119. *The Fischer Indole Synthesis. Part III. The Cyclisation of the Phenylhydrazones of Some 2-Substituted* cyclo*Hexanones.*

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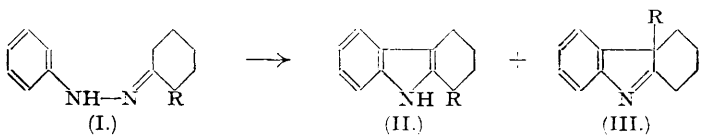
Cyclisation of the phenylhydrazones of a number of 2-substituted *cyclo*hexanones has been effected using both dilute sulphuric acid and glacial acetic acid. Whereas sulphuric acid favoured the formation of the neutral tetrahydrocarbazole, the basic tetrahydrocarbazolenine was the principal product formed when glacial acetic acid was used. A detailed investigation of the action of a large number of cyclising agents on the phenylhydrazone of 2-methyl*cyclo*hexanone has also been made. Certain of the tetrahydrocarbazoles obtained have been dehydrogenated by using palladised charcoal.

IT is well known that the phenylhydrazones of 2-substituted *cyclo*hexanones (I) may be cyclised to form both a neutral tetrahydrocarbazole (II) and a basic tetrahydrocarbazolenine (III).



(I.) (II.) (III.)

Pausacker and Schubert (*J.*, 1949, 1384) found that when R = Me the ratio $\frac{\text{yield of (II)}}{\text{yield of (III)}}$ (hereafter termed *a*) was 2·1 when dilute sulphuric acid was used, whereas Lions (*J. Proc. Roy. Soc. N.S.W.*, 1938, **71**, 206) found that, when R = Et, *a* was 0·13 with glacial acetic acid as the cyclising agent. As this comparison is made on two different substances, it was decided to study the influence of these two cyclising agents on compounds of type (I). The results are summarised in Table I.

TABLE I.

	Dilute sulphuric acid.			Glacial acetic acid.		
R.	Yield of (II), %.	Yield of (III), %.	*a*.	Yield of (II), %.	Yield of (III), %.	*a*.
Methyl	45	21	2·1	6 *	61	0·10
Ethyl	44	28	1·6	13	76	0·17
iso*Propyl*	44	18	2·4	16	70	0·23
cyclo*Hexyl*	29	17	1·7	9	79	0·12
Phenyl	54	19	2·8	27	69	0·39

* Appreciable amounts of *N*-acetylphenylhydrazine were also isolated.

It is thus seen that in every case dilute sulphuric acid gives mainly the tetrahydrocarbazole and glacial acetic acid mainly the tetrahydrocarbazolenine, thus substantiating the results already quoted. An *a priori* hypothesis would predict, by qualitative reasoning, that the stronger acid (sulphuric) should produce a greater proportion of base, whereas the reverse has been found to be the case. This marked difference could be ascribed to different mechanisms operating in these two reactions, although a number of other factors must be considered before any definite conclusion is reached.

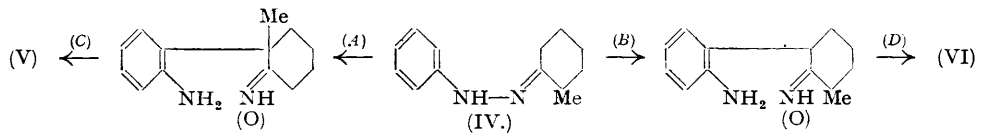
One noteworthy difference is that with glacial acetic acid only one phase is present and in

dilute sulphuric acid two phases are involved. This may be paralleled with the fact that the Cannizzaro reaction (cf. Alexander, *J. Amer. Chem. Soc.*, 1947, **69**, 289) probably proceeds *via* a different mechanism dependent on whether or not the reaction is homogeneous. When the phenylhydrazone of 2-methyl*cyclo*hexanone (IV) was cyclised in aqueous acetic acid containing 20, 40, 60, 80, and 89% of water (by volume) respectively, the percentage yield of the major product, 11-methyltetrahydrocarbazolenine (V), was 56, 55, 57, 58, and 40% compared with 61% when glacial acetic acid was used. In the first case the reaction mixture was homogeneous throughout, in the second case it was initially heterogeneous and became homogeneous on heating, and in the last three cases it was heterogeneous throughout. It thus appeared that the reaction was not influenced by the number of phases present.

It was thus possible that the difference in reaction may be ascribed to the acid strength of the cyclising agent. When (IV) was refluxed with aqueous solutions of approximately equal molar strength of acetic, monochloro- dichloro- and trichloro-acetic acid, the yields of (V) were 40, 42, 51, and 53% respectively (*N.B.* all these reaction mixtures were heterogeneous). The K values of these acids are $1{\cdot}85 \times 10^{-5}$, $1{\cdot}55 \times 10^{-3}$, $5{\cdot}14 \times 10^{-2}$ and $1{\cdot}2 \times 10^{0}$ (?) and yet it is seen that the relative yields of (V) do not vary markedly and tend to increase with increasing acid strength. In view of the remarkable difference between the action of glacial acetic acid and dilute sulphuric acid, this result is very confusing, particularly when it is realised that trichloroacetic acid approaches sulphuric acid in strength, although it has been found that trichloroacetic acid is weaker than sulphuric acid in strong (>2N.) solutions. Thus it would appear that acid strength is not the deciding factor.

Finally, it was considered that as the apparently heterogeneous reaction in aqueous acetic acid gave the same results as when glacial acetic acid was used, the reaction may actually take place in a single phase, as the hydrazone will be partly soluble in the boiling aqueous acetic acid. On the other hand, it would be virtually insoluble in the aqueous sulphuric acid and so the difference between these two reactions may, after all, be due to the number of phases. Accordingly, the cyclisation of (IV) was investigated using alcoholic solutions of sulphuric acid and anhydrous hydrogen chloride. Under these conditions, the initial reactants were soluble, as were the products, with the exception of salts which precipitated during the reaction when hydrogen chloride was used. In the case of sulphuric acid, it was found that although the yield of (V) was greater and the yield of 1-methyltetrahydrocarbazole (VI) was correspondingly smaller, when alcohol was substituted for water as a diluent, the yield of (V) did not approach that obtained with glacial acetic acid. In the case of hydrogen chloride also, the alcoholic solution gave a larger yield of (V) than did the aqueous solution. It may be noted that hydrochloric acid gave a higher yield of (V) than aqueous sulphuric acid of approximately the same normality. Finally dry gaseous hydrogen chloride and a solution of (IV) in dry boiling benzene gave the most surprising results since the yield of (V) was then even greater than with glacial acetic acid and only a very little (VI) was obtained.

In order to harmonise these apparently conflicting findings, it is supposed, on the basis of the accepted mechanism for this reaction (for a summary, see Pausacker and Schubert, *loc. cit.*), that the reaction may proceed as follows:



Now the cyclising agents which favour the formation of (V) are glacial acetic acid, aqueous solutions of acetic acid and its three chloro-derivatives, and hydrogen chloride in benzene The other reagents, in the order in which they favour the yield of (VI), are aqueous sulphuric acid, aqueous hydrogen chloride, alcoholic sulphuric acid, and alcoholic hydrogen chloride. Mr. A. N. Hambly, of this Department, has kindly pointed out that of the first series of media, acetic acid and benzene are protogenic and aprotic respectively, whereas in the latter series both ethyl alcohol and water used are amphiprotic. This suggests that when we have a medium which permits the manifestation of the basic properties of (IV) (*i.e.*, reaction with a proton), then reaction *A*, followed by reaction *C*, is favoured. On the other hand, a medium which tends to decrease the basic characteristics of (IV), by competitive reaction with protons, favours reaction *B* which possibly proceeds by a different mechanism from reaction *A*. Thus the order observed for the second series of solvents may also be explained as water is more protophilic than alcohol and, in addition, there are some indications (cf. " Introduction to

Electrochemistry," Glasstone, p. 310) that sulphuric acid may be more protophilic than hydrochloric acid.

It would now seem that when aqueous solutions of the various acetic acids are used, the reactions must take place in a medium which favours the basic behaviour of (IV). This fact may be accommodated by assuming that the various acetic acids may be dissolved partly in the water and partly in the (IV) (in contrast to the statement made above) and the reaction leading to the principal formation of (V) actually takes place in the acetic acid–(IV) phase.

Thus the different actions of these cyclising agents may be explained by assuming that (IV) has a different proton affinity in the various media used. Up to now, the different formulations of the mechanism of the Fischer indole synthesis have not taken into account the exact role played by the acid catalyst. It would appear in the reaction studied that two alternative mechanisms are simultaneously possible, dependent on the relative proton availability present in the medium. Thus, in future discussions of this reaction it will be necessary to consider, in greater detail, the part played by the catalyst. A kinetic investigation of this reaction is now proceeding with this aim in view.

Experimental.

M. p.s are not corrected.

Preparation of 2-Substituted cyclo*Hexanones.*—2-Methyl-, 2-ethyl-, and 2-*iso*propyl-*cyclo*hexanone were prepared by alkaline hydrolysis of the corresponding 2-carbethoxy-2-alkyl-*cyclo*hexanones, produced by condensation of the appropriate alkyl iodide with the sodio-derivative of 2-carbethoxy-*cyclo*hexanone.

2-*cyclo*Hexyl*cyclo*hexanone was prepared by chromic acid oxidation of 2-*cyclo*hexyl*cyclo*hexanol (cf. Ungnade, *J. Org. Chem.*, 1948, **13**, 361).

2-Phenyl*cyclo*hexanone was prepared by the action of phenylmagnesium bromide on 2-chloro*cyclo*hexanone (Newman and Farbman, *J. Amer. Chem. Soc.*, 1944, **66**, 1551).

Preparation of the Phenylhydrazones.—Equimolar amounts of phenylhydrazine and *cyclo*hexanone were heated (0·5 hour) on the water-bath, first at atmospheric pressure and then under reduced pressure until all the water was expelled.

Cyclisations of the Hydrazones.—The hydrazones were refluxed (0·5 hour) with aqueous sulphuric acid (1 ml. of concentrated acid and 9 ml. of water per g. of hydrazone) or glacial acetic acid (9 ml. per g. of hydrazone). When sulphuric acid was used, the neutral fraction was isolated by extraction with ether and washing first with dilute sulphuric acid and then with water. The 1-substituted tetrahydrocarbazole was isolated by distillation. The sulphuric acid solution and washings were basified with sodium hydroxide solution, and the 11-substituted tetrahydrocarbazolenine isolated by ether-extraction, followed by distillation. When glacial acetic acid was used, the excess of acid was removed by distillation under reduced pressure and the residue treated with water, extracted with ether, and separated into neutral and basic fractions as described above. For yields see Table I. Tables II and III summarise the physical, chemical, and analytical data.

Table II.

1-Substituted tetrahydrocarbazoles.

	Base.				Picrate.		
Substituent.	B. p./mm.	Formula.	Found: N, %.	Reqd.: N, %.	M. p.[d]	Found: N, %.	Reqd.: N, %.
Ethyl[a]	184—186°/0·8	—	—	—	142°[1]	13·2	13·1
iso*Propyl*	190°/0·6	$C_{15}H_{19}N$	6·9	6·6	117[2]	13·1	12·7
cyclo*Hexyl*	195°/0·4	$C_{18}H_{23}N$	5·6	5·5	140[3]	12·1	11·6
Phenyl[b]	187°/0·3[c]	$C_{18}H_{17}N$	5·8	5·8	133[1]	11·9	11·7

[a] Lions (*loc. cit.*) gives b. p. 200—205°/16 mm. [b] Appreciable amounts of 2-phenyl*cyclo*hexanone were also obtained when dilute sulphuric acid was used. [c] M. p. 99°; crystallised from light petroleum (b. p. 40—60°). [d] Crystallisation from light petroleum of b. p.: [1] 100—120°, [2] 60—90°, [3] 95—135°.

Table III.

11-Substituted tetrahydrocarbazolenines.

	Base.					Picrate.			
Substituent.	B.p./mm.	M. p.[b]	Formula.	Found: N, %.	Reqd.: N, %.	M. p.	Solvent.[d]	Found: N, %.	Reqd.: N, %.
Ethyl[a]	142°/1·0	—	$C_{14}H_{17}N$	—	—	152°[c]	A	12·8	13·1
iso*Propyl*.....	166°/0·5	81°	$C_{15}H_{19}N$	6·3	6·6	178	B	13·1	12·7
cyclo*Hexyl* ...	164°/0·4	79	$C_{18}H_{23}N$	5·9	5·5	171	A	11·6	11·6
Phenyl	184°/1·0	125	$C_{18}H_{17}N$	5·6	5·8	184	A	11·9	11·7

[a] Lions (*loc. cit.*) gives b. p. 160—161°/16 mm. [b] Crystallised from light petroleum (b. p. 40—60°). [c] Lions (*loc. cit.*) gives m. p. 147°. [d] Solvents: A, ethanol; B, light petroleum (b. p. 100—120°).

Dehydrogenation of the Tetrahydrocarbazoles to form Carbazoles.—The 1-substituted carbazole (1·0 g.) was heated for 4 hours at 280—300° with palladised charcoal (0·25 g.) in a stream of hydrogen. The product was extracted with acetone and crystallised from light petroleum (b. p. 40—60°) after distilling off the acetone. The physical, chemical, and analytical data are summarised in Table IV. Picrates were crystallised from benzene.

TABLE IV.

1-Substituted carbazoles.

	Base.				Picrate.		
Substituent.	M. p.	Formula.	Found : N, %.	Reqd. : N, %.	M. p.	Found : N, %.	Reqd. : N, %.
Ethyl	74°	$C_{14}H_{13}N$	7·1	7·2	158°	13·15	13·2
iso*Propyl*	64	$C_{15}H_{15}N$	7·1	6·7	152	12·8	12·8
Phenyl	133	$C_{18}H_{13}N$	5·7	5·8	151	12·4	11·9

*Cyclisation of the Phenylhydrazone of 2-Methyl*cyclo*hexanone in Various Conditions.*—The hydrazone (30 g.) was refluxed for 0·5 hour with the cyclising agents shown in Table V and then worked up as described above. When extraction indicated a small yield of 1-methyltetrahydrocarbazole (VI), only the 11-methyltetrahydrocarbazolenine (V) was purified by distillation.

TABLE V.

Cyclising agent, nature.	amount.	Water, ml.	% Yields of (V).	(VI).	Cyclising agent, nature.	amount.	Water, ml.	% Yields of (V).	(VI).
AcOH,	270 ml.	—	61	6	$CCl_3{\cdot}CO_2H$,	77·5 g.	191	53	—
,,	216 ml.	54	56	—	Conc. H_2SO_4,	30 ml.	270	21	45
,,	162 ml.	108	55	—	,,	30 ml.	(EtOH,	36	33
,,	108 ml.	162	57	—			270 ml.)		
,,	54 ml.	216	58	—	Conc. HCl,	108 ml.	192	38	40
,,	27 ml.	214	40	—	HCl, gas,	44 g.	(EtOH,	44	19
$CH_2Cl{\cdot}CO_2H$,	45 g.	206	42	—			270 ml.)		
$CHCl_2{\cdot}CO_2H$,	61 g.	201	51	—	C_6H_6 *	270 ml.	—	65	4

* Continuously saturated with dry HCl.

Analyses are by Messrs. N. Lottkowitz and N. Gamble. The author thanks his colleagues for many helpful discussions.

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