess of the (+)-base] were dissolved in warm ethyl methyl ketone (1300 ml.). The solution was allowed to cool to room temperature and was then seeded with " (+)-dinitrobenzoate " (0·1 g.). The salt which crystallised overnight (72·5 g.) had m. p. 143°, and $[\alpha]_D$ +38·9° corresponding to 72·2% of the (+)-isomer and a 29% resolution of the (±)-base. " (±)-Dinitrobenzoate " (71·5 g.) was then added to the mother-liquors which then contained (±)-base (100 g.) and (−)-base (14·5 g., 29% excess). Solvent was added to restore the original volume and, after being heated until all had dissolved, the solution was allowed to cool and was then seeded with " (−)-dinitrobenzoate " (0·1 g.). The second crop of salt (69 g.) had $[\alpha]_D$ −44·8° and thus contained 83% of (−)-isomer, representing a resolution of 35·6%. This procedure was repeated until a total of 672 g. of (±)-base had been added (as dinitrobenzoate) and 18 crops of salt [alternately (+) and (−)] of optical purity 72—94% had been obtained, corresponding to 277 g. of (+)-base and 273 g. of (−)-base. The (+)-dinitrobenzoate (248 g.), recrystallised from acetone (2500 ml.), gave (+)-chlorpheniramine 3,5-dinitrobenzoate (204 g.), m. p. 145—146°, $[\alpha]_D$ +53·35° (*c* 2 in $CHCl_3$). The purified salt was suspended in water (1 l.) and basified with N-sodium hydroxide solution (500 ml.), and the base extracted into benzene (1500 ml.). The benzene extract was washed with water, dried by azeotropic distillation (*ca.* 200 ml.), and treated with a solution of maleic acid (48 g.) in hot acetone (300 ml.). (+)-Chlorpheniramine hydrogen maleate (151 g., 92%) which separated was filtered off, washed with benzene, and dried *in vacuo* at 60°. It had m. p. 113—114°, $[\alpha]_D$ +23·1° (*c* 1·6 in H_2O) and was identical with that prepared from base resolved with di-*p*-toluoyltartaric acid. Similarly from recrystallised " (−)-dinitrobenzoate " {m. p. 145—146°, $[\alpha]_D$ −54·1 (*c* 2 in $CHCl_3$)} was obtained (−)-chlorpheniramine hydrogen maleate, m. p. 113°, $[\alpha]_D$ −23·7° (*c* 1·2 in H_2O).

Resolution of Pheniramine.—(±)-*NN*-Dimethyl-3-phenyl-3-2′-pyridylpropylamine (24 g.) and (−)-*OO*-di-*p*-toluoyltartaric acid (19·3 g.) were dissolved, by warming, in N-hydrochloric acid (50 ml.), ethanol (100 ml.), and water (50 ml.). The solution was cooled, crystallisation was induced by scratching, and the mixture was left overnight. The crystals which separated (31·5 g.; m. p. 144°) were thrice recrystallised from aqueous ethanol (50%), giving impure (− −)-*NN*-dimethyl-3-phenyl-3-2′-pyridylpropylamine *OO*-di-*p*-toluoyltartrate (19 g.), m. p. 147—148°, $[\alpha]_D^{21}$ −90° (*c* 2 in EtOH) (unchanged on further recrystallisation). The salt was suspended in water, and 5N-sodium hydroxide (25 ml.) was added. The base obtained by ether-extraction {6·5 g., $[\alpha]_D$ −8° (*c* 9 in EtOH)} was dissolved in isopropyl acetate (50 ml.) and treated with a solution of 3,5-dinitrobenzoic acid (5·3 g.) in acetone (15 ml.). The solid which separated was recrystallised five times from acetone, giving (−)-NN-*dimethyl*-3-*phenyl*-3-2′-*pyridylpropylamine* 3,5-*dinitrobenzoate*, m. p. 169—170°, $[\alpha]_D^{20}$ −54·0° (*c* 1·15 in $CHCl_3$) (Found: C, 61·1; H, 5·3; N, 12·6. $C_{23}H_{24}N_4O_6$ requires C, 61·05; H, 5·35; N, 12·4%).

The dinitrobenzoate (2·5 g.) was suspended in water, N-sodium hydroxide was added, the liberated base was extracted into ether, and the ethereal solution was dried (KOH) and evaporated. The residual oil was distilled, giving (−)-NN-*dimethyl*-3-*phenyl*-3-2′-*pyridylpropylamine*, b. p. 113°/0·2 mm., n_D^{21} 1·5542, $[\alpha]_D^{19}$ −36·3° (*c* 1·3 in EtOH) (Found: C, 79·7; H, 8·6; N, 11·4. $C_{16}H_{20}N_2$ requires C, 80·0; H, 8·4; N, 11·7%).

The *hydrogen maleate*, prepared in isopropyl acetate from the (−)-base and maleic acid, after two recrystallisations from isopropyl acetate had m. p. 97—98°, $[\alpha]_D^{22·5}$ −30·4° (*c* 1 in H_2O) (Found: C, 67·5; H, 6·6; N, 8·1. $C_{20}H_{24}N_2O_4$ requires C, 67·4; H, 6·8; N, 7·9%). The base (13 g.) obtained from the original (− −)-di-*p*-toluoyltartrate mother-liquors by basification with 5N-sodium hydroxide was similarly treated with 3,5-dinitrobenzoic acid. The salt obtained was recrystallised seven times from acetone, giving (+)-NN-*dimethyl*-3-*phenyl*-3-2′-*pyridylpropylamine* 3,5-*dinitrobenzoate*, m. p. 169°, $[\alpha]_D^{19}$ +55·1° (*c* 1·2 in $CHCl_3$) (Found: C, 60·8; H, 5·4; N, 12·2%).

This was converted as for the (−)-isomer into (+)-NN-*dimethyl-3-phenyl-3-2′-pyridylpropylamine*, b. p. 116°/0·2 mm., $n_D^{17·5}$ 1·5550, $[\alpha]_D^{19}$ +37·5° (*c* 2 in EtOH) (Found: C, 80·35; H, 8·6; N, 11·25. $C_{16}H_{20}N_2$ requires C, 80·0; H, 8·4; N, 11·7%). The *hydrogen maleate*, prepared as above, after recrystallisation from isopropyl acetate had m. p. 95—96°, $[\alpha]_D^{22}$ +30·9° (*c* 2 in H_2O) (Found: C, 67·2; H, 6·85; N, 7·9%).

(±)-NN-*Dimethyl-3-phenyl-3-2′-pyridylpropylamine 3,5-Dinitrobenzoate.*—(±)-*NN*-Dimethyl-3-phenyl-3-2′-pyridylpropylamine (37 g.) in acetone (350 ml.) was treated with a solution of 3,5-dinitrobenzoic acid (33 g.) in acetone (150 ml.). The solid which separated on cooling was recrystallised from acetone, giving the *salt* (54 g.), m. p. 157° (Found: C, 61·55; H, 5·4; N, 12·3%).

Resolution of Pheniramine 3,5-Dinitrobenzoate.—(±)-*NN*-Dimethyl-3-phenyl-3-2′-pyridylpropylamine (5 g.) and 3,5-dinitrobenzoic acid (2·2 g.) were dissolved in warm ethyl methyl ketone (150 ml.), and the solution was cooled to room temperature and seeded by adding crystals of the dinitrobenzoate of the (−)-base (0·06 g.). The salt which separated overnight (3·6 g.) had m. p. 154° and $[\alpha]_D$ −4·6° and thus contained 8·4% of the (−)-isomer. This represents a resolution of 5·1%. Racemic dinitrobenzoate (3·8 g.) was added to the mother-liquors, and the solvent was made up to the original volume. The salt was dissolved by heating and the solution was again cooled and seeded with a trace of the dinitrobenzoate of the (+)-base. The second crop of salt (2·25 g.) had m. p. 160°, and $[\alpha]_D$ +39·6° corresponding to 72% of the (+)-isomer and a resolution of 29%. This procedure was repeated until 9 crops had been collected during which 16 g. of (±)-base had been added. Several recrystallisations of the optically impure salts [7·75 g. of (+)-salt, 69% pure; 11·8 g. of (−)-salt, 49% pure] gave the pure dinitrobenzoate of (+)-pheniramine, with m. p. 168° and $[\alpha]_D$ +55·7°, and of (−)-pheniramine with m. p. 168°, $[\alpha]_D$ −55·3° (*c* 2 in $CHCl_3$).

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