ipso-Attack Involving both Displacement and Rearrangement Reactions in the Electrophilic Substitution of Indoles by Aryl Diazonium Salts

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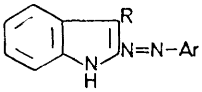
Summary Di-indolyl-methanes react with *p*-nitrophenyldiazonium ion to afford both 3-*p*-nitrophenylazo-indoles and 3-(*p*-nitrophenylazo)-2,3′-di-indolylmethane by displacement and rearrangement respectively.

In our studies of electrophilic substitution in indole and its simple alkyl derivatives we have found that initial attack on the indole nucleus probably always occurs at the 3-position.[1] If this is already substituted the incoming group subsequently rearranges to the 2-position; in the case of certain intramolecular reactions the substituent already present may migrate instead.[2]

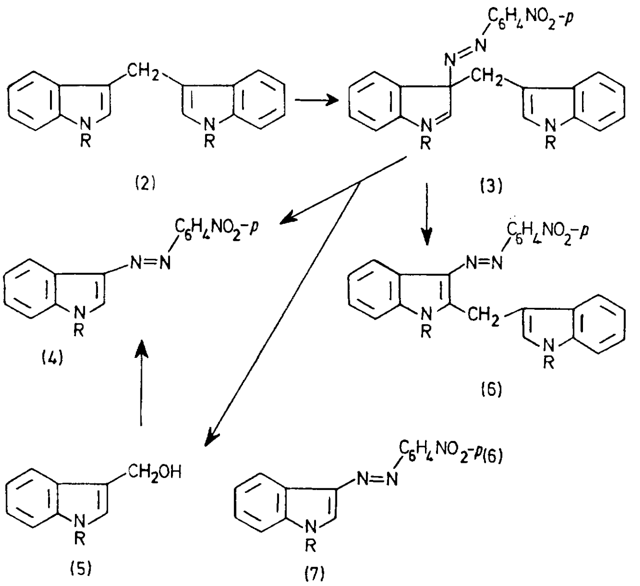


(1)

In this connection it was of interest to explore the reactions of 3-substituted indoles with the weakly electrophilic aryl-diazonium salts. Simple 3-alkyl-indoles give rise to 3-alkyl-2-aryl-azo-indoles (**1**) and there is a considerable amount of indirect evidence that these reactions, like those already reported, involve primary attack at the 3-position followed by rearrangement.[3,4] We now describe direct evidence for this substitution and migration process.

Treatment of 3,3-di-indolyl-methane (**2a**) with *p*-nitrobenzenediazonium tetrafluoroborate (2 equiv.) in aqueous solution afforded 3-*p*-nitrophenylazo-indole (**4a**) in $>$ 90% yield; the methylene bridging group was eliminated as formaldehyde which was isolated in 27% yield as its dimedone derivative after careful distillation of the aqueous solution. With only 1 equiv. of diazonium salt a mixture of the azo derivative and starting material were obtained; an intermediate in this reaction was thought to be the hydroxymethyl indole (**5**) formed as shown in the Scheme, and kinetic studies with this compound (prepared independently) showed that it reacts with the diazonium salt at a much faster rate than the di-indolylmethane.

When the azo-coupling reaction was carried out in acetonitrile, two coloured products were obtained as well as a small amount of tarry decomposition products. The less polar of these two materials was shown to be the *p*-nitrophenylazoindole (**4a**) (45%) whilst the other was isolated as an unstable dark red solid, which decomposed slowly when kept, or very rapidly on heating. The electron-impact mass spectrum showed strong ions at *m/e* 257, 138, 108, 92, 80, and 65, all but the ion at *m/e* 257 being characteristic of *p*-nitroaniline, the only thermal decomposition product which could be characterised. However, the field desorption spectra at low wire currents showed only the molecular ion at *m/e* 395 ($C_{23}H_{17}N_5O_2$), but on increasing the wire current this ion diminished in intensity and was replaced by two ions at *m/e* 257 and 138. The n.m.r. spectrum of this red material confirmed that it was derived from substitution of the aryldiazonium ion into the diindolyl methane. Careful comparisons with the spectra of other related 3- and 2-arylazoindoles (at both 100 and 220 MHz) allowed assignment of the structure (**6a**) shown; in particular the position of the 4-proton resonance (at τ 1·40 in Me_2SO) was particularly revealing because the corresponding proton resonated at τ 1·56 in the 3-arylazoindole (**7**) and at τ 2·26 in the 2-aryl azoindole (**1**, R = Me, Ar = *p*-$NO_2C_6H_4$) [measured in $(CD_3)_2CO$]. This assignment was also supported by the visible spectrum of (**6a**) which showed λ_{max} 422, shifted to 554 nm on addition of alkali (owing to ionisation of the NH proton); the corresponding shift for the simple 3-arylazoindole (**7**) was from 424 to 555 nm, whereas the 2-arylazoindole (**1**, R = Me, Ar = *p*-$NO_2C_6H_4$) absorption only shifted from 425 nm to 475 nm in alkali. Attempts to confirm the structure by alternative syntheses have, however, so far been unsuccessful.



a; R = H
b; R = Me

Scheme

Similar results were also obtained with the analogous 1,1′-dimethyldi-indolylmethane (**2b**), both the aryl azoindole (**4b**) and the 3-arylazo-2,3′-di-indolylmethane (**6b**) being obtained.

It is thus clear that in these reactions the incoming electrophile (the aryldiazonium salt) attacks the already substituted 3-position [*cf.* structure (**3**) in the Scheme], either displacing it completely, or alternatively causing it to migrate to the neighbouring 2-position. Di-indolylmethanes were chosen for these experiments because of the known high migratory aptitude of 'benzylic' species and also because the well known Van den Bergh test for bilirubin involves a similar cleavage of a di-pyrrolylmethane unit.[6] The novelty of the present reactions is that not only does cleavage occur as a result of electrophilic attack by the diazonium salt, but that the competitive reaction involving rearrangement of the indolyl methyl group also occurs simultaneously. Furthermore, in the previous cases in which electrophilic attack caused migration of a 3-substituent to the 2-position the reactions involved either intramolecular cyclisation,[2] or electrophilic attack on the indolyl Grignard derivatives rather than on the free indoles.[1,5]

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