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# ENANTIOMERIC CYCLIC BINAPHTHYL PHOSPHORIC ACIDS AS RESOLVING AGENTS.

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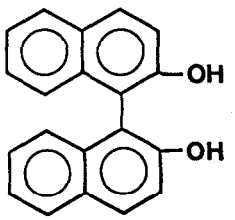
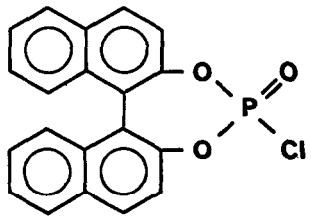
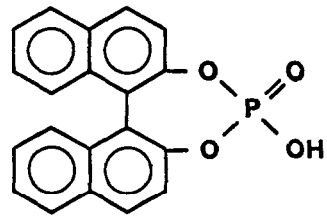
The use of some chiral atropisomeric compounds in resolution is very limited (1,2). Here we describe enantiomers of binaphthyl phosphoric acid, which are readily accessible and which we have found to be widely applicable as resolving agents.




I




II



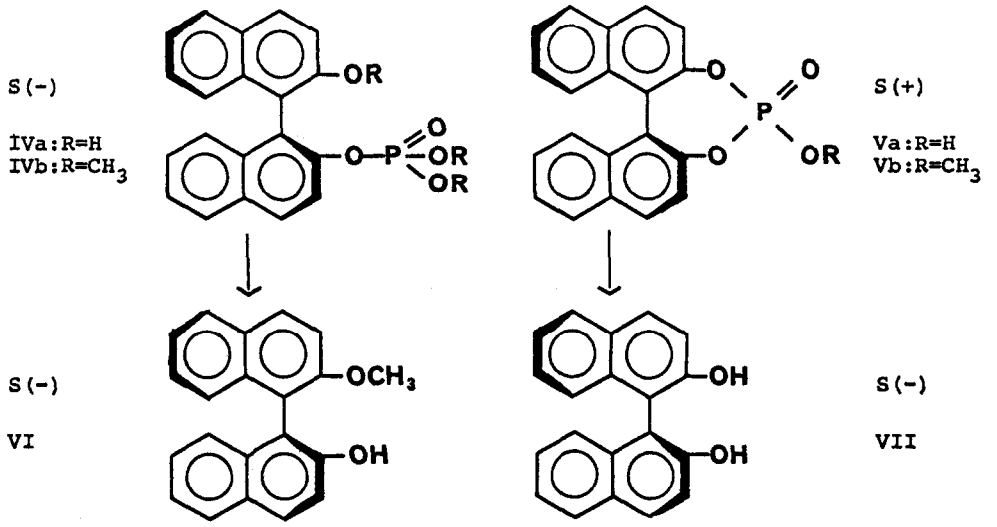

III

Binaphthol (I) (3) reacts with phosphorus oxychloride yielding the cyclic derivative (II) which, under mild hydrolytic conditions (water at room temperature) is easily transformed (4) into the stable cyclic phosphoric acid derivative (III). III can be easily resolved into its optically active forms via the cinchonine salt : 18.45 g of (I) binaphthyl phosphoric acid and 16.00 g of cinchonine was dissolved in 230 ml of hot methanol; 100 ml of $H_2O$ were slowly added and the solution was allowed to cool to room temperature. After 24 hr , the precipitate (11.8 g) was collected, crystallized from MeOH/$H_2O$ (2:1) and dissolved in EtOH. This solution, upon acidification, yields a crystalline precipitate : 5.9 g. Recrystallization from EtOH yields (+) binaphthyl phosphoric acid : $[\alpha]_J^{22} = + 530°$ (MeOH, c = 1.35).

The loevorotatory isomer can be obtained by a similar procedure using cinchonidine as the resolving base.

In order to establish the absolute configuration of the enantiomeric acids III, we prepared the corresponding methyl esters Vb (diazomethane) of the

(+) enantiomer : m.p. = 216°; $[\alpha]_J^{22}$ = + 544° (MeOH,c = 0.22) (Racemate : m.p. 211°). This ester is cleaved by $LiAlH_4$ in THF, giving in almost quantitative yield, the binaphthol VII, $[\alpha]_J^{22}$ = - 39.6° (THF,c = 1.05) the absolute configuration of which is known (X-ray diffraction) to be S (5)

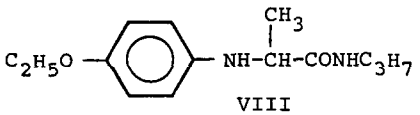



The opening of the cyclic phosphate system requires hydrolysis under drastic conditions. Vb yields IVa after 3 hours refluxing in N NaOH, the methyl ester (IVb) of which is obtained by treatment with diazomethane : m.p. = 147 - 148°; $[\alpha]_J^{22}$ = - 33.5° (MeOH,c = 0.4) (Racemate : m.p. = 118°).

IVb, cleaved by $LiAlH_4$, gives the expected binaphtholmonomethyl ether (VI) : m.p. = 85 - 87°; $[\alpha]_J^{22}$ = - 39.4° (c = 0.65, THF) (Racemate : m.p. = 152 - 153°).

The cyclic binaphthylphosphoric acids are strong acids and the enantiomers form well crystallized salts with a wide variety of organic bases : they therefore represent a useful tool for the resolution of amines. Thus some amines which we were unable to resolve using other known chiral acids, were resolved using the above binaphtylacids very easily and in high yields.

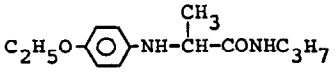
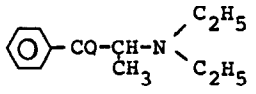
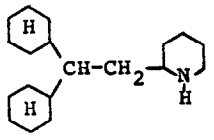
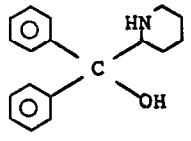
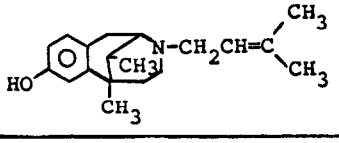
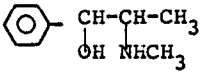
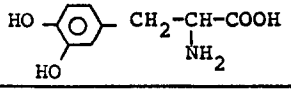
As an example, we describe the resolution of racemic α -p-ethoxy-phenylamino-N-propyl propionamide VIII (6):




VIII

3.6 g of racemic VIII and 4.90 g (+) binaphthyl phosphoric acid are stirred in 225 ml of hot acetone. The mixture is allowed to settle overnight at 4°C, and the precipitate is recrystallized from MeOH/acetone.

## BASES RESOLVED WITH (+)-BINAPHTHYLPHOSPHORIC ACID (TABLE I)

| STRUCTURE OF BASE | ENANTIOMER OBTAINED | YIELD % | RECRYSTALLIZATIONS | |
|---|---|---|---|---|
| | | | (+)-BNP SALT | ENANTIOMER |
|  | (+) | 80 | 3 | 1 |
|  | (+) | 30 | 3 | oil |
|  | (-) | 50 | 2 | - |
|  | (+) | 55 | 1 | 1 |
|  | (+) | 60 | 1 | 1 |
|  | (-) | 20 | - | - (isolated as HCl salt) |
|  | (-) | 62 | 1 | 1 |

The pure salt is then dissolved in MeOH and 6N.HCl is added in order to reach pH= I- The precipitated (+) binaphthylphosphoric acid is filtered off. The remaining solution is extracted with ether and washed with 2 N ammonium hydroxyde solution. The organic layer is dried and evaporated yielding 1.55 g of the pure base, m.p. = 83°, $[\alpha]_J^{22}$= + 42° ($CHCl_3$,c = 0.73).

Further examples of resolutions are shown in Table I.

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