INDOLES

VIII*. ELECTRONIC AND CONFORMATIONAL FACTORS IN THE SYNTHESIS OF TRYPTAMINES

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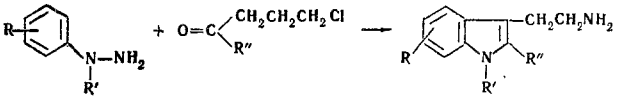
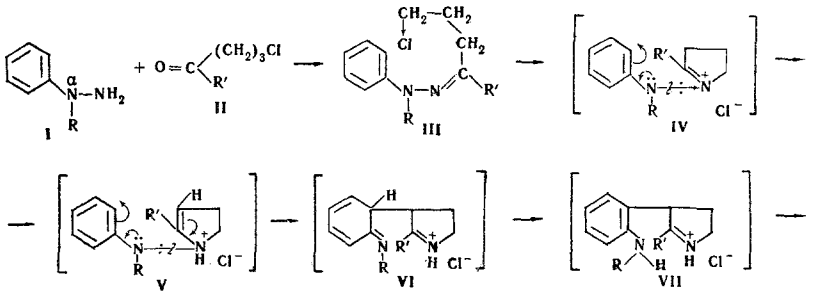
Some factors affecting the formation of tryptamines from arylhydrazines and halogenocarbonyl compounds have been studied. It has been shown by calculations using the LCAO MO method that the β-nitrogen atom of the arylhydrazone must undergo intramolecular quaternization, and the formation of a C–C bond takes place by electrophilic attack of the benzene ring. It has been shown that conformational factors play an important part in the reaction, sometimes changing the direction of the process. Thus, γ-chloropropyl phenyl ketone, which exists only in the syn form, cyclizes into 1,3-diphenyltetrahydropyridazine and not into 2-phenyltryptamine.

We have previously reported the reaction between arylhydrazines and 1,4-halogenocarbonyl compounds, leading to tryptamines under fairly mild conditions [2-6].



With the aim of a more accurate approach to the possible mechanism of the process, we have calculated some initial systems by the LCAO MO method in Hückel's approximation. The calculation was carried out with the optimum values of the Coulomb and resonance integrals given previously [7].

According to our earlier ideas on the mechanism of the process [3], which have been partially confirmed by studies with labelled nitrogen [4], the basic stage of the process is the intramolecular quaternization of the β-nitrogen atom (III → IV).



*For Communication VII, see [1].

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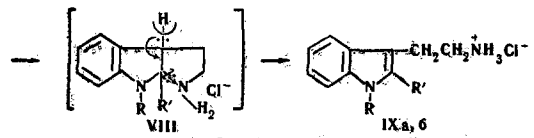
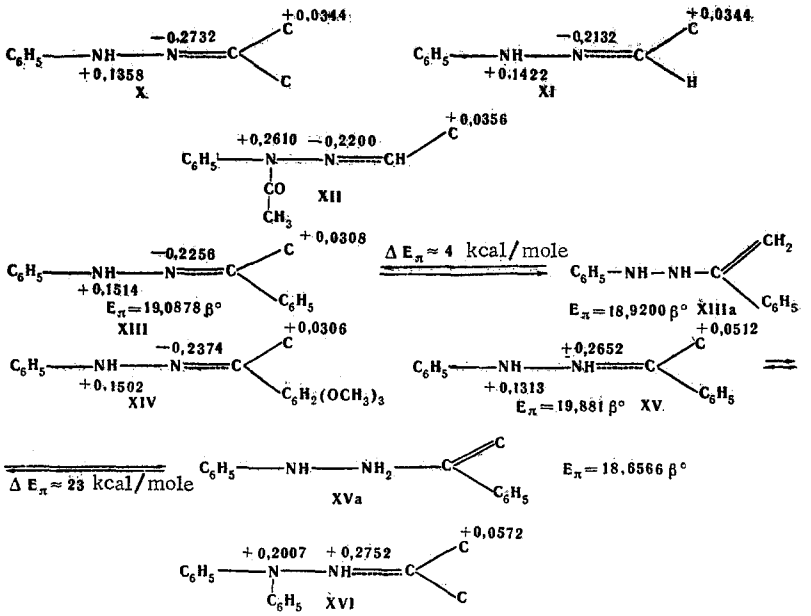


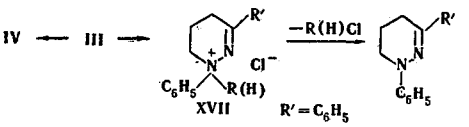
VIII IXa, б

I R = C_6H_5; II R' = C_6H_5; III R = R' = C_6H_5; IX а R = H, R' = C_6H_5; б R = R' = C_6H_5

A comparison of the π-electronic densities on the α- and β-nitrogen atoms of various hydrazones (X-XIV) clearly shows that the β-nitrogen atom is far more basic (even taking into account the fact that for nitrogen atoms the π-electronic density does not always correlate accurately with basicity). Thus, the formation on quaternization of N-anilinopyrrolines IV, and not the tetrahydropyridazine systems XVII, is completely normal.



The probability factor, always leading to the easier formation of 5-membered, rather than 6-membered, rings in such reactions [8] probably plays no insignificant role.



The figures obtained by calculation (compare XIII-XIIIa) confirmed the now generally accepted conclusion of the existence of arylhydrazones in the hydrazone and not the enehydrazine form – the latter is less favorable (4 kcal/mole even for acetophenone hydrazone, where it is stabilized by conjugation).

From a consideration of π-electron densities both in the quaternized molecules of hydrazones and their enhydrazine forms (XV, XVI) and in the hydrazones themselves (X-XIV) it is clear that the formation of the C–C bond at the stage (V → VI) must be the result of an electrophilic attack on the aromatic nucleus, since there is always an increased electron density in the ortho position of the nucleus, and the attacking carbon atom is electrophilic. In actual fact, although for the anilinopyrroline produced (IV ⇌ V) the hydrazone form IV is energetically more favorable (compare XV-XVa) by approximately 23 kcal/mole, it is naturally the tautomeric enhydrazine form V, in which atoms 1 and 6 are sufficiently close for the joining of the C–C bond (see Fig. 1) that takes part in the reaction. This can be well seen

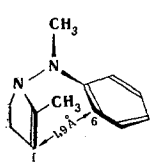
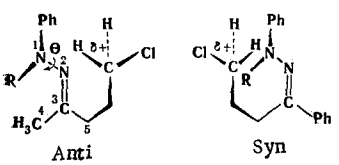


Fig. 1



Anti Syn

Fig. 2

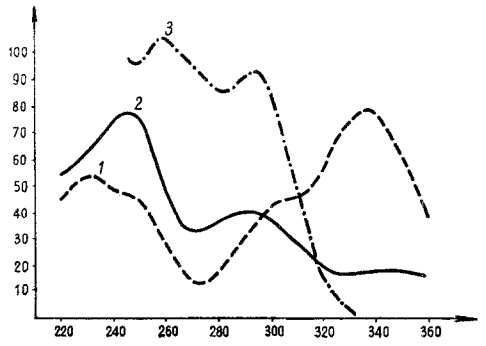


Fig. 3. 1) 1,3-Diphenyltetrahydropyridazine; 2) diphenylhydrazone of propiophenone; 3) diphenylhydrazone of γ-chloropropyl phenyl ketone.

from a consideration of a Dreiding model. In our opinion, this stage takes place in the manner of a "push-pull" reaction (rearrangement of 1,6-conjugated systems) with the synchronous formation of a C–C bond and the cleavage of the N–N bond (see scheme 1).

In addition to electronic factors, conformational factors have a considerable influence on the course of the process. Thus, in the reaction of phenylhydrazine with γ-chloropropyl phenyl ketone (IIa), XVII is formed, in addition to the expected IXa. Cyclization took place at the α atom even in the reaction of IIa with α-benzyl phenylhydrazine, with the formation of the same compound XVII through the splitting out of benzyl chloride from the unstable quaternary salt.

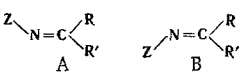
The π-electron densities on the nitrogen atoms in the molecules of acetone and acetophenone phenylhydrazones (compare X and XIII) do not differ sufficiently to cause reorientation in intramolecular alkylation. Conversely, a conformational analysis of the molecules of the hydrazones satisfactorily explains the reason for the change in the direction of the reaction.

According to general ideas on the configuration of molecules with multiple bonds, atoms 1-5 (see Fig. 2, anti form) must exist in one plane. A consideration of Dreiding models clearly shows that the hydrazine fragment of the molecules must be rotated around the N–N bond by an angle θ of not less than 35°; otherwise the steric interactions of substituents 4 and 5, on the one hand, and of the phenyl nucleus and R, on the other hand, would be too great. We obtained confirmation of the acoplanarity of the phenylhydrazone molecules by UV spectroscopy [9], our results being in agreement with the former hypothesis of their nonplanar structure [10]. Thus, it can be seen from Fig. 3 that for the almost planar 1,3-diphenyltetrahydropyridazine (XVII) there is a strong band (λ_{max} 337 nm, log ε 3.99), which characterizes the whole conjugated system (π-p–π–π) and also several weaker bands of quasi-autonomous systems: π–π, λ_{max} 245 nm, log ε 3.77, and π-p-p, λ_{max} 306 nm, log ε 3.75.

In the case of propiophenone diphenylhydrazone, because of the rotation of the diphenylamine fragment, the intensity of the long-wave maximum is considerably lower (λ_{max} 348 nm, log ε 3.54) and it becomes quite poorly expressed. For γ-chloropropyl phenyl ketone diphenylhydrazone (IIIa), there are no bands at all characterizing the whole conjugated system, which is apparently due to a further increase in the angle θ because of the interaction of the $Cl\leftarrow\overset{\delta+}{C}<$ c fragment with the π electrons of the β-nitrogen atom and a further increase in the angle of rotation.

Let us consider the mutually opposite arrangement of the chloropropyl residue and N–N bond as illustrated in Fig. 2, anti form.

It is known that for structures A and B (extremely close to our structure as illustrated in Fig. 2), when R = CH_3 the equilibrium A/B (syn/anti) ratio rises rapidly when R' changes from a CH_3 group to ethyl, isopropyl, tert-butyl, and phenyl groups [11, 12], although, according to Karabatsos and Krumel [13], $\Delta F_{36°}$ for the transition of the syn isomers into the anti isomers is only about 2 kcal/mole for sterically unhindered forms.



In the anti form (Fig. 2) the steric conditions exist for the convenient attack of the $Cl\leftarrow\overset{\delta+}{C}<$ fragment only on the most basic β-nitrogen atom (Dreiding model) and the formation of tryptamines takes place readily. Where R' = C_6H_5, in view of π–π conjugation the phenyl nucleus attempts to lie in the plane of fragment 2, 3, 4 (see Fig. 2). In this case, the existence of the anti form becomes sterically impossible and the hydrazone can exist in practice only as the syn form (Fig. 2). This form is the most favorable both from the energetic and from the spatial points of view. The mutual arrangement of the nitrogen atoms

and the $Cl\leftarrow\overset{\delta+}{C}\diagup$ fragment in it is such that only the α- and not the β-nitrogen atom can undergo electrophilic attack, even though the latter is the more basic.

For an indirect confirmation of these ideas, we performed the reaction of the diphenylhydrazine Ia and the chloroketone IIa. Since the basicity of the α-nitrogen atom in this case was very greatly reduced, the formation of a pyridazine appeared unlikely. In actual fact, under ordinary conditions there was the formation of the hydrazone IIIa, which could not be quaternized at the $\alpha-N$ atom because of its feeble basicity but could be at the $\beta-N$ atom because of its existence in the syn configuration. Only under considerably more severe conditions (160°C, 5 h) did isomerization of the syn form into the anti form and the production of the tryptamine IXb take place. The difficulty of quaternization was not caused by the presence of the phenyl substituent on the $\alpha-N$ atom, since the action of diphenylhydrazine on γ-chloropropylmethyl ketone at 60°C readily gave 2-methyl-1-phenyltryptamine (see Experimental).

EXPERIMENTAL

1,3-Diphenyl-1,4,5,6-tetrahydropyridazine (XVII). A. A solution of 18.25 g (0.1 mole) of γ-chloropropyl phenyl ketone in 20 ml of methanol was added to a hot solution of 10.8 g (0.1 mole) of phenylhydrazine in 260 ml of 90% methanol. The reaction mixture was boiled for 8 h. The precipitate that deposited was filtered off with suction and was recrystallized three times from methanol. This gave 14.5 g (52.5%) of the tetrahydropyridazine XVII, mp 127-128°C (from methanol), R_f 0.81 (Al_2O_3 of activity grade II, benzene–chloroform (17:3) system, spots revealed with iodine). UV spectrum*: λ_{max} 236, 245, 306, 337 nm; log ε 3.83, 3.77, 3.75, 3.99 (in acetonitrile). IR spectrum†: 1585 cm^{-1} (conjugated C=N), 1595, 1490 cm^{-1} (phenyl). PMR spectrum‡: triplet, 3.54 ppm (J = 5.5 Hz) due to the protons of the 6-methylene group: sextet, 2.08 ppm (J = 5.5 Hz) due to the protons of the 5-methylene group; and triplet, 2.48 ppm (J = 5.5 Hz) due to the protons of the 4-methylene group. Found, %: C 81.61; 81.52; H 6.88; 6.82. $C_{16}H_{16}N_2$. Calculated, %: C 81.32; H 6.82.

B. Similarly, when solutions of 19.8 g (0.1 mole) of α-benzylphenylhydrazine in 90% methanol and of 18.2 g (0.1 mole) of γ-chloropropyl phenyl ketone in methanol were boiled, 10.3 g (43.5%) of the tetrahydropyridazine XVII was obtained with mp 126-127°C (from methanol), R_f 0.81 under the same conditions. It gave no depression of the melting point with the sample described above. The IR and UV spectrum of the two samples were also identical.

1,2-Diphenyltryptamine. A solution of 18.4 g (0.1 mole) of α,α-diphenylhydrazine in 150 ml of ethylene glycol was treated with 18.2 g (0.1 mole) of γ-chloropropyl phenyl ketone. The reaction mixture was heated in an oil bath at 160°C for 5 h. Pronounced resinification took place. The reaction mixture was diluted with 1 liter of hot 0.1 N hydrochloric acid, and was filtered hot through activated carbon to remove the resin. The solution was made alkaline with 40% caustic soda solution to pH 10 and the tryptamine that had separated out was extracted with two 100-ml portions of hot benzene. The benzene was distilled off in the vacuum of a water pump. The residue consisted of dark crystals of 1,2-diphenyltryptamine, which were washed with absolute ether. This gave 6.6 g (20%) of pure 1,2-diphenyltryptamine with mp 151-153°C (from benzene containing petroleum ether). R_f 0.81**. PMR spectrum (in pyridine): singlet at 2.55 ppm due to the protons of an amino group, broad singlet at 3.08 ppm due to the protons of α- and β-methylene groups. UV spectrum: λ_{max} 223, 260, 296 nm; log ε 2.43, 4.15, 4.16. Found, %: C 84.51; 84.48; H 6.75; 6.70. $C_{22}H_{20}N_2$. Calculated, %: C 84.57; H 6.45. The picrate was obtained in absolute ether with a molar amount of picric acid and was recrystallized from a small amount of methanol, mp 204-206°C (decomp.). Found, %: C 62.00; 61.98; H 4.31; 4.28. $C_{22}H_{20}N_2 \cdot C_6H_3N_3O_7$. Calculated, %: C 62.09; H 4.28. The hydrogen tartrate was obtained in the minimum amount of hot absolute ethanol with a molar amount of a solution of tartaric acid in hot methanol and was recrystallized from methanol, mp 223-225°C (decomp.).

*The UV spectra were taken on EPS-3T (Hitachi) spectrophotometer in ethanol (if the solvent is not specified).

†The IR spectra were taken on a Jasco-JRS spectrometer with an NaCl prism in a KBr tablet.

‡The PMR spectra were taken on a JNM-4H 100 instrument with a working frequency of 100 MHz in $CDCl_3$ solution using tetramethylsilane as internal standard. The chemical shifts are given in the δ scale.

**Here and below, "rapid" paper of the Volodarskii mill, pyridine–water–n-butanol (1 : 1 : 1) system, Ehrlich's revealing agent.

γ-Chloropropyl Phenyl Ketone Diphenylhydrazone. A solution of 18.4 g (0.1 mole) of α,α-diphenylhydrazine in 150 ml of tert-butanol was treated with 19.2 g (0.1 mole) of γ-chloropropyl phenyl ketone. The reaction mixture was heated in the boiling water bath for 5 h, and the precipitate that had deposited was filtered off with suction and recrystallized from aqueous methanol. This gave 16.4 g (47%) of hydrazone with mp 213-215°C. UV spectrum: λ_{max} 224, 258, 296 nm; log ε 4.35, 4.12, 4.06 (in acetonitrile). Found, %: C 75.65; 75.43; H 6.10; 6.01. $C_{22}H_{21}ClN_2$. Calculated, %: C 75.70; H 6.06. When equivalent amounts of the hydrazone and pyridine were mixed, the quaternary pyridinium salt with mp 245-248°C (from aqueous methanol) deposited. Found, %: C 75.75; 75.60; H 5.96; 5.90. $C_{27}H_{26}ClN_3$. Calculated, %: C 75.79; H 6.12.

Propiophenone Diphenylhydrazone. A flask with a Dean and Stark trap was charged with 18.4 g (0.1 mole) of α,α-diphenylhydrazine and 13.4 g (0.1 mole) of propiophenone. Dry benzene was added in amount equal to the volume of the trap, and the mixture was boiled with the distillation of water for 5 h. The oil formed crystallized after purification in a column of Al_2O_3 of activity II. mp 81-82°C (from methanol). Yield 21.6 g (72%), R_f 0.85 (Al_2O_3 of activity grade II, benzene system, spots revealed with iodine). Found, %: C 83.63; 83.63; H 6.78; 6.72. $C_{21}H_{20}N_2$. Calculated, %: C 83.96; H 6.71. UV spectrum: λ_{max} 247, 293, 238 nm; log ε 4.18, 3.88, 3.53 (in acetonitrile).

2-Methyl-1-phenyltryptamine. A solution of 12.1 g (0.1 mole) of γ-chloropropyl methyl ketone in 20 ml of methanol was added to a boiling solution of 18.4 g (0.1 mole) of α,α-diphenylhydrazine in 200 ml of methanol. The reaction mixture was boiled for 8 h, and then the solvent was distilled off in the vacuum of a water pump, the residue was dissolved in 160 ml of hot 0.1 N hydrochloric acid, and the neutral impurities were extracted with ether (2 × 50 ml). The aqueous solution was made alkaline with 30 ml of 40% caustic soda solution and the 2-methyl-1-phenyltryptamine that separated out was extracted with hot benzene. The benzene extract was filtered, the benzene was driven off, and the residue was distilled in vacuum in a current of nitrogen. This gave 18 g (72%) of the tryptamine, with bp 175-176°C (2 mm); R_f 0.79. PMR spectrum: singlet at 1.81 ppm due to the protons of an amino group; singlet at 2.48 ppm due to the protons of the 2-CH_3 group; broad singlet at 3.22 ppm due to the protons of the α- and β-methylene groups. The aromatic protons give a series of poorly-resolved signals in the region from 7.35 to 8.05 ppm. UV spectrum: λ_{max} 220, 264, 283, 293 nm; log ε 4.56, 4.03, 3.97, 3.95. Found, %: C 81.44; 81.29; H 7.39; 7.32. $C_{17}H_{18}N_2$. Calculated, %: C 81.55; H 7.25. Picrate* mp 164-165°C. Found, %: C 57.54; 57.50; H 4.84; 4.60. $C_{17}H_{18}N_2 \cdot C_6H_3N_3O_7$. Calculated, %: C 57.62; H 4.42. Tartrate* mp 167-169°C (decomp.).

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*Obtained in a similar manner to the corresponding derivative of 1,2-diphenyltryptamine.