NEW ACTIVATED ESTERS OF N^{α},N^{im}-DI-tert-BUTOXYCARBONYLHISTIDINE WITH INCREASED STORAGE STABILITY

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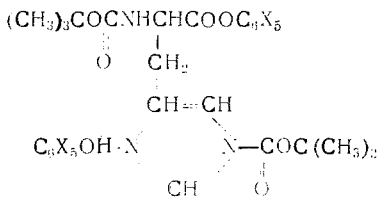
Among various various N^{α},N^{im}-disubstituted derivatives of histidine used in peptide synthesis, the most accessible is apparently N^{α},N^{im}-di-tert-butoxycarbonylhistidine (di-Boc-histidine) [1–3]. This histidine derivative has well recommended itself both in the classical variant of peptide synthesis and in the synthesis of peptides on a polymeric support, and therefore the study of new methods for using di-Boc-histidine in peptide condensation is of definite practical interest. In this connection, we made an attempt to obtain the pentafluorophenyl ester of di-Boc-L-histidine, since the active esters of protected histidines have been studied little.

In the standard variant the synthesis of activated esters, i.e., with an equimolar ratio of the components of the reaction and the use of dicyclohexylcarbodiimide as condensing reagent, the pentafluorophenyl ester of di-Boc-histidine was obtained in the form of a semi-solid resin, and in this form it proved to be unstable on storage. If, however, a complex of dicyclohexylcarbodiimide with three molecules of pentafluorophenol [4] was used as condensing agent, the activated ester was obtained in the crystalline form with mp 100–102°C (decomp.), $[\alpha]_D^{20}$ −8.6° (c 1, dioxane), R_f 0.6 [Silufol plates; benzene–methyl ethyl ketone–acetic acid (100:50:1)]. The same crystalline product was obtained when dicyclohexylcarbodiimide and pentafluorophenol were added to the reaction mixture separately, with the pentafluorophenol taken in somewhat more than two equivalents. The crystalline pentachlorophenol ester of di-Boc-L-histidine was obtained similarly: decomp. p 104–105°C, $[\alpha]_D^{20}$ −9.9° (c 1; dioxane).

According to the results of elementary analysis, the crystalline pentahalophenyl esters of di-Boc-L-histidine contain an extra molecule of the pentahalophenol, apparently bound into an ion pair with the tertiary nitrogen of the imidazole ring.



where X = F, Cl.

In contrast to the resinous pentafluorophenyl ester and the N-hydroxysuccinimide ester of di-Boc-histidine that we obtained previously [2], the new activated esters proved to be extremely stable on storage. They did not lose their crystalline form after storage for a year in the refrigerator. On thin-layer chromatography, only a small amount of impurity appeared at the start which, however, scarcely changed the physicochemical characteristics of the products and their capacity for peptide formation. Both freshly-obtained and the long-stored activated esters of di-Boc-histidine take part normally in the peptide condensation reaction, the pentafluorophenyl ester being more active than the pentachlorophenyl ester, while, moreover, pentachlorophenol is more difficult to separate from the peptide.

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SYNTHESIS OF 2-BENZOYLAMINO- AND PHENYLSULFONYLAMINOBENZOXAZOLES

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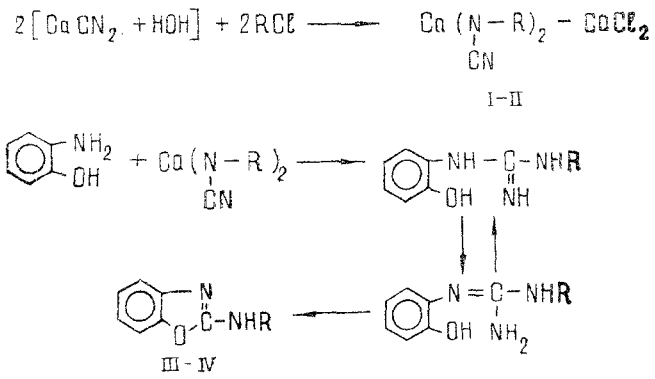
In the interaction of o-aminophenol with cyanoalkyl carbamates, the primary reaction products are N-alkoxycarbonyl-N-(o-hydroxyphenol)guanidines [1]. It was of interest to trace whether this is the case in the reaction of o-aminophenol with N-acylcyanamides. With this aim, and also in order to synthesize biologically active substances, we have performed the reaction of o-aminophenol with N-benzoylcyanamide (I) and N-phenylsulfonylcyanamide (II). The latter were prepared from 0.1 mole of calcium cyanamide, 40 ml of water, and 0.05 mole of the appropriate acylating agent. To a solution of compound (I) obtained in this way, with stirring, 0.04 mole of o-aminophenol, 0.12 mole of concentrated HCl (when less than 0.80 mole of acid was added, intermediate compounds were formed) were added and the mixture was heated to 90-100°C for 2 h. Then it was cooled to 20°C and the resulting precipitate was filtered and recrystallized from ethanol to give 2-benzoylaminobenzoxazole (III) with mp 202-204°C; according to the literature [2]: mp 190°C. In the similar treatment of compound II the yield of 2-phenylsulfonylaminobenzoxazole (IV) was 55%, mp 244°C (according to the literature [3]: mp 246-247°C for the compounds synthesized from N-dichloromethylene-sulfonamide).



where III R = C_6H_5CO-, IV R = $C_6H_5SO_2$-.

The structures of the compounds synthesized were shown by their IR and mass spectra. In the IR spectrum of (III) there are absorption bands characteristic for C=O groups in amides (1650 cm^{-1}) and for NH groups (3300 cm^{-1}). There is no displacement of the absorption in the carbonyl region that is characteristic for the imino structure. In the mass spectra of the same compound there is the peak of the molecular ion with m/z 238 (M^+). As shown by the detection of metastable transitions, the breakdown of the M^+ ion takes place mainly through an ion with m/z 134 (2-aminobenzoxazole) which arises from the M^+ ion by the ejection of benzoyl ($M - C_6H_5CO$). In the mass spectrum of (IV) there is the peak of the molecular ion with m/z 274, and in the IR spectra there are bands at 1150 and 1315 cm^{-1} (sulfonamide group). The mass spectra of the intermediate products contain the peaks of the molecular ions.

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