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RESOLUTION OF ASYMMETRIC ORGANOPHOSPHORAMIDES AND THEIR STEREOSPECIFIC TRANSFORMATIONS

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The resolution and reactions of optically active organophosphorus compounds in which phosphorus is the asymmetric center has been the subject of a considerable amount of recent interest (1). Optically active phosphoryl and thiophosphoryl compounds have been prepared either by the resolution of suitable derivatives or by synthesis from resolved phosphonium salts (1). In particular, the method of resolution of alkyl alkylphosphonothioic acids developed by Aaron and co-workers (2) has made available intermediates from which a number of optically active derivatives have been prepared by nucleophilic displacement reactions (3). By far the majority of the evidence (1,3) indicates that such displacements occur with inversion of configuration at the phosphoryl and thiophosphoryl centers.

We wish to report the preparation and certain stereospecific transformations of l-1-[(diethylamino)phenylphosphinothioyl]-2,3-dimethylimidazolium iodide (I), based upon the use of the imidazolium group as both a resolving "handle" and facile leaving group in nucleophilic displacement reactions. This represents a unique method which we believe may possess general utility in the preparation of a variety of optically active phosphoryl and thiophosphoryl compounds.

Refluxing a solution of racemic N,N-diethyl 2-methylimidazol-1-yl phenylphosphinamidothioate (dl-IIa) (4) and methyl α-d-camphorsulfonate in ether resulted in the precipitation of crystalline diastereomeric dl-1-[(diethylamino)-phenylphosphinothioyl]-2,3-dimethylimidazolium α-d-camphorsulfonate**,

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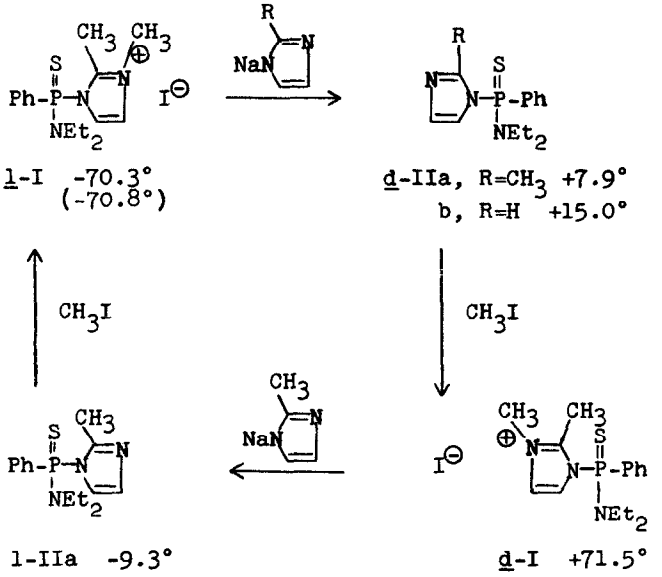
**Satisfactory elemental and nmr analyses were obtained on all new compounds. Specific rotations were obtained on chloroform solutions using a Hilger polarimeter.

mp 132-134°, $[\alpha]_D^{25}$ +41.2° (c 1.8), in 90% yield. Two recrystallizations of this salt mixture from benzene* gave a 10% yield of one diastereomer, mp 133.0-135.0°, $[\alpha]_D^{25}$ -2.9° (c 1.3). This diastereomer was warmed (50°) with a slight excess of sodium iodide in acetone for 30 min. Filtration removed sodium α-d-camphorsulfonate and evaporation of the acetone filtrate gave a 70% yield of l-I, mp 194-196.5°, $[\alpha]_D^{25}$ -70.3° (c 1.2), after recrystallization from methanol-ether at room temperature.

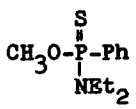
The reactions shown in Scheme I, which includes the specific rotations of each compound, were of two types: nucleophilic displacement of the 2,3-dimethylimidazolium group with 2-methylimidazol-1-yl or imidazol-1-yl anion and formation of the methiodide salt of the product in the case of d- and l-IIa. Thus, reaction of equimolar quantities of l-I, $[\alpha]_D^{25}$ -70.3°, and 2-methylimidazol-1-yl sodium (5) in 1,2-dimethoxyethane at 0° gave a 66% yield of d-IIa, mp 80-83°, $[\alpha]_D^{25}$ +7.9° (c 1.3). Treatment of d-IIa with excess methyl iodide at room temperature gave a 76% yield of d-I, mp 194.0-196.5°, $[\alpha]_D^{25}$ +71.5° (c 1.8). The conversions d-I → l-IIa → l-I were carried out in the same way.



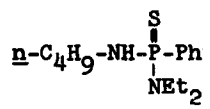
*The nmr spectra of the residues from evaporation of the benzene liquors indicate that this is not a simple fractional crystallization; considerable decomposition occurred in benzene. Because of this the recrystallizations were carried out as rapidly as possible.

That each reaction with 2-methylimidazol-1-yl sodium occurred stereospecifically with 100% inversion, within experimental limits, can be seen by comparing the specific rotations of each pair of enantiomers of I and IIa formed by the reactions shown in Scheme I. The series l-I → d-IIa → d-I → l-IIa → l-I represents a completed cycle whose final product had a specific rotation (-70.8°) identical, within experimental limits, with that of the starting material (-70.3°). d-IIb was prepared similarly by the reaction of imidazol-1-yl sodium with l-I. The crude d-IIb obtained as a syrup was found to be optically stable neat and in chloroform solution at room temperature, but it racemized completely on crystallization from cyclohexane and gave a racemic methiodide salt on treatment with methyl iodide under the conditions outlined above for d-IIa.

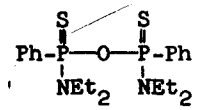
The generality of the stereospecific displacement of the dimethylimidazolium group was indicated by the reaction of l-I with potassium methoxide and n-butylamine to give d-methyl N,N-diethyl phenylphosphonamidothionate (III) and d-N,N-diethyl N'-n-butyl phenylphosphonodiamidothionate (IV), respectively. Stirring



III



IV



V

equimolar amounts of potassium methoxide and l-I in methanol at 0° for 2.5 hr. resulted in an 82% yield of d-III, obtained as a colorless oil, $[\alpha]_D^{25}$ +73.4° (c 1.4). Refluxing equimolar amounts of l-I and n-butylamine in 1,2-dimethoxyethane for 20 hr. resulted in the production of d-IV (81%), also obtained as a colorless oil, $[\alpha]_D^{25}$ +17.2° (c 1.1). In these two cases the stereospecificity and course of the reaction could not be directly evaluated although they very likely proceeded, as in the examples given above and similar examples given in the literature (1,3), with inversion.

Equivalent amounts of sodium hydroxide and dl-I, stirred at room temperature for 20 hr. in a benzene-water mixture, gave N,N,N',N'-tetraethyl phenylpyrophosphonodiamidodithioate (V) as a 1:1 mixture of dl and meso forms. Reaction of our l-I, $[\alpha]_D^{25}$ -70.3°, in the same way gave, approximately, a 93:7 mixture

(by nmr analysis) of optically active and meso forms of V. One recrystallization of this crude product afforded d-V, mp 83-85°, $[\alpha]_D^{25}$ +109° (c 1.1). Knowing the ratio of optically active and meso forms of V formed from l-I and assuming that the reaction with hydroxide ion was stereospecifically quantitative, it follows that the optical purity of l-I, $[\alpha]_D^{25}$ -70.3°, was 86%. This was the lower limit of optical purity since some racemization could have occurred in the formation of V.

All of the optically active compounds encountered in the course of this work were found to be optically stable in their purified state or in chloroform solution. The optical stability of the salt I coupled with the ease of replacement of the dimethylimidazolium group under mild conditions recommends the use of compounds similar in structure to I in preparing other optically active organophosphorus compounds.

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