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The Synthesis and Reactions of Dehydro Phenylalanine Anilide

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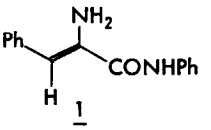
Dehydro amino acids[3] (DHA) and the peptides (DHP) in which these occur have been known for some time. Bycroft[4a] has postulated that DHA may be biosynthetic intermediates in the conversion of L- to D-amino acids and in the formation of numerous peculiar amino acid derivatives (penicillin, cephalosporin, viomycin) during microbial metabolism. Gross[4b] and coworkers have shown the presence of dehydroalanine and butyrine in the microbial peptides nisin and subtilin and Meyers[4c] reported that a fungal peptide, tentoxin, contained a dehydrophenylalanine residue. Early syntheses of DHP by Bergmann[5a] and Greenstein[5b] allowed the synthesis of simple dehydro di- and tripeptides and more recently Shin[6a] has reported a glycyl DHP synthesis while Rich[6b,c] has developed a more general method for the synthesis of DHP. The only recently reported syntheses of DHA derivatives having free amino groups are those reported by Shin[7], in which several DHA esters were prepared. We report here the synthesis of another N-deblocked amino acid derivative, dehydrophenylalanine (DHPhe) anilide (1) by a new method potentially useful for the synthesis of DHA.



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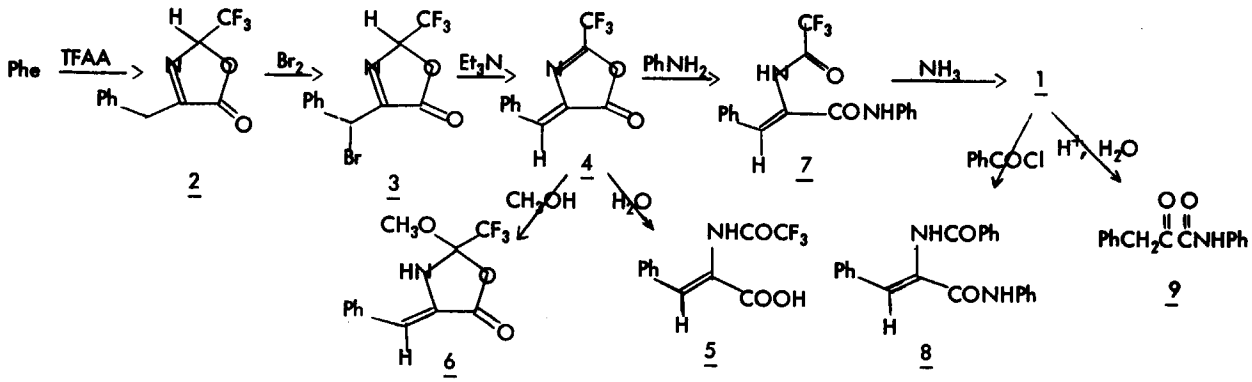
In general, there are two approaches to the synthesis of DHA; (a) synthesis of the carbon chain containing the double bond by a condensation reaction of the Erlenmeyer type[8], or (b) introduction of the double bond into the carbon chain of the intact amino acid. The method of Rich[6] depends for its generality on the first method, while our approach has been of the second type.[9] The sequence of reactions used in the synthesis of 1 is shown in Scheme I. It had been previously reported by Weygand[10] and coworkers that amino acids can be converted into pseudo azlactones of the type 2 and that these could be brominated at the position α to the ring, as in 3. We found that when 3 was treated with triethylamine in ether solution, the hydrobromide precipitated immediately and the unsaturated azlactone (4) could be isolated in 77% yield. Aqueous acetone rapidly converted 4 into the expected acid 5 in good yield, but attempts to prepare the corresponding methyl ester by methanolysis failed. Surprisingly, a crystalline compound having the elemental analysis of a methanol adduct of 4, but showing spectroscopic data consistent with structure 6 was isolated from the mixture. The presence of N-H and C=O peaks at 3340 and 1795 cm^{-1}

in the infrared spectrum, CH_3O (3.43 ppm), N-H (5.56 ppm) and vinyl proton (6.46 ppm) absorptions in the pmr spectrum and a singlet at 86.4 ppm in the ^{19}F nmr spectrum confirmed structure 6. The authentic methyl ester was prepared from 5 using diazomethane. The anilide (7) was obtained directly from 4 or, more conveniently, in 83% yield by treatment of the bromo compound 3 with excess aniline.

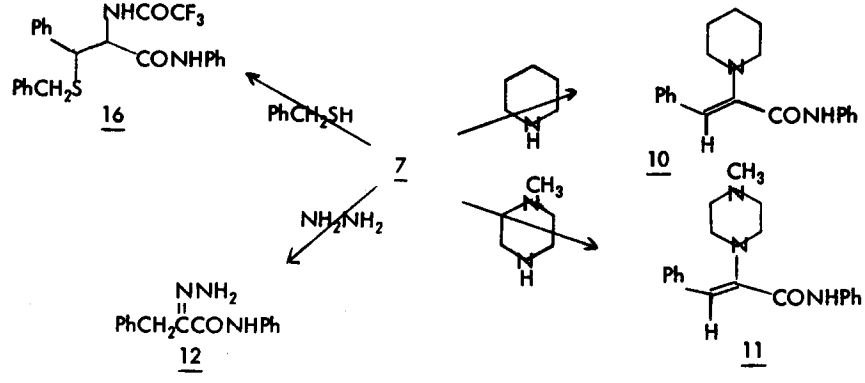
We envisioned the use of "unsaturated" azlactones of the type 4 in the synthesis of dehydro peptides, since their reactions with amino acid esters should give N-trifluoroacetyl dehydro peptides which might then be N-deblocked and coupled with "activated" amino acids to complete the dehydro peptide synthesis. In order to study the deblocking step, we elected to study the reactions of the anilide (7) with various deblocking agents. It has been reported that sodium hydroxide and ammonium hydroxide[11a], Amberlite IR-4B ion exchange resin[11b], imidazole[11c] various amines[11d] and alcoholic sodium borohydride[11e] can be used to remove the trifluoroacetyl group. Neither sodium nor ammonium hydroxide, the ion exchange resin, imidazole or sodium borohydride reacted with 7 to any extent, as shown by tlc examination of the reaction mixtures. The blocking group was, however, removed by treatment of a solution of 7 with gaseous ammonia over a fifteen hour period, and crystalline 1 was isolated in 74% yield. Elemental analyses and spectral analyses, ir (Nujol) 3390 (NH), 1655 (C=C), 1625 cm^{-1} (C=O); pmr (d_6-DMSO) δ 5.06 (s, 2H, NH_2, exchanged in D_2O), 6.12 (s, 1H, vinyl H), 7.00-7.78 (m, 10H, $2C_6H_5$), 10.01 ppm (s, 1H, CONHPh, exchanged in D_2O), were consistent with structure 1. This structure was further secured by its conversion to the benzamido anilide (8), an authentic sample of which was prepared by treatment of the appropriate unsaturated azlactone with aniline. Hydrolysis of 1 to phenyl pyruvanilide (9) was also carried out.

Some surprising results were obtained when 7 was treated with piperidine and N-methylpiperazine in an attempt to deblock it. An exchange reaction occurred (Scheme II) giving piperidino and piperazino cinnamanilides 10 and 11 in 80-90% yields. When treated with hydrazine hydrate, anilide 7 gave a mixture of products from which the hydrazone 12 was isolated in 33% yield. The formation of the products (10, 11, 12) from 7 leads us to propose (Scheme III) that 7 may react with nitrogen nucleophiles by addition to an imine intermediate (13) giving 14 which eliminates trifluoroacetamide to form the observed products (15). In the case of the reaction with hydrazine, the hydrazone structure is more stable than the enamine form (15). It is quite probable that this same mechanism obtains during the reaction of 7 with ammonia although we have no evidence for this. This is made more probable by the fact that neither ammonia nor the secondary amines reacted with the corresponding saturated compound, N-trifluoroacetylphenylalanine anilide, under identical reaction conditions. In spite of the fact that reactions of 7 appear to be occurring through intermediate 13, no spectral evidence for its presence in solutions of 7 was ever obtained. This mode of addition of secondary amines to DHA derivatives appears to be specific to trifluoroacetyl derivatives, since it has been reported by Greenstein[12] that amines add to N-benzoyl DHA derivatives in Michael fashion giving β-substituted amino acid derivatives. A report by Schmidt[13] describes a special case in which intramolecular addition of an amide nitrogen atom to the α-carbon of

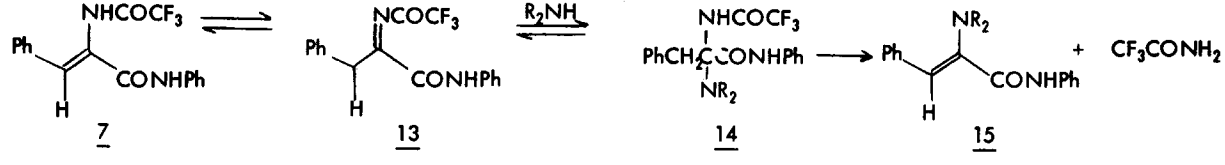
SCHEME I



SCHEME II



SCHEME III



a dehydroalanine residue occurred spontaneously, while no addition to a dehydrophenylalanine moiety took place. We, in fact, examined the reaction of the N-benzoyl compound 8 with N-methylpiperazine. After three days at room temperature no reaction (tlc) had occurred and even after the addition of a trace of triethylamine and refluxing for five days, 69% of 8 was recovered. The crude remainder finally afforded an 8% yield of the crystalline piperazino compound, 11. In contrast, benzyl mercaptan added to 7 giving the expected β-addition product (16) in good yield. It is difficult to explain the difference in behavior of the N- and S-nucleophiles toward 7. Possibly, the greater basicity of amines facilitates establishment of the 7 $\rightleftharpoons$ 13 equilibrium allowing the α-addition to occur.

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