365. *The Mechanism of the Coupling of Diazonium Salts with Heterocyclic Compounds. Part III.* Indazole.*

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The mechanism of the coupling of diazonium compounds with indazole has been studied by determining the variation in the rate of coupling with diazosulphanilic acid over the pH range 8·5—10·1. The results indicate that the reaction involves only the small proportion of anion in equilibrium with the neutral indazole molecule in these solutions.

The observed orientations for various electrophilic substitutions in indazole are briefly reviewed in the light of the mechanism now established.

Some kinetic evidence suggests that the azo-compound formed initially in this reaction undergoes a further reaction with another molecule of the diazonium compound.

Our previous investigations of the coupling mechanism with heterocycles containing a secondary nitrogen atom in a five-membered ring have shown that sometimes the neutral molecule is involved [1] and sometimes the anion obtained by ionization of the proton from the secondary nitrogen atom.[2] These observations clarify apparent anomalies for the orientation of electrophilic substitutions since the orientation expected for the neutral molecule may differ from that in the anion.[3,4] In the case of indazole the observed orientations suggest that in electrophilic substitutions different forms of indazole are involved in different cases because nitration occurs at the 5-position,[5] while diazo-coupling [6] and iodination in alkaline solution [7] yield 3-substituted indazoles. Since the last two reactions involve alkaline solutions while nitration occurs in acidic media, the implication is that the former result from substitution in the indazole anion and the latter in the neutral molecule or cation. We have now established this for diazonium coupling by determining the manner in which the rate of reaction varies with the pH of the solution.

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* Part II, *J.*, 1957, 2398.

[1] Binks and Ridd, *J.*, 1957, 2398.

[2] Brown, Duffin, Maynard, and Ridd, *J.*, 1953, 3937.

[3] Bassett, Brown, and Penfold, *Chem. and Ind.*, 1956, 892.

[4] Brown and Heffernan, *J.*, 1956, 4288.

[5] von Auwers and Kleiner, *J. prakt. Chem.*, 1928, **118**, 75.

[6] Bamberger and von Goldberger, *Annalen*, 1899, **305**, 350.

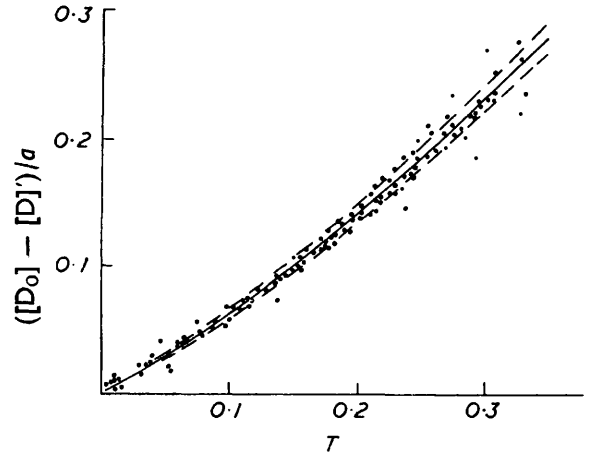
[7] von Auwers and Lohr, *J. prakt. Chem.*, 1924, **108**, 297.

EXPERIMENTAL

Indazole (L. Light & Co.) was recrystallized from water and from ligroin (b. p. 60—80°) to constant m. p. 147° (corr.). Sulphanilic acid, sodium nitrite, and buffer reagents were of " AnalaR " quality. The R-acid was B.D.H. purified sodium salt. Buffer solutions were made from appropriate quantities of borax, boric acid, or carbon dioxide-free sodium hydroxide solution; the concentrations were adjusted to produce an ionic strength of 0·05. Kinetic runs were performed substantially as described in Part I [2] except that the reaction was stopped by running 5 ml. aliquot parts into a mixture of 25 ml. of saturated borax and 1·0 ml. of 1·0% R-acid sodium salt solution, and in the diazotization hydrobromic acid was used in place of hydrochloric acid plus sodium bromide.

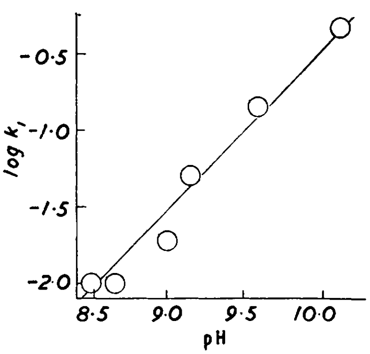
A Hilger Spekker colorimeter was used to determine the concentration of azo-compound produced by the coupling of unchanged diazosulphanilic acid and the R-acid. The " infinity " readings were always small but proportional corrections were applied.

FIG. 1. *Variation of k_1 with* pH *at* 25°.



Top line: $k_1 = 0{\cdot}052$, $k_2 = 6$.
Middle line: $k_1 = 0{\cdot}050$, $k_2 = 6$.
Bottom line: $k_1 = 0{\cdot}050$, $k_2 = 5$.

FIG. 2. *Determination of k_1 and k_2 from kinetic data at* pH 9·15.



Evaluation of Reaction Rate Constants.—Runs performed with a large excess of indazole gave appreciable deviations from first-order kinetics. This was initially suspected to be due to concurrent diazonium decomposition which for a variety of diazonium compounds shows [8] considerable deviations from first-order kinetics at higher pH values. However, decomposition of diazosulphanilic acid solutions was too slow to be responsible for the observed deviations. The deviations were found to depend upon the indazole concentration and it was then found possible to account for the observed kinetic curves in terms of two consecutive second-order steps involving the diazonium compound, together with a slow concurrent diazonium decomposition. It is tempting to assume a second coupling of the diazosulphanilic acid with the monoazo-compound first formed because the latter is an anion owing to the presence of the sulphonate group and so may be sufficiently reactive to undergo a rapid second coupling. We have not so far isolated such a bisazo-compound from the reaction mixtures but we hope to investigate this further.

The rate constants for the two steps were evaluated by a modification of Wideqvist's method.[9, 10] In this a correction is first determined for the concurrent diazonium decomposition. Under the conditions of our experiments the initial stages of the decomposition followed very nearly zero-order kinetics. The zero-order rate constants used for correcting for decomposition are given in Table 1. The rates could not be made completely reproducible and the uncertainty

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[8] Brown and Penfold, unpublished results.
[9] Wideqvist, *Arkiv Kemi*, 1955, **8**, 545.
[10] Brown and Coller, *Austral. J. Chem.*, 1958, **11**, 90.

in the listed values may be as great as 50%. However, this has little effect on the determination of the rates of coupling since the decomposition corresponds to only a small correction term.

TABLE 1. *Decomposition of diazosulphanilic acid at* 25°.

Initial concn. × 10^4	2·0	20·0	20·0	2·0	2·0	2·0
pH	8·50	8·65	9·00	9·15	9·60	10·10
k_0 (mole l.$^{-1}$ sec.$^{-1}$ × 10^{10})	6	90	200	50	100	250

TABLE 2. *Coupling of diazosulphanilic acid with indazole at* 25°.

10^4[D]$_0$	2·0	20·0	20·0	2·0	2·0	2·0
No. of runs	3	3	6	11	4	3
Range of a × 10^3	5·4—8·1	7·1—11·4	1·7—11·9	1·6—8·1	2·9—5·1	2·1—5·1
pH	8·50	8·65	9·00	9·15	9·60	10·10
10^2k_1 (l. mole^{-1} sec.$^{-1}$)	1·0 ± 0·1	1·0 ± 0·05	1·8 ± 0·2	5·0 ± 0·2	14·0 ± 1·0	46·0 ± 1·0
k_2 (l. mole^{-1} sec.$^{-1}$)	8 ± 3	5 ± 2	5	6 ± 1	7 ± 1	8 ± 1

From each value of the diazonium concentration determined in a coupling run the variable $T = \int_0^t([\mathrm{D}]_0 - [\mathrm{D}])\mathrm{d}t$ was evaluated by numerical integration, [D] being the observed diazonium concentration. Next an amount k_0t was subtracted from [D] to obtain the "corrected" concentration [D]′, and $([\mathrm{D}]_0 - [\mathrm{D}]')/a$, where a was the initial indazole concentration, was plotted against T. By this procedure it can be shown [9, 10] that for two consecutive second-order steps the points from all runs at a given pH fall on the same curve, namely:

$$([\mathrm{D}]_0 - [\mathrm{D}]')/a = [2(k_1 - k_2) + (2k_2 - k_1)\mathrm{e}^{-k_1T} - k_1\mathrm{e}^{-k_2T}]/(k_1 - k_2)$$

where k_1 and k_2 are the second-order velocity constants for the consecutive reactions. The statistical iterative method suggested by Wideqvist for determining k_1 and k_2 from such curves was found to oscillate too violently be convenient, probably because k_2 is considerably greater than k_1. It was easy to find the two rate constants by trial and error, the fitting of the earlier part of the curve being sensitive to k_1 and of the later part of the curve to k_2. In Fig. 1 the line of best fit (judged by eye) and two curves illustrating variations corresponding to our estimated uncertainties in k_1 and k_2 are shown. Values found for the velocity constants, and their estimated uncertainties, are given in Table 2.

Discussion of Results.—The graph of log k_1 against pH is shown in Fig. 2, a line of slope unity being included with the experimental points. The line of best fit found by a weighted least-squares procedure with the points weighted in inverse ratio to the estimated uncertainty in log k_1 has a slope of 1·09 with 95% confidence limits of ±0·2. Therefore within our limits of accuracy the experimental data conform to the equation

$$-\mathrm{d}[\mathrm{D}]/\mathrm{d}t = k[\mathrm{OH}^-][\mathrm{HIn}][\mathrm{D}]$$

where [OH$^-$] is the actual concentration of hydroxyl ion and [HIn] and [D] represent analytical concentrations of indazole and diazosulphanilic acid respectively. Since [11] the pK_a of the diazonium cation is about 11 and the pK_a of indazole is probably considerably greater, the experimental results agree with either of the following two mechanisms: (i) DOH + HIn $\longrightarrow$ Products, or (ii) $\mathrm{D}^+ + \mathrm{In}^- \longrightarrow$ Products. It is now accepted that diazonium coupling involves electrophilic attack by the diazonium cation, not by the diazohydroxide or diazoate [12] and so scheme (i) must be rejected in favour of (ii). It therefore follows that the heterocycle reacts by way of the small equilibrium proportion of anion present in solution.

The observed orientation in the coupling reaction is thus indicative of the relative reactivities of the various ring positions in the anion rather than in the free base. The preferential attack of the 3-position is in agreement with qualitative molecular-orbital

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[11] Wistar and Bartlett, *J. Amer. Chem. Soc.*, 1941, **63**, 413.
[12] Zollinger, *Chem. Rev.*, 1952, **51**, 347.

predictions with the assumption that both tertiary nitrogen atoms are *less* electronegative than the ring carbon atoms.[3]

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