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Aminobenzylphosphonic Acid의 광화학적 분할과 합성에 관한 연구

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Modified Preparation and Resolution of Aminobenzylphosphonic Acid

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요 약. Benzaldehyde, diethylphosphite와 암모니아를 상압에서 반응시켜 diethyl *dl*-1-aminobenzylphosphonate를 합성하였다. 이 화합물의 *D*-mandelic acid 염으로부터 diethyl (−)-1-aminobenzylphosphonate hydrochloride를 분리한 후 산으로 가수분해시켜 (+)-1-aminobenzylphosphonic acid를 얻었다.

ABSTRACT. By fractional crystallization *D*-mandelic acid salt of diethyl-*dl*-1-aminobenzylphosphonate prepared from benzaldehyde, diethylphosphite and ammonia at the atmospheric pressure, gave diethyl(−)-1-aminobenzylphosphonate. (+)-1-Aminobenzylphosphonic acid was obtained by acidic hydrolysis of diethyl(−)-1-aminobenzylphosphonate hydrochloride.

INTRODUCTION

In 1947, the organic chemist Chavane[1] mentioned the possibility that the C–P compounds could exist in nature, based on his observations of the stability of synthetic aminophosphonic acids. But his expectation has been more than fulfilled by successive discoveries of a series of aminophosphonic acids. These compounds have a wide distribution, and appear to be ubiquitous constituents in lower animals.[2]

Although the biosynthetic mechanism of these compounds remains obscure, the aminophosphonic acids have attracted considerable biological interest because of their structural similarity to the biologically important amino carboxylic acids.[2,3] The naturally occurring amino carboxylic acids are generally optically active and play an important role in biochemical reactions within organisms.[4] In many cases, one of the optically active isomers has more biological activity than the other. 2-Aminoethylphosphonic acid was the first natural C–P compounds isolated from rumen ciliated protozoa and sea anemones.[5] Since 2-aminoethylphosphonic acid is not asymmetric, we do not expect optical activity. However, Kittredge and Hughes[6] have detected 2-amino-3-phosphonopropionic acid in aqueous-ethanolic extracts of the Zoanthid Zoanthus sociatus. Since this molecule is asymmetric, this naturally

occurring compound would be expected to be optically active, but the authors did not study this property.

In 1965, Kim[7] separated *N*-benzoyl-(+)-1-aminoethylphosphonic acid by fractional crystallization of the brucine salt of *N*-benzoyl-*dl*-1-aminoethylphosphonic acid. Gilmore and McBride[8] reported to prepare the optically active aminobenzylphosphonic acid by condensing the optically active phenylethylamine and benzaldehyde to form the Schiff's base. This paper is concerned with the synthesis and resolution of aminophosphonic acids, and as a model compound 1-aminobenzylphosphonic acid was employed, which is the simplest asymmetric compound containing phenyl group and is an analogue of phenylglycine.

RESULTS and DISCUSSION

Chalmers and Kosolapoff[9] prepared diethyl-1-aminobenzylphosphonate hydrochloride by Mannich-type reaction. Hydrolysis of the ester produced the free aminophosphonic acid. In their sythesis, benzaldehyde, ammonia in ethanol and diethylphosphite were heated in an autoclave, yielding 18-31% of diethyl 1-aminobenzyl phosphonate.

$$(C_2H_5O)_2P(O)H + NH_3 + C_6H_5CHO \longrightarrow (C_2H_5O)_2\overset{\overset{O}{\|}}{\underset{\underset{NH_2}{|}}{P}}CHC_6H_5$$

When we used the same method for preparing diethyl *dl*-1-aminobenzylphosphonate hydrochloride, the over-all yield was never greater than 30%. Passage of ammonia into a mixture of benzaldehyde and diethylphosphite in ethanol also showed low yields. But, change of ethanol to *n*-butanol, with some increase of refluxing temperature, gave over-all yield of 77 %. It is believed that further studies of these reactions, particularly, the study of the reaction temperature may result in additional increase in yields. The hydrochloride of this ester was readily hydrolyzed by refluxing for 50 min with 1:1 mixture of acetic acid and 15% hydrochloric acid.

It is often difficult to find the desirable diastereoisomeric salt and the right solvent system to give a satisfactory separation of the diastereoisomeric salts. In this work, the attempt with diethyl 1-aminobenzylphosphonate and *D*-mandelic acid gave a salt which was separated into one of the pure diastereoisomeric salts simply by fractional crystallization from ether. After the fourth recrystallization of the diastereoisomeric salt from a relatively large volume of ether, further recrystallizations produced no further change in the rotation. The specific rotation of this *D*-mandelic acid salt of diethyl(−)-1-aminobenzylphosphonate was $[\alpha]_D^{20} = -43.7°$ in ethyl alcohol. By the passage of dry hydrogen chloride, the optically pure diethyl(−)-1-aminobenzylphosphonate hydrochloride was obtained. The specific rotation of this product was $(\alpha)_D^{20} = -5.3°$ in ethanol. After acidic hydrolysis, (+)-1-aminobenzylphosphonic acid was isolated finally. The rotation was $(\alpha)_D^{20} = +23.9°$ in 1 *N* NaOH. The optically active diethyl(+)-1-aminobenzylphosphonate hydrochloride was recovered from the mother liquor in a white, crystalline state. The rotation of this product was $(\alpha)_D^{20} = +1.9°$ in ethanol. By acidic hydrolysis, the optically impure (−)-1-aminobenzylphosphonic acid was obtained. The rotation was $(\alpha)_D^{20} = -8.7°$ in 1 *N* NaOH. With the hope of being able to separate the pure (−)-1-aminobenzylphosphonic acid, other optically active acid salt of diethyl 1-aminobenzylphosphonate was attempted to prepare in several solvents, but these combinations did not show any crystalline states of the diastereoisomeric salts.

EXPERIMENTAL

Preparation of Diethyl *dl*-1-aminobenzylphosphonate hydrochloride

Attempt by the method of Chalmers and Kosolapoff[9]; distilled benzaldehyde (31.8 g) and 41.4 g. of diethylphosphite were placed into a stainless steel autoclave. To this mixture was added a solution of dry ammonia in 300 m*l*. of absolute ethyl alcohol (saturated at 0°) and the autoclave was heated and stirred for 10~12 hrs at 100°. The cooled reaction mixture was evaporated to dryness, the residue was taken up in 1:1 mixture of absolute ethanol and diethyl ether, and dry hydrogen chloride was passed into the solution. The yellowish precipitate of the diethyl ester hydrochloride of the desired acid was filtered off and recrystallized from 1:1 mixture of ethanol and ether, yielding 25.0 g (29.6 %) of diethyl-1-aminobenzylphosphonate hydrochloride, m. p 158~160° (ref.[9] 158~159°).

Anal. Calcd. for $C_{11}H_{19}O_3NPCl$: N, 5.01; P, 11.09. Found: N, 4.98; P, 10.98.

Attempt at Atmospheric Pressure. Into a mixture of benzaldehyde 31.8 g, diethylphosphite 41.4g and 300 m*l*. of ethanol, dry ammonia gas was passed and refluxed for 10hr. The cooled reaction mixture was treated with the same method as above, yielding 4.2 g(5.1 %) of diethyl-1-aminobenzylphosphonate hydrochloride. IR spectrum(4000~400 cm^{-1}) of this compound was completely identified with diethyl 1-aminobenzylphosphonate hydrochloride prepared as above, and melted at 159~160°.

A mixture of benzaldehyde 16.0 g, 13.8 g of diethylphosphite and 30 m*l* of butyl alcohol was treated with dry ammonia at 120°, according to the same method as described above. Diethyl 1-aminobenzylphosphonate hydrochloride thus obtained was 21.6 g (76 %). IR spectrum and melting point were completely identified with that prepared as above.

Hydrolysis of Diethyl 1-Aminobenzylphosphonate hydrochloride. A mixture of diethyl 1-aminobenzylphosphonate hydrochloride 28 g, 50 m*l*. of 15 % hydrochloric acid and 15 m*l*. of acetic acid was refluxed for 50 min. The solvent was then evaporated under reduced pressure, giving a white paste-like residue, which was dissolved in 60 m*l* of ethanol. After treating the mixture with propylene oxide, the white crystal appeared was recrystallized in 1:1 mixture of ethanol and water, yielding 14.9 % of *dl*-1-aminobenzylphosphonic acid (80 %). The pure compound had a melting point of 271~273′ and has been reported[9] to melt at 272°.

Anal. Calcd. for $C_7H_{10}O_3NP$: N, 7.49; P, 16.58; neut. equiv., 93.5: Found; N, 7.42; P, 16.48; neut. equiv., 94.5.

Resolution with *D*-Mandelic Acid. To the diethyl *dl*-1-aminobenzylphosphonate hydrochloride (20 g, 0.078 mole) suspended in ether (150 m*l*) was added 4*N* sodium hydroxide, keeping the temperature of the suspension below 0° with an ice bath. To the mixture enough anhydrous potassium carbonate was added untill the water layer disappeared. After the evaporation of the solvent the ether layer gave a clear liquid of diethyl *dl*-1-aminobenzylphosphonate (16.0 g, 72 %). IR: $N-H_{(s)}$;3450, $N-H_{(a)}$; 1610, P=O; 1250.

Sixteen gram (0.066mole) of diethyl-*dl*-1-aminobenzylphosphonate and 10.03 g(0.066mole) of *D*-mandelic acid were combined in 200 m*l* of ether and the salts fractionated as usual. Successive crops were systematically recrystallized from eiher, and after four crystallizations gave 2.61g(21%) of the (−)-diethylphosphonate salt, m. p 40°; $[\alpha]_D^{20}$ −43.7° (*c* 1.0; ethanol). The foot fractions gave more soluble (+)-diethylaminophosphonate salt but this was not completely purified. The (−)-diethylaminophosphonate salt

was decomposed as usual and the diethyl (−)-1-aminobenzylphosphonate hydrochloride was obtained with dry hydrogen chloride, recrystallized in 1:1 mixture of ethanol and ether, and dried; yield, 77 %; $[\alpha]_D^{20}$ −5.3° (*c* 2.5, ethanol); m.p 168~171°.

Anal. Calcd. for $C_{11}H_{19}O_3NPCl$: N, 5.01; P, 11.09 Found; N, 5.08; P, 10.98.

The impure diethyl (−)-1-aminobenzylphosphonate hydrochloride obtained similarly from the more soluble salt had $[\alpha]_D^{15}$ −1.9° (*c* 4.2, water). *D*-Mandelic acid for re-use was recovered in 80 % yield.

Hydrolysis of the pure diethyl (−)-1-aminobenzylphosphonate hydrochloride by the same method as *dl*-form, gave (+)-1-aminobenzylphosphonic acid, yield, 77 %, $[\alpha]_D^{20}$ +23.9° (*c*1.0, 1*N* NaOH), m.p 271~273°.

Anal. Calcd. for $C_7H_{10}O_3NP$: N, 7.49; P, 16.58: Found; N, 7.53; P, 16.53.

Hydrolysis of the impure diethyl (+)-1-aminobenzylphosphonate hydrochloride by the same method as *dl*-form, gave (−)-1-aminobenzylphosphonic acid, yield 81%, $[\alpha]_D^{20}$ −8.7° (*c* 2.2, 1 *N* NaOH).

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