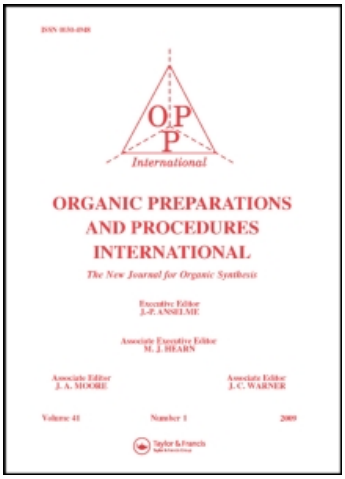

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N-ACETYL-L-TYROSINE ETHYL ESTER

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N-ACETYL-L-TYROSINE ETHYL ESTER

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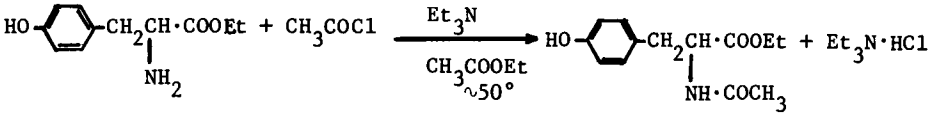
In connection with our studies of the mode of reactivity of polyfunctional epoxides with tyrosine and its derivatives, we noted a number of shortcomings pertaining to the syntheses of N-acetyl-L-tyrosine ethyl ester. First of all, as pointed out by Barnes and his group[2], the literature data on melting points of this compound differ widely, ranging from 78-97°. Secondly, the known methods of synthesis of this compound appear rather complicated, time-consuming, and give low yields. If one considers that the known methods[2-8] utilize N-acetyl-L-tyrosine[9] as the starting material, the overall yields of the ester would range from 25-50%, based on tyrosine. Also, as pointed out by du Vigneaud and Meyer[9], acetylation of optically active tyrosine with acetic anhydride in the presence of sodium acetate, causes racemization and diacylation. These by-products lower the yield of the N-mono acyl ester and introduce difficulties in the processes of purification of the product[7]. Considering all these shortcomings, we felt it of interest to reinvestigate the preparation of N-acetyl-L-tyrosine ethyl ester. As a result, we developed a very convenient and highly efficient procedure for the synthesis of this compound, utilizing tyrosine ethyl ester (or its salt) as the starting material.



The ester can be prepared very conveniently, with the quantitative yields, using the procedure of Dymicky, Mellon, and Naghski[10].

Our studies indicate that N-acetyl-L-tyrosine ethyl ester forms a monohydrate very easily, which can be dehydrated in vacuum at 56°/0.1 mm. The monohydrate, when dried in vacuum at room temperature melts at 60°, with gradual dehydration and a gradual increase of the melting point. The dehydrated, very pure N-acetyl-L-tyrosine ethyl ester melts sharply at 96-97° $[\alpha]_D^{25}$ = +25.2, (c.2, ethanol). Products with melting points between 60 and 96° represent a mixture of partially dehydrated materials. The purity of the dehydrated product has been confirmed by elemental analyses, IR and NMR spectra.

It is of interest to note that recrystallized material from benzene melts at 96-97°. Correct analyses require pure benzene and drying at 56°/0.1 mm.

EXPERIMENTAL

N-Acetyl-L-Tyrosine Ethyl Ester Monohydrate.

Procedure A. - To a solution of 10.46 g (0.05 mole) of tyrosine ethyl ester,[10] and 5.05 g (0.05 mole) of triethylamine in 200 ml dry ethyl acetate contained in a 500 ml three-necked reaction flask, equipped with a condenser, stirrer, addition funnel, and mounted in an oil bath, controlled at about 50° was added dropwise with stirring 3.93 g (0.05 mole) of acetyl chloride, in 100 ml dry ethyl acetate. Within about one hour the addition was completed, and the reaction mixture was allowed to react further for two hours. The white precipitate of triethylamine hydrochloride was filtered and washed with ethyl acetate. The combined filtrates were then concentrated in vacuum, at 25°/0.1 mm, until a dry residue is obtained, giving 12.39 g (99%) of the crude product. The mate-

rial is then recrystallized from water, 25 ml/g, and dried in vacuum at 25°/0.1 mm, giving about 90% of pure product, mp ≈ 60-65°; $[\alpha]_D^{25}$ = +23.53, (c.2, EtOH).

Anal. Calcd. for $C_{13}H_{17}NO_4 \cdot H_2O$: C, 57.98; H, 7.11; N, 5.19. Found: C, 57.86; H, 7.17; N, 5.14.

N-Acetyl-L-Tyrosine Ethyl Ester.

The material obtained above was dried in vacuum, at 56°/0.1 mm, to constant weight, yielding quantitative amount of dehydrated product, mp. 96° $[\alpha]_D^{25}$ = + 25.2, (c.2, EtOH).

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.13; H, 6.68; N, 5.57. Found: C, 62.05; H, 6.80; N, 5.53.

Procedure B. - If tyrosine ethyl ester hydrochloride is used as the starting material, then one uses a two molar ratio of triethylamine and follows the same method as given above. The yield of the product is the same, as given under A.

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