CHEMISTRY

1961

SovietRxiv

Abstract

Full Text

CHEMISTRY

N. N. SUVOROV and N. P. SOROKINA

THE INFLUENCE OF THE STRUCTURE OF ARYLHYDRAZONES ON THEIR CONVERSION INTO INDOLE DERIVATIVES

(Presented by Academician M. M. Shemyakin, September 1, 1960)

Recently the mechanism of the E. Fischer reaction has been the subject of lively discussion ([1,2]). As a result of the investigations carried out, it may be considered quite accurately established. However, the question of the influence of substituents in the arylhydrazone molecule on the yield of the indole derivative has not yet been studied in sufficient detail.

Earlier, one of us, jointly with V. K. Antonov ([3]), V. P. Mamaev and L. B. Shagalov ([4]), clearly showed a sharp increase in the yield of the indole derivative upon introduction, into the *n*-position relative to the hydrazo group, of electron-donor substituents. Having at our disposal a method ([5]) for "decomposing" the E. Fischer reaction into 3 stages in accordance with the mechanism of J. and R. Robinson ([6]), we decided to trace what changes in the arylhydrazone molecule, and at precisely which stage, favorably affect the conversion of the latter into an indole derivative.

In carrying out the acetylation of a series of arylhydrazones (phenylhydrazones of acetic and propionic aldehydes, acetone, methyl ethyl ketone, cyclohexanone; *n*-tolylhydrazone of methyl ethyl ketone; *n*-methoxyphenylhydrazones of acetic aldehyde, acetone, methyl ethyl ketone; *n*-nitrophenylhydrazones of methyl ethyl ketone and cyclohexanone) with acetic anhydride in the presence of *n*-toluenesulfonic acid, we in all cases, except acetaldehyde, obtained the corresponding (N, N'-diacetyl-β-arylhydrazino)-alkenes. This is in complete agreement with the well-known work of A. E. Arbuzov and Yu. P. Kitaev ([7]), who experimentally proved that arylhydrazones are in tautomeric equilibrium with the corresponding enehydrazines.

In the case of the phenylhydrazone and *n*-methoxyphenylhydrazone of acetaldehyde, acetylation causes cleavage of the molecule with formation of α, β-diacetylphenylhydrazine and *N*-acetyl-*n*-anisidine, respectively. However, it is known that the phenylhydrazone of acetaldehyde, under the conditions of the E. Fischer indole reaction, gives no indole. Considerably more interesting results were obtained in studying stage II of the E. Fischer reaction—the *o*-benzidine rearrangement.

Thus, saponification of 2-(N,N'-diacetyl-β-phenylhydrazino)-butene-2 (II, $R = H$) and its n-methyl-substituted analogue with aqueous sulfuric acid (1 : 1) gives 2,3-dimethyl- (or, respectively, 2,3,5-trimethyl-) indole, while boiling with 5% aqueous alkali leads to formation of the product of the o-benzidine rearrangement—3-acetylamino-2-(o-aminophenyl)-butene-2 (III, $R = H$) ([5]) (or its methyl-substituted analogue, respectively). At the same time, 2-(N,N'-diacetyl-β-(n-nitrophenyl)hydrazino)-butene-2 (II, $R = NO_2$, m.p. 98–99°) in both cases does not undergo the indicated rearrangement, but is saponified with formation of n-nitrophenylhydrazine and methyl ethyl ketone.

Found, %: C 58.10; H 5.78; N 14.65; 14.70; Ac 28.13
$C_{14}H_{17}O_4N_3$. Calculated, %: C 57.73; H 5.84; N 14.43; Ac 28.80

On the other hand, the analogous p-methoxy derivative (II, R = OCH_3, mp 65-66.5°), on heating for 2 h with 5% ethanolic caustic potash solution, gives, in 85% yield, 5-methoxy-2,3-dimethylindole (IV, R = OCH_3, mp 110–112°, λmax 228 mμ, log $\epsilon = 4.36$; λmax 288 mμ; log $\epsilon = 3.95$).

Found, %: C 65.81; H 7.35; N 10.33; 10.66; Ac 31.3
$C_{15}H_{20}O_3N_2$. Calculated, %: C 65.22; H 7.24; N 10.14; Ac 31.1

$$\text{(I)} \xrightarrow[(\text{TsOH})]{\text{Ac}_2\text{O}} \text{(II)} \qquad \text{(III)} \xrightarrow{\text{H}^+} \text{(IV)}$$
$$\text{(II)} \xrightarrow{\text{KOH}} \text{(III)}$$

These examples convincingly show that electron-acceptor groups hinder, while electron-donor groups facilitate, the course of the o-benzidine rearrangement; moreover, in the latter case the third stage is also facilitated—the closure of the pyrrole ring.

Since it is well known that introduction of a methoxy group into the aniline molecule in the p-position to nitrogen increases, while a nitro group decreases, the affinity of the latter for a proton, and since alkylation at the amino group, similarly to the introduction of an electron-donor substituent, increases the basicity of the amine, it was of interest to trace whether such substitution at the nitrogen of a hydrazone affects the course of the Fischer reaction.

It is known that the yields of indole derivatives are higher in the case of asymmetric phenylalkylhydrazones than with unsubstituted ones ([8]). Earlier we also showed the positive influence of a methyl group on stages II and III of the reaction using our method ([9]). However, there was a statement in the literature by Perkin and Plant ([10]) concerning the conversion of the α-acetyl-α-phenylhydrazone of cyclohexanone into 9-acetyl-1,2,3,4-tetrahydrocarbazole, which seemed to refute the influence of the basicity of the nitrogen atom bound to the aromatic nucleus on the ease of the Fischer reaction. Repeating the work of the English investigators and obtaining the above-mentioned phenylhydra-

zone directly from α-acetyl-α-phenylhydrazine and cyclohexanone, we showed that in this case the process proceeds with loss of the acetyl group and formation of the free (mp 117–119°), and not the acetylated, tetrahydrocarbazole.

Finally, comparing the instability of the enehydrazine from acetaldehyde and the smooth formation of 1-(N,N′-diacetyl-β-phenylhydrazino)-propene-1 (bp 142–145° at 2 mm) from the phenylhydrazone of propionaldehyde, it should be assumed that the latter is explained by the inductive effect of the terminal methyl group.

Found, %: C 67.35; H 6.98; N 11.98; 12.13
$C_{13}H_{16}N_2O_2$. Calculated, %: C 67.24; H 6.89; N 12.06

The latter, apparently, also facilitates the course of the *o*-benzidine rearrangement. In this respect it is interesting to note that the above-mentioned enehydrazine rearranges on boiling with 5% alcoholic alkali in 1-

acetylamino-2-(o-aminophenyl)-propene-1 (m.p. 109–110.5°), which under the action of hydrochloric acid forms skatole.

Found, %: C 69.22; 69.05; H 7.29; 7.44; N 15.03; Ac 22.61
$C_{11}H_{14}O_2N$. Calculated, %: C 68.95; H 7.36; N 15.00; Ac 22.60

At the same time, the isomeric 2-(N,N′-diacetyl-β-phenylhydrazino)-propene-1 (m.p. 94–95°), obtained from phenylhydrazone of acetone, does not undergo the *o*-benzidine rearrangement on alkaline saponification, but is saponified to phenylhydrazine, although on boiling with aqueous sulfuric acid (1:1) it forms 2-methylindole.

Found, %: C 67.34; 66.81; H 7.05; 6.95; N 11.92; 12.04; Ac 36.4
$C_{13}H_{16}O_2N_2$. Calculated, %: C 67.24; H 6.89; N 12.06; Ac 37.0

All-Union Scientific Research
Chemical-Pharmaceutical Institute
named after S. Ordzhonikidze

Received
29 VIII 1960

REFERENCES

1. N. N. Suvorov, V. P. Mamaev, V. M. Rodionov, *Synthesis of Indole Derivatives from Arylhydrazones*, Reactions and Methods of Studying Organic Compounds, issue 9, Moscow, 1959, p. 9.

2. Yu. P. Kitaev, *J. Gen. Chem. USSR*, 28, 336 (1959).

3. N. N. Suvorov, V. K. Antonov, DAN, 84, 971 (1952); N. N. Suvorov, V. K. Antonov, E. M. Rokhlin, DAN, 91, 1345 (1953).

4. N. N. Suvorov, V. P. Mamaev, L. B. Shagalov, DAN, 93, 835 (1953); 101, 103 (1955).

5. N. N. Suvorov, N. P. Sorokina, Yu. N. Sheinker, ZhOKh, 28, 1090 (1958).

6. G. Robinson, R. Robinson, J. Chem. Soc., 113, 639 (1918); 125, 827 (1924).

7. A. E. Arbuzov, Yu. P. Kitaev, DAN, 113, 577 (1957); ZhOKh, 27, 2328 (1957).

8. A. Michaelis, Ber., 30, 2809 (1897).

9. N. N. Suvorov, N. P. Sorokina, Yu. N. Sheinker, ZhOKh, 29, 979 (1959); 30, 2055 (1960).

10. W. Perkin, S. Plant, J. Chem. Soc., 119, 1825 (1921).

Note: Figure translations are in progress. See original paper for figures.