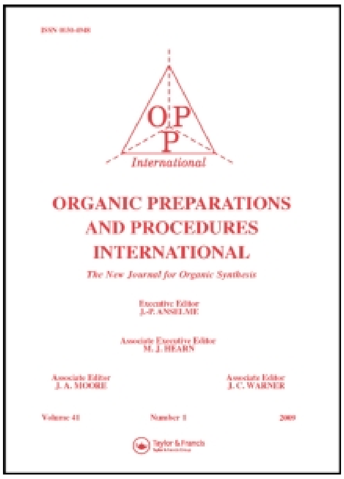

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OPTICAL RESOLUTION OF 4,6,4',6'-TETRACHLORODIPHENIC ACID

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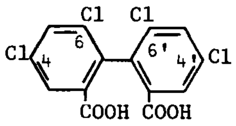
Shortly after the existence of optical isomerism in the biphenyl series was established, Ingersoll and Little[1] described the use of the optical isomers of 6,6'-dinitrodiphenic acid for the optical resolution of racemic bases. Since that time, the isomers of this specific acid have been used for optical resolutions on a few occasions. One case was a resolution that had failed when several other resolving acids were used[2] and another involved 2-methylazaferrocene.[3] Because of the well-known variation in potency among the optical isomers of many pharmacologically active organic bases,[4,5] there is a continuing need for new resolving acids that can be used in cases where currently available acids have failed.

We suspect that optical isomers in the diphenic acid series have not been popular as resolving agents because of their tedious synthesis which in turn has prevented their commercial availability. When the large-scale preparation of racemic 4,6,4',6'-tetrachlorodiphenic acid was described,[6] an attempt was made[7] to scale up its optical resolution by brucine.[8] The attempt failed because of the need for an excessive volume of solvent during the recrystallization of the brucine salts.



We describe here a simple procedure for the optical resolution of the tetrachlorodiphenic acid in which (+)-dehydroabietylamine[9] (DHAA) and brucine were used consecutively to give 36-40% yields (18-20% of racemic acid taken) of each optical isomer of the acid. The racemic acid can be resolved in a conventional procedure with either base alone, but the procedure described here is much more efficient. In the case of both acid isomers the more soluble amine salts were characterized so that future estimates of the optical purity of such salts can be made from values of their specific rotations.

EXPERIMENTAL

The amine salts described here were formed by neutralization of equimolar quantities of the amine and acid; impure samples of the normal brucine salts of (+) and (-)-tetrachlorodiphenic acid were described previously.[8] Chloroform used in this work was freshly purified anhydrous material that contained no ethyl alcohol stabilizer. The specific rotations of the acid isomers are unusually sensitive to the presence of alcohol; this phenomenon is being studied further. Specific rotations were measured in a 1 dm tube; the experimental error for all values was about ±1°.[10]

To a boiling solution of 50 g (0.132 mole) of 4,6,4',6'-tetrachlorodiphenic acid[6,11] (mp. 265-270°) in 2 l. of boiling 95% ethyl alcohol there was added rapidly a boiling solution of 37.6 g (0.132 mole) of DHAA (Aldrich 10,519-8) in 630 ml of alcohol. The mixture was allowed to boil for a few minutes and then was stored in a covered beaker at room temperature to give needles, which were washed with 200 ml of alcohol to give 20 g of salt. An additional 5 g of product of equal optical purity was obtained by concentrating the filtrate to 600 ml. The 25 g obtained amounted to a 57% yield of the DHAA salt of (-)-4,6,4',6'-tetrachlorodiphenic acid, mp. 271-272° decompn., $[\alpha]_D^{24}$ +39.5° (c, 0.7; MeOH). These constants were unchanged when a portion was recrystallized from ethyl alcohol (60 ml/g).

Anal. Calcd. for $C_{14}H_6Cl_4O_4 \cdot C_{20}H_{31}N$: C, 61.36; H, 5.60; Cl, 21.31; N, 2.10. Found: C, 61.09; H, 5.48; Cl, 21.05; N, 2.17.

All washings and mother liquors from the above were combined and evaporated to dryness to give 59 g of impure DHAA salts, $[\alpha]_D^{27}$ +6° (c, 1; MeOH). Recrystallization of a small portion of this material from ethyl alcohol gave the DHAA salt of the (+)-acid with about 90% optical purity. No attempt was made to develop a practical procedure for the preparation of optically pure (+)-acid from the impure DHAA salt.

(-)-4,6,4',6'-Tetrachlorodiphenic acid was prepared from its DHAA salt by adding solid Na_2CO_3 to a stirred suspension of 25 g of salt in a mixture of 200 ml of water and 100 ml of ether until the aqueous phase reached pH 10. The two clear layers were separated and the aqueous phase was washed with two 50-ml portions of ether. The aqueous phase was stirred at 60° until the odor of ether was absent and then was acidified carefully to pH 2 with 6N HCl. The colorless solid that precipitated was washed with water and dried at 65° to give 9 g (36% overall) of the (-)-acid, mp. 250-253°, $[\alpha]_D^{25}$ -140° (c, 1.3; $CHCl_3$). Recrystallization of a portion from benzene containing a little ethyl acetate raised the melting point to 253-258° but caused no significant change in the specific rotation.

Crude (+)-acid was obtained from the crude DHAA salts exactly as described above; 59 g gave 25 g, mp. 235-270°. To a solution of the 25 g (0.066 mole) of crude (+)-acid in 350 ml of boiling acetonitrile was added rapidly a hot dry (Na_2SO_4) solution of 30.8 g (0.066 mole) of brucine tetrahydrate in 350 ml of acetonitrile. The brucine salt precipitated within one minute. The suspension was refluxed for 24 hr,[12] the insoluble salt was washed on the filter with hot acetonitrile, and then was dried at 65° to give 39 g, $[\alpha]_D^{28}$ -29° (c, 1.4; $CHCl_3$). A suspension of this material in 1100 ml of fresh acetonitrile was refluxed vigorously for 24 hr and the insoluble salt was isolated and washed as before to give 22 g of the brucine salt of (+)-4,6,4',6'-tetrachlorodiphenic acid, mp. 265-267° decompn., $[\alpha]_D^{28}$ -42° (c, 1.4; $CHCl_3$).[13]

Anal. Calcd. for $C_{14}H_6Cl_4O_4 \cdot C_{23}H_{26}N_2O_4$: C, 57.38; H, 4.16; Cl, 18.31; N, 3.62. Found: C, 57.41; H, 4.17; Cl, 17.61; N, 3.86.

All mother liquors from the above work were evaporated to dryness to give a recovery of 31 g of mixed brucine salts from which essentially racemic acid was subsequently isolated.

(+)-4,6,4',6'-Tetrachlorodiphenic acid was prepared from 22 g of its brucine salt by the same procedure used for the isolation of the (-)-acid; $CHCl_3$ was used, instead of ether, to extract brucine. We obtained 10 g (40% overall) of the (-)-acid, mp. 248-254°, $[\alpha]_D^{25}$ +144° (c, 1.2; $CHCl_3$). Recrystallization of a portion from benzene containing a little ethyl acetate raised the melting point to 255-260° but caused no significant change in the specific rotation.

The DHAA salt of (+)-4,6,4',6'-tetrachlorodiphenic acid was prepared by mixing a hot solution of 1 g (0.0026 mole) of the (+)-acid in 25 ml of absolute ethyl alcohol with a hot solution of 0.74 g (0.0026 mole) of DHAA in 25 ml of the same solvent. The mixture was allowed to stand at room temperature and deposited colorless needles which, after drying at 65°, had mp. 260-265° decompn., $[\alpha]_D^{30}$ -8.1° (c, 1.4; MeOH).

Anal. Calcd. for $C_{14}H_6Cl_4O_4 \cdot C_{20}H_{31}N$: C, 61.36; H, 5.60; Cl, 21.31; N, 2.10. Found: C, 60.79; H, 5.52; Cl, 20.73; N, 2.11.

The brucine salt of (-)-4,6,4',6'-tetrachlorodiphenic acid was prepared by mixing rapidly a hot solution of 1 g (0.0026 mole) of the (-)-acid in 25 ml of acetonitrile with a hot solution of 1.2 g (0.0026 mole) of brucine tetrahydrate in 25 ml of the same solvent. The mixture was boiled for a few minutes and deposited in the boiling solution a crystalline salt which, after drying at 65°, had mp. 261-264° decompn., $[\alpha]_D^{25}$ +41° (c, 1.3; $CHCl_3$).

Anal. Calcd. for $C_{14}H_6Cl_4O_4 \cdot C_{23}H_{26}N_2O_2$: C, 57.38; H, 4.16; Cl, 18.31; N, 3.62. Found: C, 57.23; H, 3.99; Cl, 18.33; N, 3.52.

When this salt was recrystallized from absolute ethyl alcohol, or when we attempted to prepare it from equimolar portions of brucine and the (-)-acid in ethyl alcohol solution, the salt that separated was found by analysis to be the very insoluble normal brucine salt, mp. 263-265° decompn., $[\alpha]_D^{20}$ -15.2° (c, 1.3; $CHCl_3$).[14]

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10. The optical isomers of tetrachlorodiphenic acid are much more soluble in $CHCl_3$ than is the racemic compound and their melting point is about 10° lower. Our inability to prepare a 1.3% solution of an acid sample in $CHCl_3$ was direct evidence that a significant amount

of racemic compound was present. It was observed that when equivalent quantities of (+)- and (-)-acids were mixed in alcohol-free $CHCl_3$ the racemic compound did not precipitate. When alcohol was present the racemic compound was isolated by evaporation to dryness and then was relatively insoluble in $CHCl_3$.

The acid had been prepared in the work described in reference 6; a portion recrystallized from ethyl acetate/benzene had mp. 265-270°.

This and the subsequent 24-hr leaching were designed to permit a more complete separation of the less soluble salt as in an analogous resolution described by S. W. Kantor and C. R. Hauser, J. Amer. Chem. Soc. 75, 1744 (1953).

The specific rotation reported for a small sample prepared in earlier work[8] was in error; the sample retained for 30 years now had $[\alpha]_D$ -35°.

An optically impure sample of this salt had been characterized previously.[8]

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