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# MECHANISM OF THE FISCHER INDOLE SYNTHESIS.

## QUANTUM-CHEMICAL INTERPRETATION OF THE REARRANGEMENT OF SUBSTITUTED CYCLOHEXANONE ARYLHYDRAZONES TO TETRAHYDROCARBAZOLES

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Calculations of a number of model structures within the scheme of the Fishcer indole synthesis were made on the basis of a bonding variant of perturbation theory in the self-consistent-field (SCF) MO LCAO method. A quantum-chemical interpretation of the effect of substituents on the course of the thermal process is given. The kinetics of the thermal and acid-catalyzed indolization of substituted cyclohexanone arylhydrazones to tetrahydrocarbazoles were studied by spectrophotometry. It was shown that the experimental data are in satisfactory agreement with the calculated values. It was concluded that a concerted mechanism (a [3,3]-sigmatropic shift) for the step involving the formation of a carbon—carbon bond in the Fischer reaction is preferred.

The mechanism of the Fischer indole synthesis continues to attract the interest of chemists [1-7]. To ascertain the details of this mechanism $^{15}$N [8] and $^{13}$C NMR [9] spectroscopy, mass spectrometry [10], and kinetic investigations [6, 11] have been used in recent years. However, some aspects of this reaction, viz., the effect of electronic factors on the rate of the process, the ratios of the resulting isomers, and the hydrazone—enehydrazine tautomerism, continue to remain unclear.

We assumed that a quantum-chemical investigation of the Fisccher reaction, in conjunction with kinetic and other experimental data, might give additional information with respect to these questions.

The calculations were made on the basis of a bonding variant of perturbation theory in the self-consistent-field (SCF) MO LCAO method (for example, see [12]). The indicated approach has been previously used to interpret the mechanisms of a number of processes [13] and to predict [14] the subsequently experimentally confirm [15] the effect of substituents on the recyclization of heterocyclic anhydro bases.

In the present study, as in [16], this approach was used to examine the step involving the formation of a C—C bond in the Fischer synthesis of indoles, which reduced to description of the interaction of the unbonded (or weakly bonded) π-electron systems of II-V (Scheme 1).

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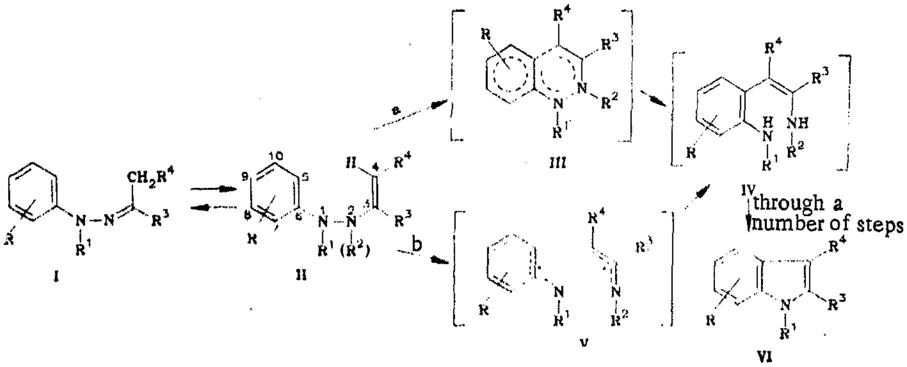
TABLE 1. Reactivity Indexes in the Fischer Indole Synthesis

| Reactivity indexes* | II | III | IV | V | Reactivity indexes* | II | III | IV | V |
|---|---|---|---|---|---|---|---|---|---|
| $P_{12}$ | 0,050 | 0,012 | −0,037 | 0 | $\pi_{12,13}$ | −0,042 | −0,045 | −0,042 | −0,039 |
| $P_{13}$ | −0,082 | 0,006 | 0,094 | 0 | $\pi_{12,45}$ | −0,019 | −0,012 | −0,013 | −0,016 |
| $P_{45}$ | −0,035 | 0,367 | 0,392 | 0 | $\pi_{13,45}$ | 0,042 | 0,028 | 0,033 | 0,033 |
| $\pi_{12,12}$ | 0,028 | 0,026 | 0,025 | 0,028 | $K_{12,45}$ | 0,240 | — | — | 0,233 |
| $\pi_{13,13}$ | 0,126 | 0,145 | 0,124 | 0,125 | $K_{12,13}$ | 0,238 | 0,261 | 0,233 | 0,231 |
| $\pi_{45,45}$ | 0,174 | 0,142 | 0,137 | 0,173 | $K_{12,45,13}$ | 0,534 | — | — | 0,502 |

*For structures II–V, $R = R^1 = R^2 = R^3 = R^4 = H$.

Scheme 1



$R = R^1 = R^2 = R^3 = R^4 = H$, donor or acceptor group

Transition state III of the concerted process was calculated as a 10-center 10 π-electron system isoconjugated with respect to cinnoline, and transition state V of the stepwise system was calculated as interacting azabenzyl and azaallyl systems (Scheme 1) (see [6, 17]).

The results of quantum-chemical calculation of structures II–V are presented in Table 1 (only the variant of the thermal process is examined).

The basis for regarding structure II as two unbonded interacting π systems is (Table 1) the smallness of the 1–2 bond order (which is equal to zero in structure V). This, on the one hand, constitutes evidence for the lability of this bond (its cleavage during the reaction) and, on the other, for the necessity to take into account second-order (with respect to $\Delta\beta_{ik}$) perturbation theory; if only one bond is formed (or cleaved) in the reactions, the self-polarizabilities of this bond serve as the reactivity index, whereas the stabilization energy ΔE, determined as the sum (difference) of the bond–bond self- and mutual polarizabilities, serves as the reactivity index if several bonds are involved. Thus, in analogy with [16], in which this approach was used to interpret the mechanism of the diene synthesis, cleavage of the 1–2 bond and the formation of the 4–5 bond can be described by the $K_{12,45}$ index

$$\Delta E = K_{12,45}(\Delta\beta^{\neq})^2 = (\pi_{12,12} + \pi_{45,45} - 2\pi_{12,45})(\Delta\beta^{\neq})^2.$$

Similarly, the $K_{12,13,45}$ index is associated with the stabilization energy of the concerted process involving cleavage of the 1–2 bond and the formation of 4–5 and 1–3 bonds. In addition to the orders of the cleaved and newly formed bonds, the bond–bond self- and mutual polarizabilities and reactivity indexes of the concerted reactions are presented in Table 1.*

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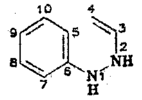
*The numbering of the atoms in Scheme 1 (which is the same for all II–V) and in Table 1 does not correspond to IUPAC nomenclature and was adopted only for convenience in the discussion.

TABLE 2. Effect of Substituents on the Reactivity Indexes in the Fischer Indole Synthesis*



| Reactivity indexes | Substituent position (j) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 7 | 8 | 9 | 10 |
| | "a" indexes | | | | | | | | |
| $\pi_{j,12}$ | −0,0145 | −0,0151 | 0,0070 | 0,0099 | 0,0030 | 0,0040 | −0,0003 | 0,0019 | −0,0010 |
| $\pi_{j,13}$ | 0,0155 | 0,0150 | −0,0048 | −0,0301 | 0,0045 | 0,0009 | −0,0004 | 0,0023 | 0,0019 |
| $\pi_{j,45}$ | 0,0082 | 0,0077 | −0,0078 | −0,0011 | −0,0034 | 0,0017 | −0,0006 | 0,0003 | 0,0015 |
| | "b" indexes | | | | | | | | |
| $\pi_{j,12,12}$ | −0,0160 | −0,0166 | 0,0088 | 0,0174 | 0,0034 | 0,0044 | −0,0003 | 0,0022 | −0,0012 |
| $\pi_{j,13,13}$ | −0,0491 | 0,0090 | −0,0219 | −0,0032 | −0,0084 | −0,0007 | −0,0008 | 0,0040 | −0,0038 |
| $\pi_{j,45,45}$ | −0,0014 | −0,0076 | 0,0038 | −0,0194 | −0,0112 | −0,0001 | −0,0100 | −0,0027 | 0,0176 |
| $\pi_{j,12,13}$ | 0,0152 | 0,0147 | −0,0056 | −0,0317 | 0,0052 | 0,0014 | −0,0004 | 0,0027 | 0,0020 |
| $\pi_{j,12,45}$ | 0,0086 | 0,0081 | −0,0089 | −0,0004 | −0,0036 | 0,0023 | −0,0007 | 0,0005 | 0,0020 |
| $\pi_{j,13,45}$ | −0,0204 | 0,0045 | 0,0092 | −0,0039 | 0,0047 | −0,0036 | 0,0008 | −0,0010 | −0,0026 |
| | "c" indexes | | | | | | | | |
| $\Delta K_{j,12,45}$ | −0,0346 | −0,0404 | 0,0304 | −0,0012 | −0,0006 | −0,0003 | −0,0089 | −0,0015 | 0,0124 |
| $\Delta K_{j,12,13}$ | −0,0955 | −0,0370 | −0,0019 | 0,0776 | −0,0154 | −0,0009 | 0,0013 | −0,0072 | −0,0090 |
| $\Delta K_{j,12,13,45}$ | −0,1549 | −0,0518 | 0,0381 | 0,0512 | −0,0100 | −0,0074 | −0,0057 | −0,0089 | −0,0006 |

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*In the case of donors $\Delta\alpha < 0$, whereas $\Delta\alpha > 0$ for acceptors.

It is apparent from Table 1 that in II, despite the negativity $P_{45}(0) = -0.035$, there is a maximum self-polarizability $\pi_{45,45} = 0.174$ eV$^{-1}$, which, by virtue of the smallness of the $|P_{45}(0)|$ modulus, means the possibility of ring closing in these positions. A similar conclusion is also valid for structure V. After the formation of this bond and cleavage of the 1—2 bond (see structures III and V, respectively) the 1—3 bond order becomes positive, which, together with the sufficiently large values $\pi_{13,13} = 0.145$ and 0.124 eV$^{-1}$, indicates the subsequent formation of an indole ring.

An analysis of the bond—bond mutual polarizabilities in II also confirms this conclusion, since, as follows from Table 1, weakening of the 1—2 bond will lead to strengthening of the 4—5 bond, and, on the other hand, strengthening of the 4—5 bond will lead to weakening of the 1—2 bond. A similar conclusion can be drawn on the basis of the data in Table 1 also for structures III-V. It is apparent that in all of the examined structures strengthening of the 4—5 bond and weakening of the 1—2 bond lead to strengthening of the 1—3 bond, which should be formed in the subsequent steps.

Thus an examination of the indexes in Table 1 makes it possible to draw the general conclusion that a concerted process involving cleavage of the N—N bond and the formation of a C—C bond (pathway a) is somewhat more preferable than reaction via pathway b.

It is apparent that the results of the calculation correctly reflect the available experimental data [1-5], although they do not make it possible to draw a definite conclusion regarding the mechanism of the II→IV transformation.

In the description of the effect of substituents on the direction of the reaction under consideration, in addition to the changes under the influence of substituents, which are characterized by scalar values $\Delta\alpha R$ and bond orders $\Delta P_{ik} = \sum_j \pi_{j,ik}\Delta\alpha_{Rj}$, one must also take into account the changes in the bond—bond self- and mutual polarizabilities $\Delta\pi_{j,ik,pq} = \frac{1}{2}\sum_j \pi_{j,ik,pq}\Delta\alpha_{Rj}$.

Thus, in addition to the atom—bond mutual polarizabilities $\pi_{j,ik}$ (the "a" indexes), the $\pi_{j,ik,pq}$ indexes (the "b" indexes) and, in the case of a concerted process, the $\Delta K_{j,ik,pq}$ indexes (the "c" indexes) should also act as characteristics of the effect of substituents on the reaction under consideration. All of these values for II are presented in Table 2.

TABLE 3. Kinetic and Thermodynamic Parameters of the Fischer Reaction for Cyclohexanone Arylhydrazones Xa–g

| Reaction conditions | Hydrazones $\pi_{ik}$ | Reaction rate constants, $K \cdot 10^5$ sec$^{-1}$ | | | | | | Acceleration factor, f | Thermodynamic parameters | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 150° | 140° | 130° | 120° | 110° | 80° | | $\Delta H^{\neq} \pm 0.2$ kcal/mole | $\Delta S^{\neq}$ eu |
| | | | | | Ethylene glycol solvent | | | | | |
| Thermal | Xa | 177,8 | 125,9 | 79,4 | 50,1 | 31,6 | 7,1 | | 14,1 | −38,3±0,4 |
| | Xb | 41,7 | 22,4 | 14,1 | 7,9 | 4,5 | 0,6 | | 17,7 | −32,7±0,6 |
| | Xc | 25,1 | 14,1 | 7,9 | 4,5 | 2,5 | 0,4 | 1 | 17,2 | −35,2±0,2 |
| | Xd | 43,7 | 25,0 | 15,4 | 8,9 | 5,6 | 0,9 | 1,7—2,3 | 15,8 | −37,2±0,3 |
| | Xe | 12,6 | 6,3 | 3,5 | 1,8 | 0,9 | 0,1 | 0,5—0,3 | 19,6 | −31,0±0,3 |
| | Xf | 50,1 | 28,3 | 17,8 | 10,2 | 6,3 | 1,0 | 2,0—2,5 | 15,0 | −39,1±0,2 |
| | Xg | 17,8 | 8,9 | 5,0 | 2,5 | 1,3 | 0,1 | 0,7—0,3 | 20,5 | −27,7±0,3 |
| | Xh* | | 35,5 | 20,9 | 13,0 | 7,1 | 1,2 | | 16,8 | −34,2±0,8 |
| Acid-catalyzed, $H_2SO_4$, 2 moles† | Xa | | | | 28,2<br>(60°) | 398,1 | 89,1 | | 13,2 | −35,5±0,4 |
| | Xb | | | 141,5 | 79,2 | 50,2 | 7,9 | | 15,8 | −32,4±0,5 |
| | Xc | 159,5 | 101,0 | 56,2 | 31,6 | 19,0 | 2,5 | 1 | 16,5 | −33,2±0,4 |
| | Xd | 416,9 | 281,8 | 199,5 | 141,3 | 97,3 | 29,2 | 2,6—11,7 | 11,5 | −42,8±0,4 |
| | Xe | 141,4 | 82,4 | 44,7 | 25,1 | 14,1 | 2,0 | 0,9—0,8 | 17,3 | −31,5±0,2 |
| | Xh | | | 158,5 | 100,0 | 56,2 | 10,0 | | 15,9 | −32,6±0,8 |
| | | | | | Decane solvent | | | | | |
| | Xc | 31,5 | 16,3 | 10,9 | | | | 1 | 17,2 | −32,3±0,2 |
| | Xd | 45,7 | 26,7 | 16,7 | 13,9 | • | | 1,5 | 15,8 | −35,4±0,2 |

*Cyclohexanone N-methylphenylhydrazone [11].

†The number of moles of the acid per mole of the hydrazone.

Their analysis shows that the introduction of electron-donor groups ($\Delta\alpha < 0$) in the 1 and /or 2 positions in enehydrazine II should, according to the "a" and "b" indexes, hinder the Fischer reaction; for example, according to the "a" indexes, this should strengthen the 1–2 bond and weaken the 4–5 and 1–3 bonds. Moreover, it follows from the $\Delta K_{j,ik,pq}$ values that these substituents should very markedly accelerate a concerted process (see the "c" indexes); the introduction of donors in the 1 position is apparently more effective than introduction in the 2 position. The effect of electron-acceptor groups is just the opposite.

The experimental data (see, for example, [18, 19]), like the results of our kinetic studies (see below), are in agreement with the latter assertion and thereby, within the framework of the adopted theoretical approach, constitute evidence in favor of a converted mechanism.

It follows from Table 2 that even within first-order (with respect to $\Delta\beta_{ik}$) perturbation theory the introduction of donors in the 3 and/or 4 positions leads to strengthening of the 4–5 and 1–3 bonds and weakening of the 1–2 bond (see the "a" indexes), which accelerates Fischer indolization. Similar conclusions can also be drawn with respect to the "b" indexes, while the indexes of the concerted mechanism indicate just the opposite; of course, in this case we are not taking steric factors into account. Experimental data [20, 21] show that the indolization of α-methylcyclohexanone phenylhydrazone [I, $R = R^1 = H$; $R^3 + R^3 = (CH_2)_4$], which leads to the formation of a mixture of indolenine and tetrahydrocarbazole, is faster by a factor of nine than in the case of the unsubstituted compound.*

The calculated data on o-substituted benzene rings relative to the hydrazine fragment (Table 2) with respect to all three indexes predict that the introduction of donor groups should facilitate the Fischer reaction; for example, with respect to the "b" indexes, $\pi_{j,12,12} > 0$, $\pi_{j,13,13} < 0$, and $\pi_{j,45} < 0$, i.e., the 1–2 bond is weakened, whereas the 1–3 and 4–5 bonds are strengthened. In addition, it follows from the calculation that an o-donor substituent increases the reactivity of precisely this center, whereas an acceptor substituent directs the reaction to the free ortho position. These data are confirmed by the results obtained

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*The reaction was carried out in an acidic medium; the rate was measured from the amount of ammonia liberated.

TABLE 4. Physicochemical Characteristics of Cyclohexanone Arylhydrazones X and Tetrahydrocarbazoles XII and XIII

| Compound | mp,* °C | mp,† °C [literature] | Found, % | | Empirical formula | Calc., % | | $R_f$ | Yield, % |
|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | | C | H | | |
| Xa | Oil | | 77,7 | 9,4 | $C_{14}H_{20}N_2$ | 77,7 | 9,3 | 0,42 | 75 |
| Xb | Oil | | 66,0 | 7,4 | $C_{13}H_{17}ClN_2$ | 66,0 | 7,2 | 0,53 | 98 |
| Xc | 75—76 | 75—76 [11] | — | — | — | — | — | — | 92 |
| Xd | Oil | | 76,5 | 8,6 | $C_{13}H_{18}N_2$ | 77,1 | 8,9 | 0,65 | 93 |
| Xe | Oil | | 65,0 | 6,6 | $C_{12}H_{15}ClN_2$ | 65,0 | 6,8 | 0,74 | 87 |
| Xf | Oil | | 76,7 | 8,8 | $C_{13}H_{18}N_2$ | 77,1 | 8,9 | 0,67 | 86 |
| Xg | 86—87 | | 65,2 | 6,9 | $C_{12}H_{15}ClN_2$ | 65,0 | 6,8 | 0,75 | 91 |
| XIIa | 89—90 | 89—90 [36] | — | — | — | — | — | — | 94 |
| XIIb | 51—52 | | 71,1 | 6,4 | $C_{13}H_{14}ClN$ | 71,1 | 6,4 | 0,81 | 84 |
| XIIc | 116—117 | 116—117 [37] | | | | | | | |
| XIId+XIIId | 82—92 | 82—90 [38] | | | | | | | 72 |
| XIIId | 129—130 | 130 [23] | | | | | | | |
| XIIe+XIIIe | 170—175 | | | | | | | | 79 |
| XIIIe | 179—180 | 178—179 [39]<br>179—180 [40] | | | | | | | |
| XII f | 143—144 | 145—146 [37]<br>141—142 [41] | | | | | | | 92 |
| XII g | 146—147 | 146—147 [37] | | | | | | | 90 |

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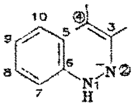
*The compounds were crystallized: Xc from 80% methanol, Xg and XIIf from hexane, XIIa,b, XIId + XIIId, XIIId, XIIe + XIIIe, XIIIe, and XIIg from methanol, and XIIc from 60% ethanol.

†The compounds were crystallized: XIIc and XIId + XIIId from ethanol–water, XIIId and XIIf by the method in [37], and XIIg from methanol.

in [21], in which it was shown that the rearrangement of hydrazone I [R = 5-$CH_3$, $R^1$ = H, $R^3$ + $R^4$ = $(CH_2)_4$] is faster by a factor of 1.9 than that of the unsubstituted analog and leads to the formation of 8-methyl-1,2,3,4-tetrahydrocarbazole. In addition, the above-presented quantum-chemical calculations (without allowance for steric factors) are in agreement with numerous examples of ipso substitution in the 5 (ortho) position of the benzene ring (the "anomalous" Fischer reaction [22]).

In the case of m-substituted hydrazine II a donor substituent in the 8 position strengthens the 4–5 bond to a greater extent than a similar substituent in the 10 position (compare the $\pi_j$ and $\Delta K_j$ indexes in Table 2). Thus reaction in the para position relative to this substituent is energically more favorable, whereas in the case of acceptor groups reaction in the ortho position with respect to it is energically more favorable, i.e., the ratio of the resulting isomeric 6- and 4-substituted indoles should be greater than unity if R is a donor and less than unity if R is an acceptor; this is confirmed by the data in [1, 5, 23].

Finally, if a donor substituent is located in the 9 position, it should, with respect to all of the reactivity indexes, promote the II→VI cyclization; on the whole, this effect is more pronounced than the effect of similar groups located in the meta position but weaker than in the case of the ortho isomers (compare the $K_{j,12,13,45}$ values in Table 2). Acceptors should hinder the II→VI transformation. In principle, these data are in agreement with the literature data [1, 3, 5] on the reactivities of p-substituted arylhydrazones in the Fischer reaction.

An analysis of the atom–atom mutual polarizabilities $\pi_{ik}$ makes it possible to describe, within the framework of the developed approach, the effect of substituents on the shift of the hydrazone I $\rightleftarrows$ enehydrazine II tautomeric equilibrium. For the quantitative characterization of this process we selected the difference in the residual π-electron charges in the 4 and 2 positions the anion 

, which, in the unsubstituted structure, is $q_4 - q_2$ = (−0.4483) − (−0.5299) = 0.0816. The positiveness of this value denotes greater negativity of the nitrogen atom, i.e., a greater probability of attachment of a proton to it as compared with the $C_4$ center and, ultimately, a shift in the equilibrium to favor the II form. The dif-

TABLE 5. Spectral Characteristics of Cyclohexanone Arylhydrazones Xa-g

| Compound | UV spectrum (ethylene glycol), $\lambda_{max}$, nm | IR spectrum (N=N, N=C), $\nu$, cm$^{-1}$ | PMR, spectrum, $\delta$, ppm |
|---|---|---|---|
| Xa | 253 (4,13),<br>295 (3,59) | 1510, 1620, wt'. | 1,68 and 2,46 (10H, mcr *), 2,27 (3H, s, $p$-$CH_3$), 2,97 (3H, s, N—$CH_3$), 6,75 ($H_3$, $H_5$, d, $J_{2,3}=J_{5,6}=8,6$ Hz), 7,06 ($H_2$, $H_6$, d, $J_{2,3}=J_{5,6}=8,6$ Hz) |
| Xb | 260 (4,17),<br>290 (3,72) | 1510, 1610, wt. | 1,69 and 2,48 (10H, mcr), 2,98 (3H, s, N—$CH_3$), 6,77 ($H_3$, $H_5$, d, $J_{2,3}=J_{5,6}=9,2$ Гц), 7,19 ($H_2$, $H_6$, d, $J_{2,3}=J_{5,6}=9,2$ Hz) |
| Xc | 275 (3,89) | — | |
| Xd | 278 (4,10) | 1500, 1620, wt. | 1,72 and 2,30 (10H, mcr), 2,36 (3H, s, $m$-$CH_3$), 7,15—7,52 (4H, m, arom., NH) |
| Xe | 278 (4,09) | 1500, 1610, wt. | 1,64 and 2,32 (10H, mcr), 6,65—7,41 (4H, m, arom, NH) |
| Xf | 278 (4,02) | 1510, 1620, wt. | 1,74 and 2,33 (10H, mcr), 2,39 (3H, s, $p$-$CH_3$), 7,08—7,70 (4H, m, arom. NH) |
| Xg | 280 (4,34) | 1500, 1600, KBr | 1,63 and 2,25 (10H, mcr), 6,88 ($H_3$, $H_5$, d, $J_{2,3}=J_{5,6}=8,8$ Hz), 7,11 ($H_2$, $H_6$, d, $J_{2,3}=J_{5,6}=8,8$ Hz) |

*The abbreviation "mcr" stands for multiplet of the cyclohexane ring.

ferences in the corresponding polarizabilities $\Delta(q_4 - q_2) = (\pi_{j_4} - \pi_{j_2})\Delta\alpha_R$, where j is the position of substitution, will, of course, be an index of the effect of substituents on this equilibrium.

Calculation gives the following values for these differences: 1) 0.0116, 3) −0.0176, 4) 0.1858, 5) −0.0066, 7) −0.0013, 8) 0.0018, 9) −0.0104, 10) −0.0089. It is apparent from the data presented above that the maximum sensitivity to substituents corresponds to the 4 position, the introduction of acceptor groups ($\Delta\alpha > 0$) in which should lead, according to what was indicated above, to a shift of the equilibrium to favor the enehydrazine. This corresponds to the available experimental data on hydrazone—enehydrazine tautomerism [24, 25]. The effect of donors is just the opposite: It hinders the formation of structure II, although, as noted above, it also promotes cyclization.

These groups in the 1 and 8 positions should have a considerably smaller effect but in the same direction, whereas they should have the opposite effect in the remaining positions of the benzene ring. When one compares the calculated coefficients in the 5 and 7 positions, one sees that the introduction of donor groups in the 5 position promotes a shift of the equilibrium to favor the enehydrazine to a greater extent than introduction in the 7 position, which also corresponds to strengthening of the 4—5 and 1—3 bonds (see above). The opposite conclusion can be drawn also with respect to the meta positions of the benzene ring — donors in the 8 position apparently will hinder the I→II transition but donors in the 10 position will facilitate it, i.e., in the latter case the effect of substituents on the I→II and II→VI transformations is just the opposite.

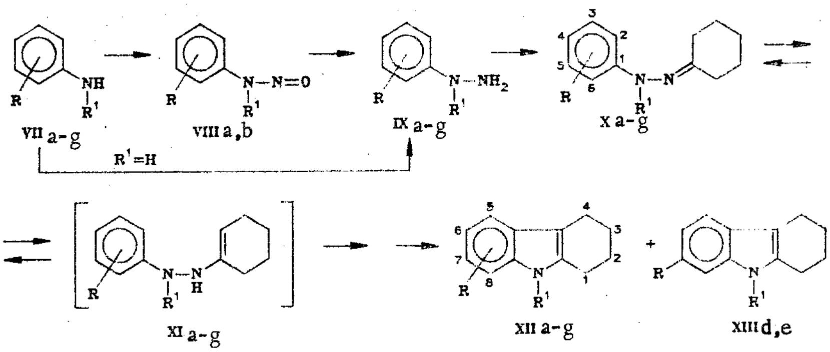
Let us emphasize that the scheme for the description of the effect of substituents was based only on quantum-chemical calculation of structure II, whereas it is possible that the effects of substituents in III-V may also be different. Let us once again also note that we have examined only thermal and not catalytic processes. Interaction of the groups present, which also should be examined within second-order (with respect to $\Delta\alpha_R$) perturbation theory and may be comparable in magnitude to the effects described by the $\pi_{ik,pq}$ values, was not taken into account in the calculation. All of these questions were left outside of the present examination.

In order to experimentally verify the results of the quantum-chemical calculations and as a continuation of previously begun investigations [6, 11] we studied the thermal and acid-catalyzed rearrangement of a number of m- and p-substituted cyclohexanone arylhydrazones Xa-g to tetrahydrocarbazoles XIIa-g + XIIId,e (Scheme 2).

TABLE 6. Spectral Characteristics of Tetrahydrocarbazoles XIIa-g

| Compound | UV spectrum (ethylene glycol), $\lambda_{max}$, nm | PMR spectrum, δ, ppm |
|---|---|---|
| XIIa | 235 (4,52), 293 (3,86), 298 sh (3,83) | 1,89 and 2,70 (8H, and mcr), 2,45 (3H, s, 6-$CH_3$), 3,59 (3H, s, N—$CH_3$), 6,96 (7-H, d.d, $J_{7,8}$=8,2, $J_{5,7}$=1,2 Hz); 7,14 (8-H, d, $J_{7,8}$=8,2 Hz), 7,25 (5-H, d, $J_{5,7}$=1,2 Hz) |
| XIIb | 239 (4,61), 294 (3,83), 300 sh. (3,82) | 1,89 and 2,69 (8H, mcr.), 3,59 (3H, s, N—$CH_3$), 7,02—7,20 (7-H, m and 8-H), 7,42 (5-H, s) |
| XIIc | 230 (4,61), 285 (4,13), 292 sh. (4,08) | |
| XIId+XIIId | 233 (4,40), 282 (3,93), 295 sh. (3,90) | 1,87 and 2,64 (H, mcr.), 2,43 (6H, d.d. 7-$CH_3$, 5-$CH_3$), 6,95—7,37 (H, m, arom.), 7,87 and 7,91 (2H, br s., NH) |
| XIIe+XIIIe | 238 (4,50), 287 (3,74), 296 sh. (3,70) | |
| XIIIe | 238 (4,48), 288 (3,74), 295 sh. (3,70) | 1,88 and 2,68 (8H, mcr.), 7,02 (6-H, d. d, $J_{5,6}$= =9,0, $J_{6,8}$=2,4 Hz), 7,24 (8-H, d, $J_{6,8}$=2,4 Hz), 7,34 (5-H, d, $J_{5,6}$=9,0 Hz), 7,60 (NH, brs) |
| XIIf | 233 (4,50), 287 (3,98), 298 sh. (3,90) | 1,91 and 2,72 (8H, mcr), 2,46 (3H, s, 6-$CH_3$), 6,94 (7H, d.d., $J_{7,8}$=8,8, $J_{5,7}$=1,3 Hz), 7,19 (8-H, d, $J_{7,8}$=8,8 Hz), 7,26 (5-H, d., $J_{5,7}$=1,3 Hz), 7,6 (NH, br.s) |
| XIIg | 238 (4,58), 292 (3,97), 299 Hz. (3,93) | 1,89 and 2,67 (8H, mcr), 7,04 (7-H, d.d, $J_{7,8}$= =8,6 and, $J_{5,7}$=2,0 Hz), 7,17 (8-H, d, $J_{7,8}$= =8,6 Hz), 7,42 (5-H, d, $J_{5,7}$=2,0 Hz), 7,65 (NH, br.s) |

Scheme 2



VII, IX—XI a, f R=p-$CH_3$, b, g R=p-Cl, c R=H, d R=m-$CH_3$, e R=m-Cl; a, b $R^1$=$CH_3$, c—g $R^1$=H; VIII a R=p-$CH_3$, b R=p-Cl, a, b $R^1$=$CH_3$; XII a, f R=6-$CH_3$, b, g R=6-Cl, c R=H, d R=5-$CH_3$, e R=5-Cl, a, b $R^1$=$CH_3$, c—g $R^1$=H; XIII d R=7-$CH_3$, e R=7-Cl; d, e $R^1$=H

Arylhydrazones X were synthesized from the corresponding anilines VIIa-g through hydrazines IXa-g. The kinetics of the rearrangement of hydrazones Xa-g to tetrahydrocarbazoles XIIa-g + XIIId,e were studied by spectrophotometry in ethylene glycol (also in decane for Xc and Xd) at various temperatures. The kinetic parameters for the indolization of hydrazones Xa-g, which is a first-order reaction, are presented in Table 3.

It follows from the data in Table 3 that over the investigated temperature range the conversion of hydrazones X to carbazoles XII + XIII is virtually independent of the nature of the solvent [for example, at 150°C the rate constants ($K \cdot 10^5$, $sec^{-1}$) for the thermal rearrangement of hydrazone Xd in ethylene glycol and decane are 43.7 and 45.7, respectively].

On the other hand, electronic factors and the acidity of the medium have a substantial effect on the course of the process.

A donor substituent (the $CH_3$ group) in the meta or para position of the benzene ring increases the rate of thermal rearrangement of hydrazones Xd and Xf as compared with unsubstituted hydrazone Xc (acceleration factors f are, respectively, 1.7 and 2.0), whereas hydrazones Xe and Xg (R = $C_1$) react more slowly (f = 0.5 and 0.7).

A similar pattern is observed for hydrazones Xa,b. These results correspond to the results of the quantum-chemical calculations. The latter are also confirmed by kinetic data obtained in a study of the indolization of m-substituted cyclohexanone N-methylphenylhydrazones [11].

The rates of thermal rearrangement of m- and p-substituted cyclohexanone arylhydrazones are close (compare, for example, Xe and Xg, and Zd and Xf), although a somewhat greater rate is always observed for the para isomers in accordance with the theoretical calculation.

The substituent attached to the nitrogen atom has an appreciable effect on the indolization of hydrazones X. It is apparent from Table 3 and the data in [11] that N-unsubstituted arylhydrazones undergo the thermal Fischer reaction more slowly than the corresponding α-N-methylphenylhydrazones Xa,b. For example, the rate constants ($K \cdot 10^5$, $sec^{-1}$) for the rearrangement (ethylene glycol, 110°C) of hydrazones Xf and Xa ($R = p-CH_3$) are, respectively, 6.3 and 31.6 (Table 3), as compared with 0.9 (Table 3) and 2.8 [11] for hydrazones Xe ($R = m-CH_3$) and cyclohexanone N-methyl-N-(m-chlorophenyl)hydrazone. These results confirm the conclusions of the quantum-chemical calculations and are in agreement with the literature data (see above).

Thus electron-donor substituents in both the aromatic ring and attached to the nitrogen atom increase the rate of the thermal Fischer reaction. Moreover, it must be noted that the maximum differences in the rates of thermal rearrangement observed for hydrazones Xe ($R = m-Cl$, $R^1 = H$) and Xa ($R = p-CH_3$, $R^1 = CH_3$) are 70 (at 80°C) and 35 and 28 (at 110°C and 120°C, respectively). In addition, in all cases the entropies of activation of the process have rather high negative values (Table 3).

The latter two conclusions, in conjunction with the kinetic and calculated data on the effect of substituents attached to the nitrogen atom, constitute evidence in favor of a concerted mechanism for the formation of a carbon–carbon bond in the Fischer reaction.

A 10-fold to 30-fold acceleration as compared with the thermal reaction is observed in the acid-catalyzed indolization of hydrazones X (Table 3). For example, at 80°C the rate constant for the rearrangement of hydrazone Xd in the presence of sulfuric acid in ethylene glycol is 29.2, as compared with 0.9 for the thermal process.

Similar acceleration has also been noted for cyclohexanone N-methylphenylhydrazones [11]. The effect of substituents in the aryl ring and attached to the nitrogen atom on the acid-catalyzed rearrangement of hydrazones X coincides with that observed for the thermal reaction, viz., electron-donor groups accelerate the process, and electron-acceptor groups retard it (compare the rate constants for hydrazones Xd and Xe with that for unsubstituted hydrazone Xc, Table 3).

In this connection, the results of quantum-chemical calculations of the thermal rearrangement of arylhydrazones can in some measure also be used to interpret the acid-catalyzed reaction, although this is not completely justified from the point of view of quantum chemistry.

Thus the calculations showed that the method that we developed can be successfully used for the quantum-chemical interpretation of Fischer indolization. On the whole, the experimental data confirmed the theoretically predicted effect of electronic factors on the rate of rearrangement of arylhydrazones and the ratios of the resulting indoles.

## EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a Bruker WH spectrometer (90 MHz). The IR spectra were recorded with a Jasco IR-S spectrometer. The UV spectra were obtained with a Hitachi EPS-3T spectrophotometer. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in a benzene–ether system (5:1) with iodine as the developer. The kinetic data were obtained by spectrophotometry with the spectrophotometer indicated above by the method in [6]. The purity of the starting amines was monitored by gas–liquid chromatography (GLC).

N-Methyl-p-toluidine (VIIa). This compound, with bp 209-210°C (bp 209-211°C [28]), was obtained from p-toluidine by methylation with dimethyl sulfate by the method in [26, 27].

N-Methyl-p-chloroaniline (VIIb). This compound, with bp 239-240°C (bp 239-240°C [29]), was similarly obtained from p-chloroaniline.

N-Methyl-N-nitroso-p-toluidine (VIIIa). This compound, with mp 50-51°C [from ethyl acetate—hexane (1:10)] [mp 51-52.5°C (from ethanol with ether)] and $R_f$ 0.76, was obtained in 88% yield from 30 g (0.25 mole) of amine VIIa by the method in [30].

N-Methyl-N-nitroso-p-chloroaniline (VIIIb). This compound, with mp 50-51°C [from ethyl acetate—hexane (1:10)] [mp 51°C [32] and 44-46°C [33]] and $R_f$ 0.71, was similarly obtained in 72% yield from 35 g (0.25 mole) of amine VIIb.

N-Methyl-N-(p-tolyl)- (IXa) and N-Methyl-N-(p-chlorophenyl)hydrazine (IXb). These compounds were obtained by reduction of 0.015 mole of nitroso compounds VIIIa and VIIIb, respectively, with a titanium reagent by the method in [34]. Compound IXa was obtained in 90% yield and had $R_f$ 0.20 and bp 95-96°C (4 mm*). Compound IXb was obtained in 96% yield and had $R_f$ 0.27 and bp 93-95°C (6 mm).

The constants of arylhydrazones IXa and IXb were in agreement with the data in [31, 35].

m-Tolyl- (IXd), m-Chlorophenyl- (IXe), p-Tolyl- (IXf), and p-Chlorophenylhydrazine (IXg). These compounds were obtained by the general method for the synthesis of arylhydrazines by diazotization of 0.2 mole of the corresponding amine VIId-g with $NaNO_2$ and subsequent reduction of the diazo compound with $SnCl_2 \cdot 2H_2O$ and decomposition of the complex with 20% NaOH. The constants of arylhydrazines IXd-g were in agreement with the literature data.

N-Methyl-N-(p-tolyl)- (Xa), N-Methyl-N-(p-chlorophenyl)- (Xb), Phenyl- (Xc), N-(m-Tolyl)- (Xd), N-(m-Chlorophenyl)- (Xe), N-(p-Tolyl)-(Xf), and N-(p-Chlorophenyl)hydrazone (Xg) of Cyclohexanone. These compounds were obtained from 0.01 mole of the corresponding arylhydrazine IXa-g by the method in [11]. The constants and yields of arylhydrazones Xa-g, as well as their spectral characteristics, are presented in Tables 4 and 5.

6,9-Dimethyl- (XIIa), 6-Chloro-9-methyl- (XIIb), 6-Methyl- (XIIf), and 6-Chloro-1,2,3,4-tetrahydrocarbazole (XIIg), Mixture of 5- and 7-Methyl-1,2,3,4-tetrahydrocarbazole (XIId + XIIId), and Mixture of 5- and 7-Chloro-1,2,3,4-tetrahydrocarbazole (XIIe + XIIIe). These compounds were obtained from 0.01 mole of the arylhydrazines (IXa,b,d-g, respectively) and cyclohexanone by the method in [11].

7-Methyl- (XIIId) and 7-Chloro-1,2,3,4-tetrahydrocarbazole (XIIIe). These compounds were obtained by repeated crystallization from methanol of the mixtures of carbazoles XIId + XIIId and XIIe + XIIIe.

The constants, yields, and spectral characteristics of the tetrahydrocarbazoles are presented in Tables 4 and 6.

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*Here and subsequently, the pressure is given in millimeters of mercury.

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