Oxidative Transformations of Coded Aromatic Amino Acids with 4-t-Butyl Iodylbenzene

Subramania Ranganathan,* Darshan Ranganathan,* Sheokumar Singh, and Dipti Bhattacharyya
Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India

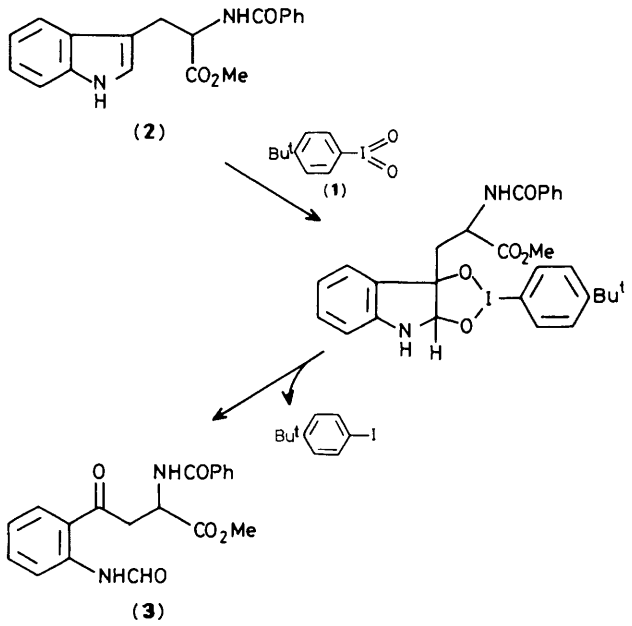
A study of the action of 4-t-butyl iodylbenzene (**1**) on the side chains of the four coded aromatic amino acids has shown that tryptophan is transformed to kynurenine, arising from (**1**) in the role of an ozone equivalent, histidine to γ-formamido glutamine, by pathways similar to those delineated for histidine catabolism, tyrosine to 3,4-dihydroxyphenylalanine quinone, and phenylalanine recovered unchanged.

The coded aromatic amino acids, namely tryptophan, histidine, tyrosine, and phenylalanine behave differently on oxidation. Consequently, from a synthetic and mechanistic viewpoint, their reaction with our recently introduced reagent, 4-t-butyl iodylbenzene was of interest.

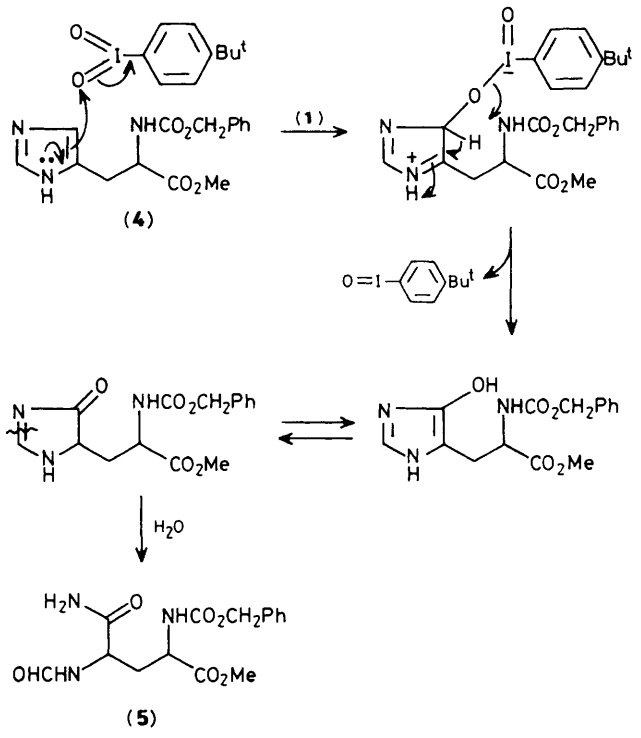
4-t-Butyl iodylbenzene (**1**),[1] behaved as an ozone equivalent on reaction with *N*-benzoyltryptophan methyl ester (**2**),† in refluxing chlorobenzene for 4 h, giving N^{α}-benzoyl-N^{ω}-formylkynurenine methyl ester (**3**) in 70% yield, Scheme 1.‡ Chiral retention in this efficient (**2**)→(**3**) procedure was established *via* transformation of (**3**), in 97% yield, to *N*-benzoylaspartic acid dimethyl ester and comparison with an authentic sample.[2] In parallel studies the (**2**)→(**3**) transformation was accomplished in 58% yield by ozonolysis in MeOH.

† All amino acids used were of the L-configuration. Spectral (i.r., n.m.r., and mass spectra) and analytical data in excellent agreement with those expected were obtained for all compounds.

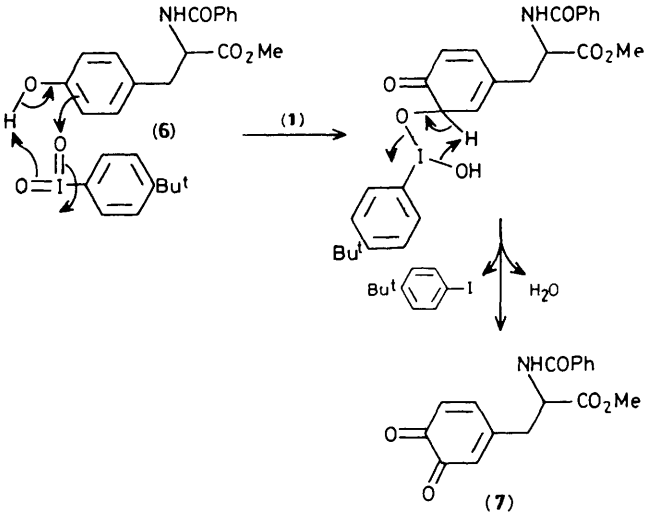
‡ In a typical procedure, a stirred solution of (**2**) (2 mmol) in PhCl (~8 ml) was admixed with solid (**1**) (3 mmol), the resulting suspension refluxed for 4 h, the clear solution thus obtained evaporated *in vacuo*, and the residue chromatographed on silica gel. Elution with PhH–EtOAc (7:3) gave (**3**) (70%), m.p. 94—95 °C(EtOAc–hexane).



Scheme 1



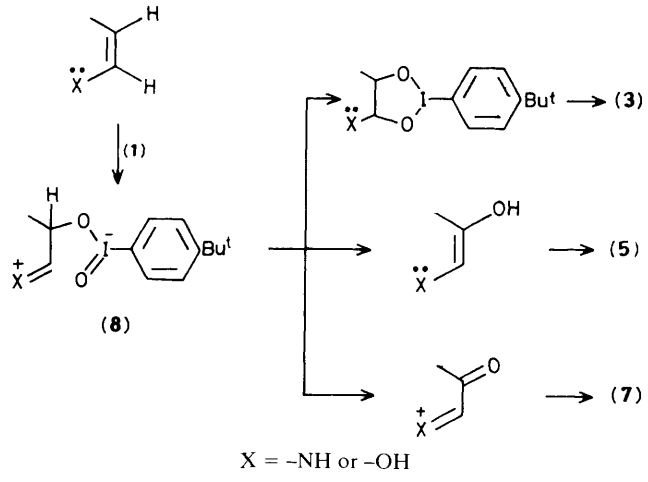
Scheme 2



Scheme 3

In both the liver and bacteria, histidine is metabolized to glutamic acid, formic acid, and ammonia. Interestingly, the reaction of (**1**) with the histidine side chain proceeded by a strikingly similar pathway. Thus, the reaction of *N*-benzyloxycarbonylhistidine methyl ester (**4**) with 1 equivalent of (**1**) in refluxing PhCl for 7 h gave a compound (38%, m.p. 175 °C) for which the structure *N*-benzyloxycarbonyl-γ-formamidoglutamine methyl ester (**5**) has been assigned on the basis of spectral and analytical data. The reaction also afforded the elimination product, benzylcarbamate (15%).§ The formation

§ Our work on the reaction of (**1**) with several protected amino acids and peptides indicates that whilst peptide bonds and benzoyl protecting groups are stable in hot PhCl, the benzyloxycarbonyl protecting group shows a tendency towards elimination.



Scheme 4

of (**5**) may be rationalized on the basis of (**1**)-mediated 4(5) hydroxylation of (**4**), leading to a 4(5)-imidazolone and subsequent hydrolysis (Scheme 2). A similar sequence of events has been established for histidine catabolism.[3] 4(5)-Imidazolones exhibit tautomerism and can be readily cleaved with acids and bases.[4]

N-Benzoyltyrosine methyl ester (**6**) was rapidly consumed (0.5 h) in refluxing PhCl containing 2 equivalents of (**1**). No acidic product arising from complete ring oxidation was observed. On chromatography the highly coloured neutral fraction gave a t.l.c. pure fraction as orange flakes, m.p. 149 °C, for which the quinone structure (**7**) has been assigned on the basis of spectral data. The formation of the rather unstable (**7**) (30%) may be understood on the basis of the known ability of $PhIO_2$ to bring about such changes (Scheme 3).[5]

Finally, *N*-benzoylphenylalanine methyl ester was recovered unchanged on treatment with (**1**) in refluxing PhCl, under a variety of conditions.

In its reactivity towards aromatic compounds, similarities exist between the behaviour of (**1**) and that of ozone and Ru^{VIII}. An important difference, however, is the requirement of an electron rich π-bond in the case of (**1**). All the oxidations reported here most likely proceed through the common intermediate (**8**), which then collapses to the diverse products (Scheme 4). Consequently, it can be concluded that, in general, lone pair liganded aromatic systems should give rise to (**8**) and that its further decomposition is likely to be dictated by subtle factors characteristic of the substrate.

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