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INVESTIGATION BY ^{1}H NMR OF DIENEDIAMINES AS STARTING MATERIALS FOR THE SYNTHESIS OF INDOLES AND BENZOFURANS BY THE NENITZESCU REACTION

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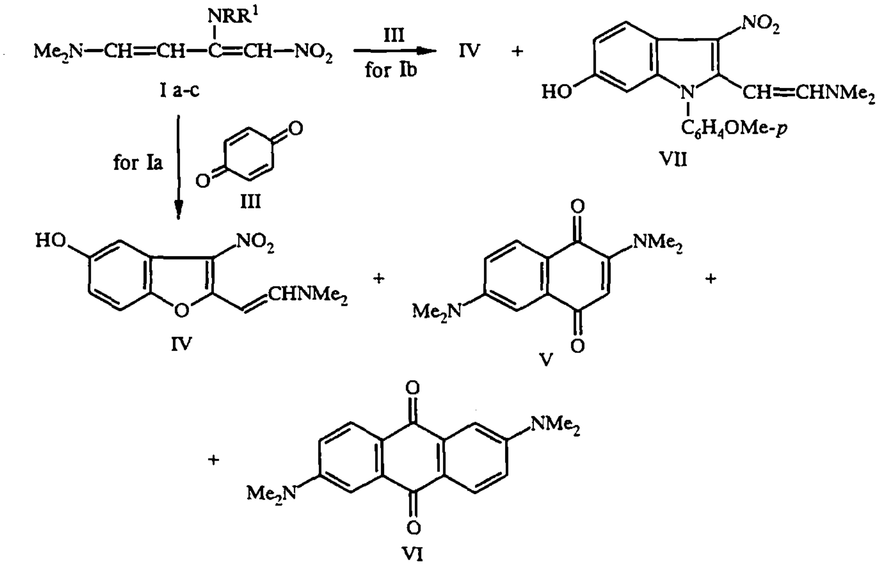
Investigations using ^{1}H NMR have been carried out on dienediamines which are starting materials for the synthesis of indoles and benzofurans by the Nenitzescu reaction. Protonation of dienediamines and special features of their configuration and conformation were studied.

We established recently that nitrodienediamines (I) [1, 2] and dienediaminoketones (II) [3, 4] may be starting materials for the synthesis of benzofuran and indole derivatives by the Nenitzescu reaction. The formation of the substituted benzofuran (IV) dominates the interaction of nitrodienediamines (I) with p-benzoquinone by the Nenitzescu reaction. In addition, the bistertiary dienediamine (Ia) reacts with quinone by a type of 1,4-cycloaddition with the formation of substituted naphthoquinones (V) and anthraquinones (VI). The reaction of nitrodienediamine (Ib), having a secondary arylamino group in the δ position, with quinone (III) also leads to benzofuran (IV) as the main reaction product. The presence of the indole derivative (VII) was detected only by mass spectrometry. The formation of products of 1,4-cycloaddition was not confirmed in this case [2]:



I a R = R^1 = Me; b R = *p*-MeOC$_6$H$_4$, R^1 = H; c R = Ph, R^1 = H

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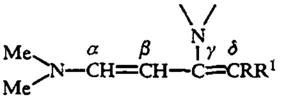
TABLE 1. Chemical Shifts (δ, ppm) in the ^1H NMR Spectra of the Bases and Protonated Forms of Dienediamines (I) and (II)



$$Me_2N\overset{\alpha}{-CH}=\overset{\beta}{CH}-\overset{\overset{\large\diagdown\!/}{N}\,|\,\gamma}{C}=\overset{\delta}{C}RR^1$$

Compound	α-CH	β-CH	δ-CH	Cδ—N(Me)2	Cδ—NHAr	R^1	Solvent
Ia	7.30 d J = 12.2 Hz	4.64 d J = 12.2 Hz	6,62 s	3,01 br s 3,14 s	—	—	$CDCl_3$
Ia ·H^+	8.36 d J = 12.2 Hz	5.21 d J = 12.2 Hz	5,94 s (2H)	3,17 s; 3,27 s; 3,37 s; 3,43 s	—	—	$CDCl_3$ + 2drop CF_3COOH
Ic	7.21 d J = 13.2 Hz	4.71 d J = 13.2 Hz	7,00 s	2,90 br s	12,2 br s 7,19...7,29 m	—	$CDCl_3$
Ic ·H^+	8.10 d J = 12 Hz	5.55 d J = 12 Hz	5,79 s (2H)	3,02 c 3,40 s	9,62 br s 7,18...7,50 m	—	$CDCl_3$ + 3drop CF_3COOH
IIa	*	4.80 d J = 13.2 Hz	5,91 s	2,86 s	13,4 br s 7,10...7,90 m	7,10...7,90 m,	$CDCl_3$
IIa· H^+	7.79 d J = 12.4 Hz	5.41 d J = 12.4 Hz	4,63 s (2H)	3,30 s	9,3 br s 7,24...8,00 m	7,24...8,00 m	$CDCl_3$ + 10drop CF_3COOH
IIb	7.26 d J = 12.4 Hz	4.81 d J = 12.4 Hz	5,91 s	2,89 s	13,4 br s 7,20...7,90 m	7,20...7,90 m	$CDCl_3$
IIb· H^+	7.81 d J = 12 Hz	5.42 d J = 12 Hz	4,62 s (2H)	2,99 s 3,31 s	9,00 br s 7,16...8,12 m	7,16...8,12 m	$CDCl_3$ + 10 drop CF_3COOH

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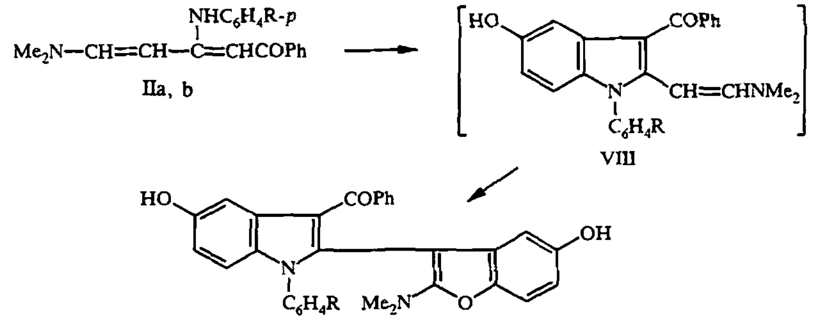
*This proton signal falls in the region of the phenyl proton signals.

Dienediaminoketones (IIa, b) react with quinone (III) in another way. Indole intermediates (VIII) are formed in this case in the initial Nenitzescu reaction and then condense further with quinone (III) leading overall to the benzofurylindole (IX) [3, 4].



IX

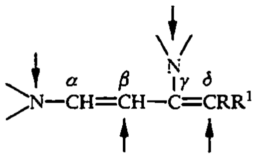
II a R-H; b R-Cl

Finally, the dienediamine (X) having two substituents cyano and ethoxycarbonyl in the δ position does not undergo the Nenitzescu reaction. Resinification of the reaction mixture was observed, seemingly unaccompanied by indole (or benzofuran) synthesis.

$$Me_2N-CH=CH-CH(NHC_6H_4OMe\text{-}p)=C(CN)COOEt$$

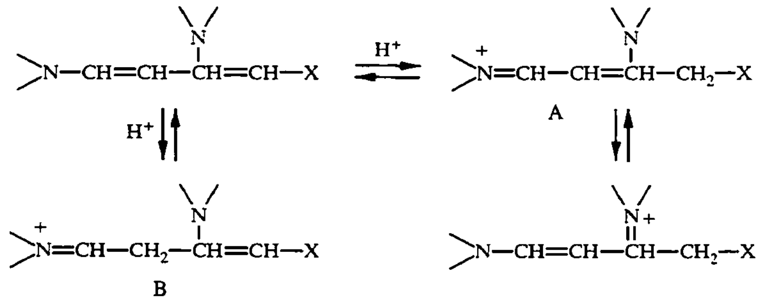
X

The aim of the present work was to study the protonation of dienediamines (I), (II), and (X), a reaction modeling to a known degree the reaction with electrophilic reactants such as quinone (III). Dienediamines are a complicated system compared with the usual enamines, and protonation may occur at the nitrogen atom of both amino groups, the β and δ carbon atoms, and in the case of dienediaminoketones at the oxygen atom of the carbonyl group as well.



In addition it seemed that a study of the configurational and conformational features of the structure of the investigated dienediamines may give additional information in order to understand the main and side processes occurring during the reaction of dienediamines with quinone.

The method used in the present work to solve these problems was ^1H NMR spectroscopy. Comparison of the ^1H NMR spectra of compounds (Ia) and (Ib) or (Ic) in deuterochloroform with the spectra of compounds (Ia, c) in $CDCl_3$ with added CF_3COOH showed that protonation occurred selectively at the δ carbon atom. As is seen from the data of Table 1 a signal for protons of the δ'-CH_2 at 5.94 ppm (2H, s, δ-CH_2) appeared in place of the signal for the proton in the δ position of compound (Ia) at 6.62 ppm (1H, s, δ-CH), and the remaining signals were displaced towards low field as might have been expected. An analogous picture was also observed for the other nitrodienediamines and dienediaminoketones (Table 1). For compound (IIb) the signal for the δ-CH group proton at 5.91 (1H, s, δ-CH) is converted on protonation into a two-proton singlet for the δ-CH_2 group protons at 4.64 ppm. The unequivocal protonation of dienediamines (I) and (II) in the δ position is probably determined by the significantly greater thermodynamic stability of cation A compared to cation B caused by the significantly greater delocalization of the positive charge in the former.



However, it is quite clear that in the basic form the electron density at the β position is greater than in the δ position. For example, signals were observed in the ^1H NMR spectrum of compound (Ia) (in $CDCl_3$) at 4.64 (1H, d, β-CH) and 6.62 (1H, s, δ-CH) and of (IIa) at 4.80 (1H, d, β-CH) and 5.91 ppm (1H, s, δ-CH) which also support such a conclusion. Based on this it might be expected that the rate of protonation at the β position (and eventually N- and O-protonation, see [5] for example) is greater than at the δ position and the overall result, viz. δ protonation, is determined solely by the thermodynamic factor. Considering that only products of δ electrophilic attack were recorded on reacting dienediamines with quinone, the data being examined may indicate that either the first stage of this process, a Michael reaction, is reversible or that β attack of the quinone leads to a weakly stable intermediate itself transformed into resin-forming compounds and not indole and (or) benzofuran derivatives.* Study of the protonation of dienediamine (X) points in favor of the fact that attack of the quinone at the β position of the dienediamines does not lead to the synthesis of the desired heterocycles, since this compound does not give Nenitzescu reaction products on interaction with quinone (III). Signals were observed in the ^1H NMR spectrum of this compound in $CDCl_3$ at 1.32 (t) and 4.21 (q) for the COOEt group, 2.82 (br s, NMe_2), 7.51 (d, J = 13.2 Hz, α-CH), 4.50 (d, J = 13.2 Hz, β-CH), 3.80 (s, OMe), 7.96 (A_2B_2 system, C_6H_4), 10.94 ppm (s, NH). On adding CF_3COOH a large pro-

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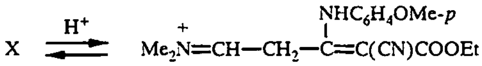
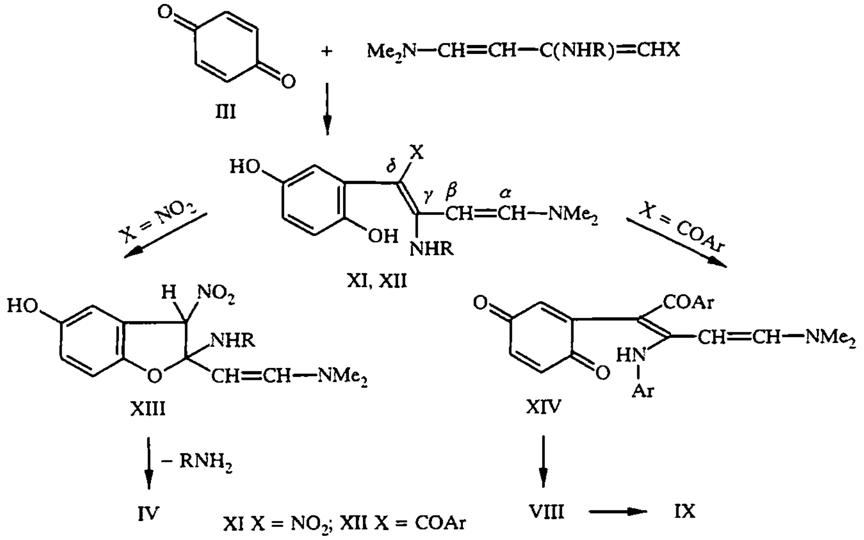
*An unequivocal answer to this problem is complicated by the circumstance that fairly strong resinification and relatively low yields of target compounds are general characteristics of the Nenitzescu reaction.

portion of the signals were displaced towards low field, signals appeared at 3.50 and 3.70 (N^+Me_2) and 8.36 (α-CH), and most importantly a signal for the CH_2 group at 4.03 ppm (2H, br s, β-CH_2), indicating the β protonation of enamine (X).* This signal was practically absent when using CF_3COOD as protonating agent (generating a CD_2 group). Consequently the β-protonation of dienediamines does in fact inhibit the course of the Nenitzescu reaction in the usual direction.



$$X \underset{}{\overset{H^+}{\rightleftharpoons}} \overset{+}{Me_2N}{=}CH{-}CH_2{-}\overset{NHC_6H_4OMe\text{-}p}{\overset{|}{C}}{=}C(CN)COOEt$$

The problem of why the Nenitzescu reaction gives mainly benzofurans for nitrodienediamines and indoles for dienediaminoketones must be considered from the stage of the reaction intermediates. It is well known [6, 7] that so-called hydroquinone adducts are formed in the first step of the reaction of quinones with enamines. In our case, these are compounds (XI) and (XII), the subsequent fate of which depends on stereochemical and electronic factors.



A significant positive charge is localized at the δ position in the hydroquinone adducts (XI) formed from nitrodienediamines due to the powerful electron-accepting effect of the nitro group. As a result there is a rapid attack at this position by an electron pair of the hydroxy group with the formation of intermediate (XIII) which is converted into the benzofuran derivative (IV) [1, 3]. In addition, depletion of the substituted hydroquinone of electrons (due to the same effect of the NO_2 group) hinders its oxidation to a quinone adduct and consequently inhibits indole synthesis for this system. We note that oxidation was not observed previously for nitroenamines [8, 9]. The situation is different for dienediaminoketones. In this case a reduction in the electron-accepting influence of the substituent leads on the one hand to a slowing of furan ring formation and on the other to an acceleration of oxidation to the quinone adduct (XIV) with subsequent indole cyclization to compound (VIII) [2, 4].

The mutual disposition of substituents and double bonds in dienediamines (I) and (II) was established with the aid of ^1H NMR spectroscopy. The nuclear Overhauser effect (NOE) was used to solve this problem. This allowed the mutual disposition of the individual groupings in the system to be established. Saturation of the signal at 7.30 ppm assigned to the α-proton of nitrodienediamine (Ia) leads to a response at the signal at 6.62 ppm (δ-H) (NOE 10-11%), i.e., these protons are close in space to one another. The doublet at 7.30 ppm reacts analogously on quenching the singlet at 6.62 ppm. On quenching the signals of the N-methyl groups at 3.02 ppm (br s) and 3.14 ppm (s), an NOE of 24% was observed for the β-proton at 4.64 ppm (d, β-CH) and 10% for the α-proton at 7.30 ppm. Consequently the spatial disposition of the groupings in compound (Ia) appear to be the following [structure (XV)].

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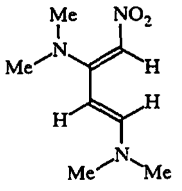
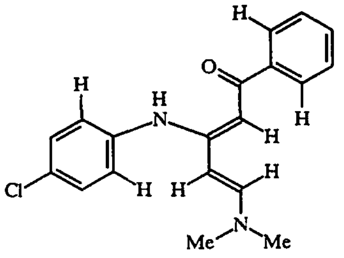
*Additional signals appear on protonation of compound (X) possibly due to hydrolytic or other processes frequently observed for enamines in acid medium.

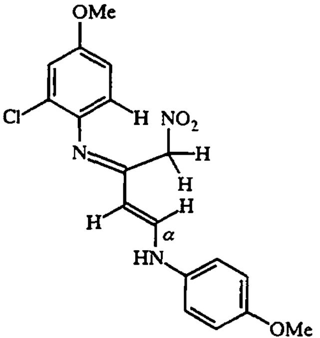


XV



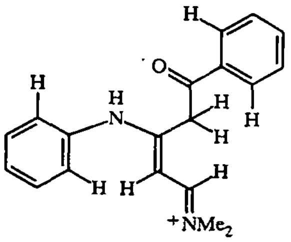
XVI

A similar picture was also observed for the dienediaminoketone (IIb). On quenching the signal for the NH group proton at 13.73 ppm, a response was observed on the ortho protons of the p-chlorophenyl nucleus (A_2B_2 system) at 7.27 ppm (5%), quenching the signal at 7.84 ppm (d, α-CH) caused an NOE on the δ-CH signal at 6.17 ppm (s) (10%). Further data, quenching signal, signal for which NOE observed, and its size: 6.17 (s, δ-CH), 7.84 (d, α-CH), 12%; 6.17 (s, δ-CH), 7.49 (o-protons C_6H_5), 8%; 4.81 (d, β-CH, J = 13.2 Hz), 7.27 (o-protons of A_2B_2 system), 6%; 4.81 (d, β-CH), 2.91 (br s, NMe_2), 6%; 2.91 (NMe_2); 4.81 (β-CH), 9%; 2.91 (NMe_2); 7.84 ppm (α-CH), 7%. The results agree in the best way possible with structure (XVI). The spatial structure based on NOE data for the nitrodienediamines (XV) is in good agreement with the possibility of 1,4-cycloaddition of the nitrodienediamine (Ia) to quinone (III). However, such a reaction encounters significant steric hindrance for dienediaminoketones (IIa, b) due to the benzoyl and, in the transition state, the arylamino residues. Probably the same also applies to compound (Ib) and to 1-p-tolylamino-3-p-methoxyphenylamino-4-nitrobutadiene (XVII) for which 1,4-cycloaddition was not recorded. To complete the picture, the spatial structure of the protonated forms of the enamines were also studied using NOE. The quenching signals and the signals displaying NOE are given under the formulas below:



XVII $\cdot H^+$

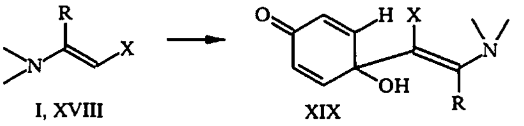
$CDCl_3$ + 10 drop CF_3COOH (one further form was observed, protonated at the δ position, with a different configuration not determined precisely). 5.74 ppm (2H, s, CH_2), 8.42 ppm (q, α-CH), 14%



$CDCl_3$ + 4 drop CF_3COOH 4.62 ppm (2H, s, CH_2), 7.85 ppm (d, J = 12 Hz, α-CH), 18%. 4.62 ppm (CH_2), 8.00 ppm (*o*-protons C_6H_5), 12%

In other words, the mutual dispositions of the bonds and substituents in the protonated forms are similar to those in the basic forms of the dienediamines.

In conclusion, we offer some considerations on the differences in behavior of dienediamines and the corresponding substituted enamines in the Nenitzescu reaction. It is known that β-nitroenamines of the type of (XVIII) (X = NO_2) react with quinone (III) to give not only benzofurans but also 6-hydroxyindoles [8]. As pointed out above, benzofura synthesis is more characteristic of the nitrodienediamines (I). The formation of 6-hydroxyindoles was explained in [8] by attack of the enamine at the quinone C=O carbon atom with the formation of a sterically extremely crowded system (XIX).



I, XVIII XIX

I R = CH=CHNMe$_2$
XVIII R = H, Me (X = NO$_2$)

R = H, for enamines (XVIII)
R = CH=CH—NR$^1_2$ for dienediamines (I)
(X = NO$_2$)

An increase in the volume of substituent R for nitrodienediamines also in our opinion leads to minimization of indole synthesis from them.

In contrast, the formation of 5-hydroxyfuran derivatives rather than 5-hydroxyindole derivatives is far more characteristic for enaminoketones [10]. It may be expected that in dienediaminoketones the introduction of an electron-donating substituent, viz. the enamine fragment, facilitates significantly the oxidation of hydroquinone adducts of type (XIV) to quinone adducts (XV) and thereby shifts the process in the direction of indolization [2, 4].

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Unity Plus 400 (MHz) spectrometer (Varian), internal standard was TMS. Substances were dissolved in CDCl$_3$ (0.5 ml), the spectrum was drawn, then CF$_3$COOH (3 to 10 drops) was added to this solution, and the spectrum drawn once again. CDCl$_3$ was used as standard (7.26 ppm).

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