365. *The Fischer Indole Synthesis. Part IV. A Kinetic Investigation.*

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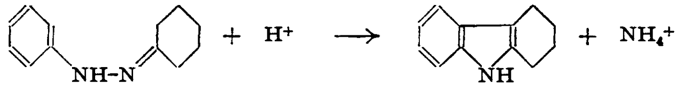
The cyclisation of a number of phenylhydrazones of *cyclo*hexanone has been followed kinetically by determining the amount of ammonia liberated during the reaction. The reaction has been found to be of the first order when carried out in an excess of glacial acetic acid and of the second order when aqueous dioxan–sulphuric acid is used. The rates for seven hydrazones in glacial acetic acid under identical conditions are compared, and a theory is advanced for the mechanism of the reaction.

Although many theories have been advanced for the mechanism of the Fischer indole synthesis (cf. Robinson and Robinson, *J.*, 1918, **113**, 639; 1924, **125**, 827; Allen and Wilson, *J. Amer. Chem. Soc.*, 1943, **65**, 611; Carlin and Fisher, *ibid.*, 1948, **70**, 3421; Pausacker and Schubert, *J.*, 1949, 1384), there is no published account of a kinetic investigation of this reaction.

If the reaction of the phenylhydrazone (I) of *cyclo*hexanone be considered, it is seen that, besides the formation of tetrahydrocarbazole (II), one mole of an ammonium salt is formed simultaneously. It was found that this reaction could be followed quite easily when glacial acetic acid or aqueous dioxan–sulphuric acid was used as a solvent. At definite time-intervals, an aliquot was poured into a large excess of water, in order to " freeze " the reaction, and the organic matter was extracted with ether. The ammonium ion formed was then determined in a standard micro-Kjeldahl apparatus.

(I.)



(II.)

Experimental.

Reagents.—AnalaR glacial acetic acid was refluxed (1 hour) with 1% (by wt.) of chromium trioxide and distilled in an all-glass apparatus protected from moisture. Redistillation gave a constant-boiling fraction, free from ammonium ions.

Dioxan was purified by refluxing it over sodium and distilling the product twice.

The various hydrazones of *cyclo*hexanone were prepared by condensing the hydrazine with *cyclo*hexanone and purified by crystallisation from an appropriate solvent immediately before use. Their m. p.s agreed with those in the literature. cyclo*Hexanone* m-*methoxyphenylhydrazone* could not be crystallised and was a viscous liquid, b. p. 165—167°/0·8 mm. (Found: N, 13·2. $C_{13}H_{18}ON_2$ requires N, 12·8%). This distilled hydrazone did not contain any free ammonia or ammonium ion.

Methods.—(a) *Glacial acetic acid as solvent.* A weighed amount of the pure phenylhydrazone (*ca.* 1 g.) was placed in a 10-ml. standard flask immersed in the constant-temperature bath. After about 15 minutes, pre-heated glacial acetic acid was added with shaking, to make the volume up to the mark. After a further 5 minutes, the first aliquot was analysed, this being taken as zero time.

At definite intervals, 1-ml. aliquots were withdrawn (by means of a standard pipette kept in a tube immersed in the bath) and run into cold water (10 ml.) contained in a separatory funnel. The aliquot was extracted with ether (10 ml.), and the ethereal extract washed (twice) with water (5 ml.). The two combined aqueous solutions were placed in a micro-Kjeldahl apparatus, and sodium hydroxide solution (4 ml., 30%) added. The ammonia liberated was distilled into 10 ml. of 0·05N-hydrochloric acid. About 50 ml. of distillate were collected. The excess of hydrochloric acid was determined with 0·05N-sodium hydroxide, methyl-red being used as indicator.

(b) *Dilute sulphuric acid as solvent.* *cyclo*Hexanone phenylhydrazone (*ca.* 2 g.) was weighed into a 50-ml. standard flask immersed in the constant-temperature bath and dioxan–water (*ca.* 15 ml.; 7 : 3) was added. After *ca.* 15 minutes, concentrated sulphuric acid (1 ml.) was added with shaking, and the mixture made up to the mark with pre-heated dioxan–water. Aliquots (5 ml.) were withdrawn at determined times and run into cold water (10 ml.). This solution was then extracted with ether (25 ml.) and the ethereal extract washed twice with 5-ml. portions of water. Ammonium ion was determined in the usual manner.

Results.—(a) *Glacial acetic acid as cyclising agent.* The results of a typical run were :

Wt. of *cyclo*hexanone phenylhydrazone = 0·9999 g. ≡ 10·65 ml. 0·0508N-HCl per aliquot.
x = ammonia formed, expressed in terms of ml. of 0·0508N-HCl.
Temp. = 44·70° ± 0·06°. $k_1 = \frac{2\cdot303}{t}\log_{10}\frac{a - 0\cdot84}{a - x}$ (sec.$^{-1}$).

t (sec.)	0	3558	6276	9960	14,574	19,866
x	0·84	2·72	3·92	5·38	6·64	7·75
$k_1 \times 10^5$	—	6·08	6·02	6·23	6·13	6·13

The results obtained by investigating the cyclisation of various hydrazones of *cyclo*hexanone in glacial acetic acid are shown in tabular form below. In each case, the value cited is the mean of the values obtained in two or more runs. The k_1 values all appear to be accurate within 2%.

R·NH·N:C$_6$H$_{10}$, R =	k(× 10^5) (44·7°).	k(× 10^5) (24·9°).	*A*.	*E*, kcals.*
p-NO$_2$·C$_6$H$_4$	Too slow to measure (1% reaction after 45 hrs. at 44·7°)			
m-MeO·C$_6$H$_4$	5·10 ± 0·07	0·744 ± 0·04	2·0 × 10^8	18·3
Ph †	6·18 ± 0·10	1·03 ± 0·02	3·2 × 10^7	17·0
β-C$_{10}$H$_7$	46·3 ± 0·8	8·36 ± 0·04	9·3 × 10^7	16·3
p-C$_6$H$_4$Me	47·0 ± 0·3	6·76 ± 0·10	2·3 × 10^9	18·5
α-C$_{10}$H$_7$	177 ± 3	29·4 ± 0·3	9·7 × 10^8	17·1
p-MeO·C$_{10}$H$_7$	Too fast to measure (97% reaction after 2 mins. at 44·7°).			
Ph	7·68 ± 0·13	[1·96% (by wt.) of water added]		
,,	9·37 ± 0·18	[5·33% (by wt.) of water added]		
,,	3·42 ± 0·03	(at 39·2°)		
,,	3·55 ± 0·02	(at 39·2°) [0·07% (by wt.) of quinol added]		

* The *E* values are accurate at least to 0·4 kcal.

† The same result was obtained when the initial weight of the phenylhydrazone was approximately doubled.

(b) *Sulphuric acid–dioxan–water as cyclising agent.* Only the phenylhydrazone of *cyclo*hexanone was investigated under these conditions. When approx. 1·5—1·6 moles of sulphuric acid per mole of the hydrazone were used, the reaction was of the second order.

t.	k_2 (mole l.$^{-1}$ sec.$^{-1}$).	
39·2° ± 0·06°	1·75 (± 0·03) × 10^{-4}	Frequency factor = 3·5 × 10^{13}
44·7° ± 0·06°	3·48 (± 0·07) × 10^{-4}	*E* = 24·7 kcals.

It was found that, when only 0·5 mole of sulphuric acid (*i.e.*, one equiv.) per mole of hydrazone was employed, the reaction stopped when 50% of the hydrazone had been used. This indicates that the ammonium hydrogen sulphate thus formed is not an effective catalyst.

In one experiment, the reaction was allowed to continue for 50 hours in order to ensure completion. A 92% yield of tetrahydrocarbazole (m. p. and mixed m. p., 118°) was isolated after addition of excess of water to the solution. An ammonium-ion determination indicated 96% conversion.

DISCUSSION.

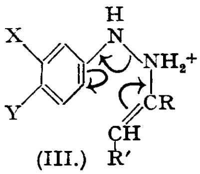
The rate of the reaction is evidently dependent on the availability of (solvated) protons in the reaction mixture, as it is seen that the " k " value increases from 6·18 × 10^{-5} in glacial acetic acid to 7·68 × 10^{-5} and 9·37 × 10^{-5} when 6·3 and 16·0 moles % of water are added. As the rate is dependent both on the concentration of hydrazone and on the acid concentration when sulphuric acid–dioxan–water is used, it is evident that the rate-determining step is the reaction between the original, or rearranged, hydrazone and a solvated proton.

Further evidence of the nature of the mechanism cannot be obtained as the values of *E* and *A* are too close to each other to allow any valid interpretation. In addition, it is found that Hammett's equation is not applicable.

With regard to the criticisms of our mechanism by Gore, Hughes, and Ritchie (*Nature*, 1949, **164**, 835), the following facts may be noted. In their examination of the reaction

$$\begin{array}{ccccl} \text{A—NH—N=B} & + & \text{C—NH—N=D} & \longrightarrow & \text{Tetrahydrocarbazole} + \text{products} \\ \text{(II.)} & & \text{or } R_2CO & & \\ & & \text{or Ph·NH·NH}_2 & & \end{array}$$

(II) is always a hydrazone which will not cyclise, and so the equilibrium of hydrazones will naturally be displaced in favour of that reactant which is removed from the system, *i.e.*, by cyclisation to form tetrahydrocarbazole. Although this work shows that hydrazone exchange may explain our mixed cyclisation results [as we have already stated (*J.*, 1949, 1386)], it does not, unfortunately, decide the crucial point, namely, whether or not, in our mixed cyclisations, cyclisation proceeds sufficiently slowly to allow exchange to be appreciable. This can only be settled by a determination of the relative rates of these two reactions. Gore *et al.* have also drawn attention to the fact that 1 : 8-dimethylcarbazole is not among the products obtained by dehydrogenating the neutral fraction from the mixed cyclisation, but this point has already been discussed (*ibid.*, p. 1386). Finally, they assume that free radicals are not involved as during the cyclisation of *cyclo*hexanone phenylhydrazone in glacial acetic acid they (*a*) obtained a 95% yield, (*b*) did not isolate benzidine (from the dimerisation of Ph·NH*) and (*c*) observed the evolution of only a small amount of carbon dioxide which they expected to be formed in large quantities by interaction of free radicals with the solvent. Although their generalised comments apply to certain free-radical reactions, the following observations may be pertinent. (i) Kharasch and Mayo (*J. Amer. Chem. Soc.*, 1933, **55**, 2468) have found that the peroxide-catalysed addition of hydrogen bromide to allyl bromide gives a 92% yield of 1 : 3-dibromopropane. (ii) Wieland, Popper, and Seefried (*Ber.*, 1922, **55**, 1816) were unable to isolate any diphenyl from the decomposition of phenylazotriphenylmethane even though free phenyl radicals are involved. (iii) The amount of interaction of these free radicals with the solvent cannot be determined and it is possible that the carbon dioxide observed by the above authors does arise from this source, and not from " a side reaction of unknown nature," particularly if it be assumed that the radicals formed have a high affinity for each other and relatively little affinity for solvent molecules. Their observation that the rapid evolution of carbon dioxide occurs as the mixture reaches the boiling point may be explained by the short duration of the reaction [$t_{\frac{1}{2}}$ (120°) = 62 seconds (calc.)]. Finally, although this reaction is indeed exothermic, it would possibly be incorrect to describe it as "strongly exothermic," and in solution one would not expect isolated points of high energy content sufficient to cause thermal decomposition of acetic acid as such phenomena are generally only noted in the gas phase at low pressure.



(III.)

With regard to the proposal by Calvin and Fisher (*J. Amer. Chem. Soc.*, 1948, **70**, 3421), it may be noted that a methoxyl group in position X (of III) would be expected to facilitate reaction, whereas in position Y it would retard reaction. This is not in accord with our results, as we found that *cyclo*hexanone *p*-methoxyphenylhydrazone cyclises immeasurably more rapidly than the *m*-methoxy-compound.

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