Diethyl Azodicarboxylate Oxidation of Some Carcinogenic Arylhydroxylamines to Nitroso Derivatives

It has been demonstrated that 2-nitrosonaphthalene[1-3], 1-nitrosonaphthalene[4] and 4-nitrosobiphenyl[5] are urinary metabolites of the corresponding arylamines in the dog. 2-Naphthylamine and 4-aminobiphenyl are both powerful bladder carcinogens in man and the dog whereas 1-naphthylamine is presumably non-carcinogenic in these species.

In order to study the carcinogenicity of these nitroso compounds in several species, a rapid and efficient method of their synthesis was sought. Existing methods are quite tedious and result in low yields.

TAYLOR and YONEDA[6] reported the oxidation of N-phenylhydroxylamine to nitrosobenzene in 89% yield with diethyl azodicarboxylate. Extending this observation, we wish to report the rapid and efficacious oxidation of N,1- and N,2-naphthylhydroxylamine and N,4-biphenylhydroxylamine to their corresponding nitroso derivatives in high yield with this reagent.

To a stirred ether solution of N,1- or N,2-naphthylhydroxylamine[7,8] cooled to 0 °C is added dropwise an ether solution containing one equivalent of freshly distilled diethyl azodicarboxylate (Aldrich). The reactions were followed by thin layer chromatography on silica gel G with petroleum ether (40–60°), acetone (4:1) and the nitroso compounds detected with 5% aqueous trisodium acetacyanoamino ferrate. After completion (under 1 h), the precipitate of diethyl hydrazodicarboxylate is removed by filtration, the ether removed in vacuo, and a benzene solution of the residue applied to a silica gel column and developed with n-hexane-benzene (7:1)[3]. The bright emerald green band of nitroso compound was collected, the solvent removed in vacuo to yield light yellow-green crystals in 90–95% depending on the purity of the naphthylhydroxylamines. The 1- and 2-nitrosonaphthalenes[1,3,7] were identical to those prepared by the $KMnO_4$ oxidation of the ammonium salts of the corresponding N-nitrosonaphthylhydroxylamines (mixed mp, IR- and UV-spectra and Rf values).

Using chloroform as a solvent, 4-nitrosobiphenyl mp 73–74 (lit.[9] mp 73–74) was prepared from N,4-biphenylhydroxylamine[10] in 90–92% yields.

Zusammenfassung. Eine schnelle und wirksame Methode für die Oxydation von N,1- und N,2-Naphthylhydroxylamin und N,4-Biphenylhydroxylamin wird beschrieben, bei der diese Hydroxylamine durch Diethylazodicarboxylat zu den entsprechenden Nitrosoderivaten, in hoher Ausbeute umgewandelt werden.

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[4-Proline, 8-Isoleucine]-Oxytocin and [4-Leucine, 8-Isoleucine]-Oxytocin, Possible Intermediates in the Evolutionary Series of Neurohypophysial Hormones: Synthesis and Some Pharmacological Properties

The biogenesis of the neurohypophysial hormones appears to involve at one stage the standard ribosomal mechanism of protein synthesis[1]. It is therefore not surprising that most of the structural differences between the homologous hormones of this group involve amino-acid replacements which can be accounted for by single base changes in the appropriate codons[2,3]. The single exception to this rule is the occurrence, in sequence position 4, of either glutamine (oxytocin, the vasopressins, vasotocin, mesotocin) or serine (isotocin, glumitocin). None of the known codons for glutamine on the one hand and for serine on the other can be interrelated by single base changes. This suggests the occurrence, as an evolutionary intermediate, of a peptide with an amino acid in position 4 which can be related to both glutamine and serine by single base changes. Proline meets this condition (Table I) but substitution of this imino acid for an amino acid (serine or glutamine) in the already conformationally constrained cyclic portion of the molecule would be expected to cause profound changes in the topochemistry of the molecule and hence probably loss of biological activity; such a mutant molecule would be unlikely to survive long enough to undergo further evolution.

Alternative links between the 4-serine and 4-glutamine series through a *single* intermediate peptide could be formulated by postulating *three* successive single base changes, one of these changes relating 2 codons for the same intermediate amino acid. Leucine and arginine meet these requirements (Table I) and of these 2 the neutral leucine seems the most likely in terms of the 'conservative' character of the change.

To facilitate the search for possible evolutionary intermediates in lower vertebrates we have synthetised the 2 peptides regarded as the most likely candidates, [4-proline, 8-isoleucine]-oxytocin (Ia) and [4-leucine,

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