442. *Aromatic Azo-compounds. Part III.* Oxidation of Azonaphthalenes and Phenylazonaphthalenes.*

By G. M. Badger and G. E. Lewis.

The rates of oxidation of the two phenylazonaphthalenes and of the three azonaphthalenes with perbenzoic acid have been determined at four temperatures. The energies of activation have been calculated, and the results interpreted in terms of the extent of conjugation of the azo-group with the ring system, and of steric hindrance.

It is concluded that the carcinogenic substance, 2 : 2′-azonaphthalene, is *not* closely related to the carcinogenic aminoazo-compounds.

Although most of the azo-compounds which produce liver cancers in experimental animals are amino-derivatives, a few carcinogens are known which do not possess an amino-group. 2 : 2′-Azonaphthalene produces liver tumours in mice, and 1 : 1′-azonaphthalene also has slight activity; but 1 : 2′-azonaphthalene is inactive (Cook, Hewett, Kennaway, and Kennaway, *Amer. J. Cancer*, 1940, **40**, 62). It seemed of interest to examine the azonaphthalenes and phenylazonaphthalenes in the light of Pullman's hypothesis (*Compt. rend.*, 1946, **222**, 1501; 1947, **224**, 1773; Pullman and Pullman, *Rev. Sci.*, 1946, **84**, 145), and the rates of oxidation of these unsubstituted azo-compounds with perbenzoic acid have accordingly been determined.

The reactions were carried out as described in Part I (*J.*, 1953, 2143), and a preliminary note on the rate constants at 25° for the azonaphthalenes has been published (Badger and Lewis, *Nature*, 1951, **167**, 403). The rates of reaction have now been determined at four temperatures, and the results are summarised in Table 1, the rate constants for *trans*-azobenzene being included for reference.

Table 1. *Rate constants and activation energies for reaction between azo-compounds and perbenzoic acid.**

Azo-naphthalene	10^3k_2 (mole^{-1} min.$^{-1}$ l.) 15°	20°	25°	30°	$\Delta H^{\ddagger}$ (kcal.)	X	Y	Z
(Azobenzene)	5·80 ± 0·07	9·02 ± 0·15	13·9 ± 0·3	20·9 ± 0·3	14·8 ± 0·3	0	0	0
2-Phenyl- ...	6·03 ± 0·10	9·40 ± 0·16	14·5 ± 0·3	22·3 ± 0·3	15·1 ± 0·4	+0·3	+0·3	0
2 : 2′-	7·23 ± 0·09	11·5 ± 0·2	17·6 ± 0·4	26·6 ± 0·3	15·1 ± 0·3	+0·3	+0·4	−0·1
1-Phenyl- ...	6·10 ± 0·1	9·46 ± 0·18	14·5 ± 0·3	22·2 ± 0·3	14·9 ± 0·4	+0·1	+0·1	0
1 : 2′-	7·34 ± 0·1	11·6 ± 0·2	17·7 ± 0·3	26·8 ± 0·3	15·0 ± 0·3	+0·2	+0·3	−0·1
1 : 1′-	0·89 ± 0·024	1·52 ± 0·07	2·46 ± 0·11	4·05 ± 0·06	17·5 ± 0·5	+2·7	+1·7	+1·0

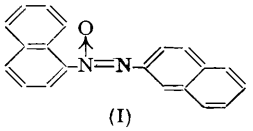
* $\Delta H_0^{\ddagger}$, $\Delta S_0^{\ddagger}$, and $\Delta F_0^{\ddagger}$ refer to the heat of activation, entropy of activation, and free energy of activation, respectively, for *trans*-azobenzene. $X = \Delta H^{\ddagger} - \Delta H_0^{\ddagger}$; $Y = T(\Delta S^{\ddagger} - \Delta S_0^{\ddagger})$; $Z = \Delta F^{\ddagger} - \Delta F_0^{\ddagger}$; all in kcal. The quantities $T(\Delta S^{\ddagger} - \Delta S_0^{\ddagger})$ and $\Delta F^{\ddagger} - \Delta F_0^{\ddagger}$ were calculated from the data at 25°.

The azoxy-compound was isolated from the reaction mixture in each case. 2 : 2′-Azonaphthalene was oxidised more rapidly than azobenzene, giving 2 : 2′-azoxynaphthalene. 1 : 1′-Azonaphthalene was oxidised rather more slowly, and gave the azoxy-compound. In the following paper (Part IV), it is shown that the *peri*-hydrogen atoms offer steric interference with the oxygen atom in 1 : 1′-azoxynaphthalene, and that this molecule cannot be coplanar. It is reasonable to conclude, therefore, that steric hindrance must be a factor in all oxidations which take place at an azo-nitrogen atom which is adjacent to the 1-position in naphthalene.

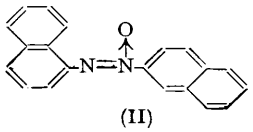
Only one azoxy-compound was obtained by oxidation of 1 : 2′-azonaphthalene and this is regarded as having the "β"-structure (II). This is supported by spectrographic evidence (Part IV), and also by the fact that 1 : 2′-azonaphthalene was oxidised at almost

* Part II, preceding paper.

the same rate as 2 : 2′-azonaphthalene. The azo-nitrogen atom adjacent to the 1-position is sterically hindered, and the isomeric azoxy-compound (I) seems not to be formed at all.

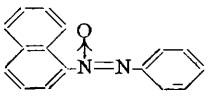


(I)
" α "-Isomer

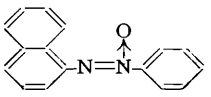


(II)
" β "-Isomer

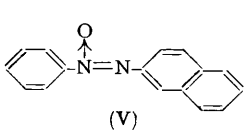
Oxidation of 1-phenylazonaphthalene likewise gave only one azoxy-compound, and spectrographic evidence (Part IV) indicates that this must be the " β "-isomer (IV). This structure is supported by the fact that the same compound was also obtained as a by-product in the preparation of 1-phenylazonaphthalene by condensation of nitrobenzene and 1-naphthylamine in the presence of sodium hydroxide at 170° (Martynoff, *Bull. Soc. chim.*, 1951, 214). It is true that the mechanism of this reaction requires elucidation, but it is significant that the isomeric azoxy-compound (III) could not be isolated from the reaction mixture.



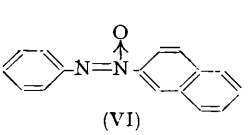
(III)
" α "-Isomer



(IV)
" β "-Isomer



(V)
" α "-Isomer



(VI)
" β "-Isomer

The oxidation of 2-phenylazonaphthalene gave an azoxy-compound, which, after recrystallisation, had m. p. 98°, and was at first thought to be homogeneous. It was subsequently found, however, that this product is a eutectic mixture of the two azoxy-compounds (V and VI) of m. p. 125° and 117°. The crude oxidation product seems to contain about 41% of the isomer of m. p. 125° and 59% of that of m. p. 117°. This ratio is almost the same as the ratio of the reaction rates of azobenzene and 2 : 2′-azonaphthalene (Table 1), so the isomers are regarded as having respectively the " α "- and the " β "-structure, (V) and (VI). This conclusion is supported by the fact that the isomer of m. p. 125° was also obtained as a by-product in the condensation of nitrobenzene with 2-naphthylamine in the presence of sodium hydroxide at 180° (cf. Ramart-Lucas, Guilmart, and Martynoff, *Bull. Soc. chim.*, 1947, 424). None of the isomeric azoxy-compound, m. p. 117°, was obtained in this reaction; had any been formed, a mixture of this isomer with the azoxy-derivative, m. p. 125°, would have been isolated, for the eutectic cannot be separated into its components by chromatography on alumina.

Discussion.—The oxidation of azo-compounds with perbenzoic acid exhibits second-order kinetics, and can be represented by the equation :

$$\mathrm{Ar{-}\overset{\cdot\cdot}{N}{=}\overset{\cdot\cdot}{N}{-}Ar' + Ph{\cdot}CO_3H = Ar{-}\overset{\cdot\cdot}{N}(\rightarrow O){=}\overset{\cdot\cdot}{N}{-}Ar' + Ph{\cdot}CO_2H}$$

Substituents may be expected to have a profound influence on the electron density around the nitrogen atoms, and it has been shown (Part II) that they have a considerable influence on the rate of reaction and on the energy of activation.

The azo-group is, of course, conjugated with the ring system, and with unsubstituted compounds the extent of conjugation must be a most important variable, depending on the ring system and the position of the azo-group. The greater the conjugation, the smaller must be the bond order of the N=N bond and the smaller the " availability " of the nitrogen " lone pairs."

According to Coulson and Longuet-Higgins (*Proc. Roy. Soc.*, 1948, *A*, **195**, 188) the conjugating power of a position is β times the self-polarisability of that position, as calculated by the method of molecular orbitals. It has also been shown that the free-valence number (whether calculated by the method of molecular orbitals, or by the valence-bond method) can also be used as an index of conjugating ability (Pullman, *Compt. rend.*, 1946, **222**, 1396; Daudel, *ibid.*, 1950, **230**, 99).

The calculated values for the 1- and the 2-position in naphthalene and for a phenyl ring are given in Table 2. All three methods indicate that the 1-position in naphthalene has a greater conjugating ability than the 2-position, and that this in turn is very slightly greater than the conjugating ability of a phenyl ring. The available experimental evidence (Badger, Pearce, and Pettit, *J.*, 1952, 1112) also indicates that the 1-position of naphthalene has a much greater conjugating ability than the 2-position.

TABLE 2. *Conjugating abilities of the two positions in naphthalene and in benzene.*

	Index of conjugating ability		
Position	Self polarisability * (M.O. method)	Free valence number † (M.O. method)	Free valence number ‡ (V.B. method)
1-Naphthyl	0·443	0·134	0·122
2-Naphthyl	0·405	0·086	0·098
Phenyl	0·398	0·081	0·073

* These values should be multiplied by $1/\beta$ (Coulson and Longuet-Higgins, *loc. cit.*).
† Burkitt, Coulson, and Longuet-Higgins, *Trans. Faraday Soc.*, 1951, **47**, 553.
‡ Pullman, *Ann. Chim.*, 1947, **2**, 5.

This is reflected in the bond orders of the ethylenic bond in stilbene and in the dinaphthylethylenes (Coulson, *J.*, 1950, 2252). The ethylenic bond in stilbene has a bond order of 1·820, that in 2 : 2′-dinaphthylethylene of 1·814, and that in 1 : 1′-dinaphthylethylene of 1·792 : *i.e.*, the greater the conjugation, the smaller the bond order.

It is well known that there is a smooth-curve relationship between the bond orders of carbon–carbon bonds and their length, but it does not seem to be so well known that a similar relationship holds for nitrogen–nitrogen bonds, the two curves being very nearly parallel. It is resonable to suppose, therefore, that the bond orders of the N=N bonds in azobenzene and in the azonaphthalenes will parallel those of the C=C bonds in stilbene and the dinaphthylethylenes. Buu-Hoï *et al.* (*Bull. Soc. chim.*, 1951, **18**, 132c) have calculated that the N=N bond in azobenzene has a bond order of 1·746; 2 : 2′-azonaphthalene must therefore have a bond order slightly less than this, and 1 : 1′-azonaphthalene must have a still smaller bond order. Moreover, as the conjugating ability is the controlling factor in each case, the " availability " of the nitrogen " lone pairs " must clearly vary in the same sequence.

Of the six compounds included in Table 1, two undergo oxidation at an azo-nitrogen which is adjacent to a phenyl ring, two are attacked at a nitrogen adjacent to a 2-position in naphthalene, and one (2-phenylazonaphthalene) gives a mixture of two azoxy-compounds. It should therefore be possible to avaluate the relative conjugating abilities of a phenyl ring and of the 2-position in naphthalene.

As Hammett has pointed out (" Physical Organic Chemistry," McGraw-Hill, 1940, pp. 118 *et seq.*). when the entropy of activation ($\Delta S^{\ddagger}$) is constant for a series of related compounds, the equation, $\Delta H^{\ddagger} = \Delta F^{\ddagger} - T\Delta S^{\ddagger}$, reduces to $\Delta H^{\ddagger} = \Delta F^{\ddagger}$. In these circumstances, differences in the heats of activation and in the free energies of activation have the same significance, and both are equal to the potential-energy change for the reaction. The experimental determination of the free energy of activation, however, is much more accurate than that of the heat of activation. Furthermore, differences in potential energy can be associated almost entirely with changes in electron density at the reacting centre.

For the five compounds which are oxidised at a nitrogen atom adjacent to either a phenyl ring or a 2-position in naphthalene, the entropies of activation are found to be constant [*i.e.*, $T(\Delta S^{\ddagger} - \Delta S_0^{\ddagger}) \sim 0$], within experimental error. The heats of activation and the free energies of activation are found to be almost identical. Therefore, in spite of the fact that there are some differences in the rates of reaction, it can only be concluded that the electron densities around the nitrogen atoms in these compounds are very nearly equal. This conclusion is in substantial agreement with the theoretical work (Table 2) which indicates that the 2-position in naphthalene has a conjugating ability which is only very slightly greater than that of a phenyl ring.

In the case of 1 : 1′-azonaphthalene, steric hindrance is clearly a factor, in addition to

the increased conjugating ability of the 1-position. It reacts very much more slowly than its isomers, and has a much greater heat of activation. The steric factor is also confirmed by the significant increase in the entropy of activation compared with either azobenzene or 2 : 2′-azonaphthalene.

Application to Problem of Carcinogenesis.—The results clearly indicate that the liver carcinogen, 2 : 2′-azonaphthalene, has an electron density around the nitrogen atoms which is almost the same as that in the non-carcinogenic substances, azobenzene and 1 : 2′-azonaphthalene. Moreover, this electron density must be very much below the value for the carcinogenic aminoazo-compounds such as *o*-aminoazotoluene and 4-dimethylaminoazobenzene (see Part II).

If it is assumed that Pullman's hypothesis is valid for the aminoazo-compounds, then it can only be concluded that 2 : 2′-azonaphthalene must act by a different mechanism. As a matter of fact this seems not unlikely. 2 : 2′-Azonaphthalene produces liver tumours in mice, but not in rats (Cook, Hewett, Kennaway, and Kennaway, *loc. cit.*; Badger, Lewis, and Reid, unpublished), although the aminoazo-compounds are quite active in the latter species.

Furthermore, it has been suggested (Cook, Hewett, Kennaway, and Kennaway, *loc. cit.*) that 2 : 2′-azonaphthalene is not active *per se*, but that it is converted into a carcinogenic substance in the liver of the mouse. It was suggested that it may be reduced *in vivo* to the hydrazo-derivative and that it may subsequently undergo the benzidine rearrangement and loss of ammonia to give 3 : 4-5 : 6-dibenzocarbazole; this substance is certainly a potent carcinogen, and although there is no direct evidence that this conversion does take place, all the available data are consistent with this view. The slight carcinogenic activity of 1 : 1′-azonaphthalene can be explained by its analogous conversion into the slightly carcinogenic 1 : 2-7 : 8-dibenzocarbazole. The aminoazo-compounds, however, may not owe their activity to a metabolic transformation of this type, but may act by a different mechanism; and with these compounds the amino-group may well be an essential feature.

Experimental

1 : 1′-*Azonaphthalene.*—This was prepared by the action of sodium sulphite and sodium acetate on diazotised 1-naphthylamine according to Cohen and Oesper (*Ind. Eng. Chem., Anal.*, 1936, **8**, 306). It was purified by chromatography on alumina from light petroleum. Development was carried out with light petroleum containing 10%, 20%, and then 30% of benzene. The 1 : 1′-azonaphthalene was less strongly adsorbed and was sharply separated from impurities which were retained near the top of the column. After evaporation of solvent and recrystallisation from ethanol, it had m. p. 190°.

2 : 2′-*Azonaphthalene.*—2-Naphthylamine was diazotised and treated with sodium sulphite and sodium acetate exactly as above. The crude product was recrystallised from 50 : 50 light petroleum–benzene (charcoal) and had m. p. 208°, unchanged after chromatography.

1 : 2′-*Azonaphthalene.*—4-Amino-1 : 2′-azonaphthalene was diazotised in alcohol, and the mixture boiled (Nietzki and Göttig, *Ber.*, 1887, **20**, 612). The tarry product was precipitated by water and extracted with light petroleum. After several washes with water, the solution was dried (Na_2SO_4) and passed through a column of alumina; development and elution as before gave a sharp separation of the product. After evaporation of solvent and recrystallisation from alcohol, the 1 : 2′-azonaphthalene had m. p. 145° (yield 45%).

1-*Phenylazonaphthalene.*—(i) 4-Phenylazo-1-naphthylamine was diazotised in alcohol, and the mixture boiled (Nietzki and Zehntner, *Ber.*, 1893, **26**, 143). The crude product was purified as for 1 : 2′-azonaphthalene. After a final recrystallisation from ethanol, 1-phenylazonaphthalene had m. p. 70° (yield 50%).

(ii) For the preparation of a large quantity of material, Martynoff's method (*loc. cit.*) was more satisfactory. After purification by chromatography and recrystallisation, 1-phenylazonaphthalene, m. p. 70°, was obtained. A small band following immediately after 1-phenylazonaphthalene on the chromatogram was also eluted. Evaporation of the solvent and recrystallisation from alcohol gave " β "-1-phenylazoxynaphthalene m. p. 84°, identical with the product (see below) obtained by oxidation of 1-phenylazonaphthalene with perbenzoic acid.

2-*Phenylazonaphthalene.*—This was prepared in quantity by condensing nitrobenzene with 2-naphthylamine in the presence of sodium hydroxide at 180° (Ramart-Lucas, Guilmart, and

Martynoff, *loc. cit.*). After purification by chromatography and recrystallisation from alcohol, it had m. p. 84°. A small band immediately following the 2-phenylazonaphthalene on the chromatogram was also eluted. Evaporation of the solvent and recrystallisation from alcohol gave " α "-2-phenylazoxynaphthalene, m. p. 125°, alone or admixed with a specimen isolated after oxidation of 2-phenylazonaphthalene with perbenzoic acid (see below).

After elution of the 2-phenylazonaphthalene and the small amount (100 mg. in 50-g. preparation) of 2-phenylazoxynaphthalene, a pale yellow band followed. It was eluted with 65% benzene in light petroleum. Evaporation of the solvent and recrystallisation from alcohol gave 1 : 2-benzophenazine as very pale yellow needles, m. p. 142° (Found : C, 83·5; H, 4·5; N, 12·5. Calc. for $C_{16}H_{10}N_2$: C, 83·5; H, 4·35; N, 12·2%). The m. p. was not depressed by admixture of the compound with an authentic specimen, and the absorption spectrum was identical with the published curve (Badger, Pearce, and Pettit, *J.*, 1951, 3199).

Isolation of Azoxy-compounds.—When the oxidation was virtually complete in each case, the reaction mixture was washed with dilute sodium carbonate and then with water, and the solvent evaporated. The crude product was then separated from traces of impurities by chromatography on alumina from light petroleum (benzene–light petroleum being used for elution). The product was finally crystallised from alcohol. (i) 1 : 1′-Azonaphthalene gave 1 : 1′-azoxynaphthalene, m. p. 127° (lit. 127°). (ii) 2 : 2′-Azonaphthalene gave 2 : 2′-azoxynaphthalene, m. p. 166° (lit. 164°). (iii) 1 : 2′-Azonaphthalene gave " β "-1 : 2′-*azoxynaphthalene* (II) as bright yellow needles, m. p. 137° (Found : C, 80·8; H, 4·6. $C_{20}H_{14}ON_2$ requires C, 80·5; H, 4·7%). (iv) 1-Phenylazonaphthalene gave " β "-1-*phenylazoxynaphthalene* (IV) as bright yellow needles, m. p. 84° (Found : C, 77·65; H, 4·9. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·9%). The m. p. was not depressed by admixture with a specimen prepared from nitrobenzene and 1-naphthylamine with sodium hydroxide (see above).

(v) Oxidation of 2-phenylazonaphthalene gave an azoxy-compound which, after chromatography, had m. p. 98·1—99·3°. Recrystallisation from alcohol gave a product melting constantly at 98°, unchanged after careful chromatography. Very slow recrystallisation from a large volume of light petroleum (b. p. 90—120°), however, deposited a small amount of material which on recrystallisation from alcohol gave pure " α "-2-*phenylazoxynaphthalene* (V) as yellow prisms, m. p. 125° (Found : C, 77·1; H, 5·1; N, 11·5; O, 6·4. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·9; N, 11·3; O, 6·45%). The m. p. was not depressed by admixture with a specimen prepared from nitrobenzene and 2-naphthylamine with sodium hydroxide (see above). The structure was confirmed by reduction to 2-phenylazonaphthalene with lithium aluminium hydride.

The other azoxy-compound was isolated following an attempt to brominate the crude product (m. p. 98·1—99·3°) in carbon tetrachloride. After 2 hr. at 0° and then 4 hr. on a water-bath, the excess of bromine was removed by shaking with sodium thiosulphate solution. After removal of the solvent, the residue was treated with a little light petroleum (b. p. 40—60°). The less soluble fraction was chromatographed on alumina from light petroleum in the usual way, and crystallisation of the product from alcohol gave pure " β "-2-*phenylazoxynaphthalene* as pale yellow needles, m. p. 117° (Found : C, 77·65, 77·4; H, 5·0, 4·9%). The product did not contain bromine and it was readily reduced to 2-phenylazonaphthalene with lithium aluminium hydride.

The eutectic for the binary system was found by the " thaw-melt " method to have the composition of 42·5% of the isomer, m. p. 125°, and 57·5% of the isomer, m. p. 117°. The m. p. of the perbenzoic acid oxidation product (98·1—99·3°) was depressed by the addition of a very small amount of isomer, m. p. 125°, and the product therefore had approximately the composition given on p. 2152.

Rate Determinations.—Rates of reaction were determined exactly as for *trans*-azobenzene (Part I), three determinations being carried out at each temperature.

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