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1-Acylindoles. VI. On the Deacylation of the N^1-Position in the Formation of a 1,2,3,4-Tetrahydrocarbazole

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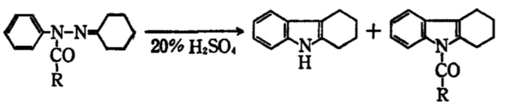
The cyclization reaction of cyclohexanone acetylphenylhydrazone to produce a tetrahydrocarbazole derivative has been reinvestigated. Although other workers obtained only a deacylated derivative in the reaction products, we found also an acylated product. It can be concluded from the experimental results that an acyl group of the N^1-position of a phenylhydrazine derivative participates only a little in the indole cyclization and that the deacetylation occurs mainly after formation of a new C–C bond.

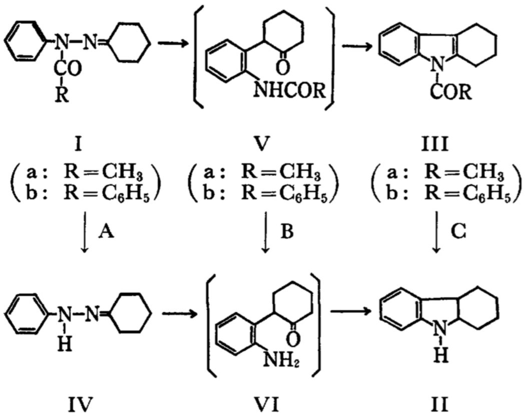
It has been found that 1,2,3,4-tetrahydrocarbazole (II) and 9-acetyl-1,2,3,4-tetrahydrocarbazole (IIIa) could be prepared by boiling cyclohexanone acetylphenylhydrazone in dilute sulfuric acid[1,2] (Scheme I).



I (a: $R=CH_3$; b: $R=C_6H_5$) II III (a: $R=CH_3$; b: $R=C_6H_5$)

Scheme I

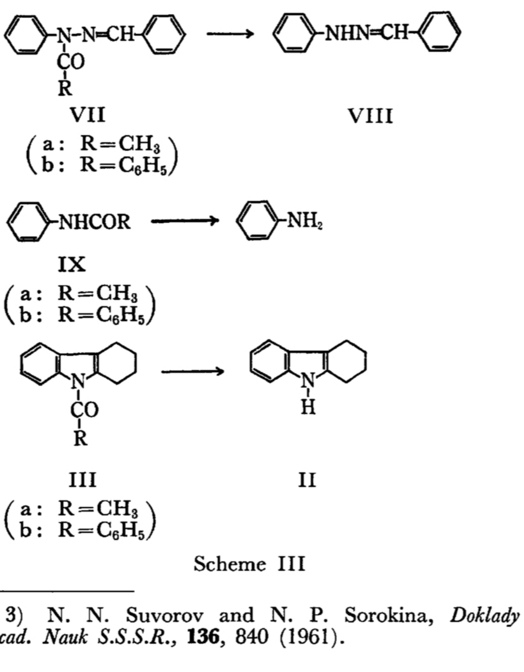
However, Suvorov *et al.* have reported that the heating of cyclohexanone acetylphenylhydrazone in 20% aqueous sulfuric acid under reflux produced 1,2,3,4-tetrahydrocarbazole, but did not give 9-acetyl-1,2,3,4-tetrahydrocarbazole, suggesting that an acyl group of the N^1 atom of the hydrazone derivative stabilizes the p-electron pair of that nitrogen atom, thus inhibiting the formation of a new C–C bond.[3] We attempted to ascertain whether the hydrolysis of the acetyl group should preceded Fischer's indole cyclization or not.



Scheme II

The processes for preparing IIIa and II from Ia are thought to be as follows (Scheme II).

II is considered to be obtained from I through Route A, B or C. Moreover, if the indole formation of an N^1-acylated compound is retarded remarkably by the substitution of the acyl group, the deacylation should precede the formation of a new C–C bond. The assumption suggests that the reaction proceeds through Route A. Therefore, II is thought to be formed from Ia *via* Route A.



Scheme III

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[1] H. Yamamoto, *J. Org. Chem.*, **32**, 3639 (1967).

[2] W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, **119**, 1825 (1921).

[3] N. N. Suvorov and N. P. Sorokina, *Doklady Acad. Nauk S.S.S.R.*, **136**, 840 (1961).

In order to make this point clear, we studied the deacylation rates of the intermediates of each step during the reaction. The following model experiments were carried out (Scheme III). From the model experiments of VII to VIII and IX to aniline, the possibilities of Route A and B may be estimated. The rates of deacylation in all the steps of the carbazole formation can be estimated to some degree from the results of these model experiments and the process of transforming III to II. In these experiments designed to transform VII to VIII, IX to aniline, and III to II, a starting material was heated under reflux in 20% aqueous sulfuric acid for a few minutes, and the reaction products were analyzed quantitatively.

Experimental

Ultraviolet Spectrometry. The ultraviolet spectra were measured with a Shimadzu RS-27 spectrophotometer, using a 1 cm quartz cell. Quantitative analyses were carried out by means of spectra taken in ethanol. The results are shown in Table 1.

TABLE 1.

Starting material (I)	Refluxing time (min)	Reaction products (mol%) III (IIIa or IIIb)	II	III+II
Ia	3	9.5	14.1	23.6
	5	10.9	21.1	32.0
	8	15.6	30.2	45.8
	12	16.0	35.6	51.6
	16	17.0	40.9	57.9
Ib	5	54.5	—	54.5
	8	65.3	3.6	68.9
	12	73.3	5.4	78.7

Thin-layer Chromatography and Photometric Analyses. The quantitative analyses of several products were carried out by thin-layer chromatography and by means of the ultraviolet absorption spectra. The products were isolated by thin-layer chromatography. The conditions for this procedure were as follows: silica gel G (Merck & Co.); thickness, 0.25 mm; solvent, carbon tetrachloride - methanol (100 : 2). The portion of the product in the thin layer was extracted with ethanol, and then the ethanol solution was analyzed by a Shimadzu RS-27 spectrophotometer. The results are shown in Table 1.

Gas Chromatography. The gas chromatographs were taken on a Yanagimoto GCG-550 F gas chromatograph. The conditions for the chromatographs of the reaction products in the process of transforming Ia to IIIa and II were as follows: column, 5% PEG-20 M 3m×1.5 mm; column temperature, 220°C; carrier gas, hydrogen; gas speed, 15 m*l*/min; internal standard substance, tribenzylamine.

For the gas chromatography of products in processes of transforming VIIa to VIII and VIIb to VIII, the conditions are changed in the following points: column temperature, 230°C and 210°C; internal standard substance, dicyclohexyl phthalate and diphenyl phthalate respectively.

TABLE 2.

Starting material (VII)	Refluxing time (min)	Reaction products (mol%) VIII	Recovery of starting material VII
VIIa	3	7.2	55.7
	5	9.9	61.7
	8	11.5	47.2
	12	18.2	39.2
	16	24.5	31.8
VIIb	3	3.4	87.1
	5	5.0	85.0
	12	4.7	78.8
	16	4.6	80.6

For the gas chromatography of products in the hydrolysis of transforming III to II, the conditions were as follows: column, 5% PEG-20M 0.75 m×3 mm; column temperature, 200°C; carrier gas, hydrogen; gas speed, 20 m*l*/min; internal standard substance, tribenzylamine.

From the areas of the individual peaks, the mol% figures were calculated for each product after a relative response date had been determined by the internal standard method using an appropriate internal standard substance. The individual peaks were identified by means of the retention times of authentic samples. The results are shown in Table 2.

Potentiometric Titration. Aniline was estimated by the potentiometric titration of a 0.1 N perchloric acid solution in glacial acetic acid, using a Hitachi-Horiba Mode M-5 glass electrode pH-meter. The results are shown in Table 3.

TABLE 3.

Starting material	Refluxing time	Reaction products (mol%) Aniline	Recovery of starting material
IXa	3	20.2	
	5	24.3	
	8	41.8	
	12	49.3	
	16	60.2	
IXb	16	0	98—99

Materials. The starting substances and authentic samples for analyses were prepared as follows:

Cyclohexanone Acetylphenylhydrazone (Ia). To a mixture of 28.8 g of cyclohexanone phenylhydrazone[4] (IV), 14 g of pyridine, and 130 m*l* of dry ether, 13.5 g of acetyl chloride were added drop by drop on cooling. Stirring was continued for additional 3 hr at room temperature. After the completion of the reaction, the filtrate was concentrated to an oily, yellow substance, which was then distilled in a bath of 165°C to give oily,

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[4] A. Baeyer, *Ann.*, **278**, 105 (1894).

yellow Ia, bp 136—141°C/0.2 mmHg (lit[2] bp 210—220°C/14 mmHg).

Cyclohexanone Benzoylphenylhydrazone (Ib). According to the above procedure, 39.2 g of cyclohexanone phenylhydrazone afforded 23.2 g of colorless prisms of Ib, mp 121—123°C (recryst. from ether). Found: C, 78.69; H, 6.76; N, 9.53%. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58%.

1,2,3,4-Tetrahydrocarbazole (II). According to the method of Perkin and Plant,[2] the heating of IV under reflux in glacial acetic acid gave white needles of II, mp 113—116°C (recryst. from aqueous alcohol).

9-Acetyl-1,2,3,4-tetrahydrocarbazole (IIIa). To a solution of 1.9 g of N^1-acetylphenylhydrazine hydrochloride in 10 m*l* of glacial acetic acid, 1.0 g of cyclohexanone was added at room temperature. The mixture was then heated at 70—75°C for 2.5 hr with stirring. After the reaction, the reaction mixture was evaporated under reduced pressure to an oily residue, to which water was added to yield an oily, brown substance. This was extracted with chloroform and dried over anhydrous sodium sulfate. The chloroform solution was concentrated to a residue, which was then recrystallized from alcohol to give white needles of IIIa, mp 77—78.3°C (lit[2] mp 77°C).

9-Benzoyl-1,2,3,4-tetrahydrocarbazole (IIIb). According to the above method, 6.4 g of white needles of IIIb, mp 83.5—84.5°C (lit.[5] mp 85°C), were prepared from 7.5 g of N^1-benzoylphenylhydrazine hydrochloride.

Benzaldehyde Acetylphenylhydrazone (VIIa). According to the method of v. Auweres and Wolter,[6] the treatment of benzaldehyde phenylhydrazone with acetyl chloride gave white needles of VIIa, mp 120—122°C (lit.[6] mp 122°C).

Benzaldehyde Benzoylphenylhydrazone (VIIb). According to the above procedure, 10 g of white needles of VIIb, mp 114—115°C (recryst. from ethanol) (lit.[6] mp 115—116°C) were prepared from 11.3 g of benzaldehyde phenylhydrazone.

Benzaldehyde Phenylhydrazone (VIII). After 5.4 g of phenylhydrazine had been added to 5.3 g of benzaldehyde, the reaction mixture was allowed to cool in an ice-water bath. The resultant precipitate was filtered and recrystallized from alcohol to give 8.3 g of white needles of VIII, mp 154—156°C (lit.[7] mp 152°C).

Acetanilide (IXa). IXa, mp 114.5—116°C, was prepared from aniline and acetic acid.[8]

Benzanilide (IXb). IXb, mp 164—165°C, was prepared from aniline and benzoic acid.[9]

General Procedure of Hydrolysis or Ring Formation. After a compound has been heated under reflux in 20% aqueous sulfuric acid for 3 min, 5 min, 8 min, 12 min, or 16 min, the reaction mixture was poured into cold water, extracted with an appropriate solvent, and analyzed quantitatively.

Results and Discussion

I was refluxed in equimolar 20% aqueous sulfuric acid to yield the deacylated compound (II) as well as the corresponding III, the yield of which was calculated with thin-layer chromatography and photometric analysis. The results are shown in Table 1.

As a model experiment, IX was heated under reflux in 20% aqueous sulfuric acid. Aniline as a hydrolyzed product of IX was quantitatively measured by the potentiometric titration. These results are shown in Table 3.

VII was hydrolyzed under reflux in 20% aqueous sulfuric acid to yield VIII, which was then quantitatively analyzed by gas chromatography (Table 2).

IIIa or IIIb was refluxed in 20% aqueous sulfuric acid. The results of analysis by gas chromatography are shown in Table 4.

TABLE 4.

Starting material	Refluxing time	Reaction products (mol%)	
		Deacylated compound (II)	Recovery of starting material III
IIIa	5	4.3	79.3
	8	4.3	78.4
	12	3.9	80.8
IIIb	8	0.0	89.2
	12	0.0	84.0

From the results shown in Table 4, the deacylation of IIIa or IIIb is so difficult under reflux in 20% aqueous sulfuric acid that it can be said that IIIa is hardly deacylated, and that IIIb is, in fact, practically not deacylated at all. Moreover, the formation of II from Ia proceeds much more rapidly than the formation of VIII from VIIa. As the deacylation rate of I to IV (Route A) is considered to be similar to that of VII to VIII, the formation of II from Ia has to proceed more rapidly than the deacylation of I to IV (Route A).

However, the results shown in Table 3 show that IXa is easily deacylated to aniline, therefore, it seems that a considerable part of the reaction intermediate, Va, is easily deacylated to VI, which is then cyclized to II.

These results suggest that Route B participates considerably in the formation of the deacylated compound, II. Therefore, the greater part of II is proved to be a product deacylated after the formation of a new C–C bond.

Under refluxing in dilute sulfuric acid, the acid-amide bonding of IXb is not easily cleaved. IIIb was prepared from Ib quantitatively, and the rate of the carbazole formation of Ib is little different from that of Ia.

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5) W. H. Perkin, *J. Chem. Soc.*, **1923**, 676.

6) K. v. Auwers and E. Wolter, *Ann.*, **487**, 79 (1931).

7) E. Fischer, *Ber.*, **9**, 887 (1876).

8) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath & Co., Boston (1957), p. 151.

9) C. N. Webb, "Org. Synth.," Coll. Vol. I, p. 82 (1956).

These results show that a considerable yield of 9-acetyl-1,2,3,4-tetrahydrocarbazole (IIIa) is given by treating cyclohexanone acetylphenylhydrazone (Ia) in 20% aqueous sulfuric acid under reflux, and that a 9-benzoyl derivative (IIIb) can be prepared in a much better yield from a corresponding hydrazone derivative (Ib) under the same conditions. In view of these facts, it can be concluded that a greater part of the deacylated compound is formed through the process of Route B.

Conclusion

In the case of $R=CH_3$, the refluxing of Ia in 20% aqueous sulfuric acid causes II as well as IIIa to be formed. II is considered to be formed mainly by the deacylation of Va to VI (Route B) on the basis of the following facts:

1. It can be concluded from the results of the model experiment (VIIa to VIII) that the deacylation of Ia is quite difficult under the same conditions.
2. The results of the deacylation of another model experiment (IXa to aniline) demonstrate that Va must be deacylated easily to VI.
3. It is very difficult for IIIa to be cleaved to II.

On the other hand, the same treatment of a compound, Ib, having $R = C_6H_5$ gave IIIb as the only product; it was nearly impossible to find II in the reaction products. This fact coincides with the results of the model experiments transforming VIIb to VIII, IXb to aniline, and IIIb to II.

It may be concluded that Fischer's indole cyclization is not notably affected by an acyl group of the N^1-position of a phenylhydrazine derivative and that deacylation mainly occurs in the step of V to VI (Route B) after the formation of a new C–C bond.