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L-ALANINATE AND GLYCINATE HYDROHALIDES AS ALCOHOL DERIVATIVES FOR CRYSTAL STRUCTURE ANALYSIS

B. Acott, R. B. Bates, and C. D. Green

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

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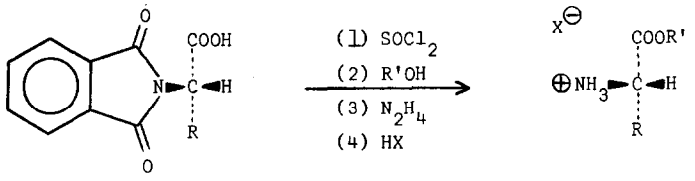
The determination of the absolute configuration of an optically active compound by X-ray analysis can be accomplished by consideration of the anomalous dispersion[1] if a sufficiently heavy atom is present, or by the introduction of an asymmetric center of known configuration into the molecule.[2] The latter method has the advantage of not requiring extra data and extra calculations, but the disadvantage that a derivative must be prepared at the start. Since a derivative is ordinarily prepared for an optically active substance to introduce a heavy atom,[3] this is not a serious disadvantage, and we believe that the latter method would be widely used if suitable derivatives were available. A good derivative for this purpose must be readily prepared, add only a few atoms, and crystallize well. We wish to report L-alaninates (Ia) to be good derivatives for molecules which contain an easily esterifiable hydroxyl group or other functional group easily converted into such a hydroxyl group. These derivatives add only six atoms (other than hydrogens) to an alcohol, generally form good crystals due to their ionic nature, permit ready change of the heavy atom for isomorphous replacement, and can be prepared in a day.

L-Alaninate hydrobromides (Ia, X = Br) were prepared in 50-80% overall yield without isolation of intermediates from nerol and l-menthol by the reaction scheme below.[4] Phthaloyl-L-alanine (IIa), prepared in quantitative yield by heating an intimate equimolar mixture of phthalic anhydride and L-alanine to 140° for 1/2 hour,[5] was converted to the acid chloride by refluxing with excess thionyl chloride for 2 hours. After removing the excess reagent under vacuum, DMF (15 ml/g alcohol), pyridine (1 eq), and the alcohol (1 eq) were added. After several hours at room temperature, ether was added, and after washing with water and evaporating the ether, the phthaloyl group was removed by refluxing for 1/2 hour with a 10% excess of hydrazine hydrate in ethanol. A large excess of water was

added, phthalhydrazide was removed by filtration, and the filtrate was made slightly acidic with the appropriate hydrohalic acid. Slow evaporation of the solution of Ia obtained by extraction of this aqueous layer with ethyl acetate provided single crystals suitable for X-ray analysis. It was possible, though not necessary, to recrystallize from ethanol-ethyl acetate or wet ethyl acetate.



IIa R = CH_3

b R = H

Ia R = CH_3

b R = H

In the case of the sterically hindered secondary alcohol daucol (preceeding communication), this procedure failed since virtually no reaction occurred between daucol and the acid chloride at room temperature, even over several days. When the solution was refluxed for one hour, the derivative formed, but with epimerization α to the carbonyl group, since the crystals obtained were found to contain a 1-1 mixture of diastereomers. Although a crystal structure analysis was carried out on these crystals, it did not reveal the absolute configuration of daucol. A much more insidious result would have been obtained if daucyl D-alaninate hydrobromide had been less soluble than daucyl L-alaninate hydrobromide and the 1-1 complex, for then L-alanine would have yielded the D-alaninate, and unless the possibility of this situation arising was recognized, the wrong conclusion could have been drawn regarding the absolute configuration of daucol.

We have been unable to prepare the L-alaninate of daucol without epimerization, and this will undoubtedly be the case with other hindered secondary alcohols. Still, this derivative should prove useful with such alcohols provided that a test such as the following one is applied and shows the alanine to be D or L. A suspension of the alaninate hydrobromide (0.7 mmoles) in ether (25 ml) is added to a stirred solution of $LiAlH_4$ (500 mg) in ether (15 ml) and the resulting solution is stirred for a further 2 hrs. The excess hydride is decomposed

by dropwise addition of water (1 ml), 15% aqueous sodium hydroxide solution (1 ml), and water (8 ml). The ether layer (containing recovered alcohol) is separated, and the aqueous layer is centrifuged to remove the white ppt, which is then washed with water (5 ml). The combined aqueous solutions are washed with ether (5 ml) to remove remaining alcohol, diluted to 25 ml, and the optical rotation of the resulting alaninol solution is measured. This procedure gave a zero rotation with daucyl D,L-alaninate hydrobromide, and $[\alpha]_D^{25}$ + 8.9 (c = 0.2,H_2O) with menthyl L-alaninate hydrobromide.[6]

When a crystalline derivative of an optically inactive alcohol is sought, the glycinate hydrohalide (Ib) should be considered rather than the alaninate hydrohalide (Ia) to retain the likelihood that the derivative will crystallize in a centrosymmetric space group. We have prepared the glycinate hydrobromide of isopropanol by a procedure analogous to the above in comparable yield. In this case, the acid chloride (of the acid IIb) is comparatively stable and is commercially available.

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FOOTNOTES AND REFERENCES

1. J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, Nature, 168, 271 (1951).

2. A. McL. Mathieson, Acta Cryst., 9, 317 (1956).

3. With the increasing success of direct methods for non-centrosymmetric structures, it might seem that this will not be the case for long. However, the anomalous dispersion method depends on scattering by a heavy atom, and in most cases it would still be necessary to put one in even if the anomalous dispersion method were to be used.

4. Satisfactory analyses have been obtained on all new compounds. From its NMR spectrum, the neryl derivative clearly retains its double bond configuration.

5. A. H. Beckett and A. F. Casy, J. Chem. Soc., 900 (1955).

6. A. Stoll, J. Peyer, and A. Hofmann, Helv. Chim. Acta, 26, 939 (1943), report α_D^{20} + 15.8 for L-alaninol; our rotation was probably low because — it was calculated assuming quantitative reduction of the ester and no loss of alaninol into the white ppt (probably the weak point) or the ether solution.