STRUCTURE OF PYRIDAZINO[3,4-b]QUINOXALINES — PRODUCTS OF THE CONDENSATION OF SUBSTITUTED o-PHENYLENEDIAMINES WITH 3,4,6-TRICHLOROPYRIDAZINE

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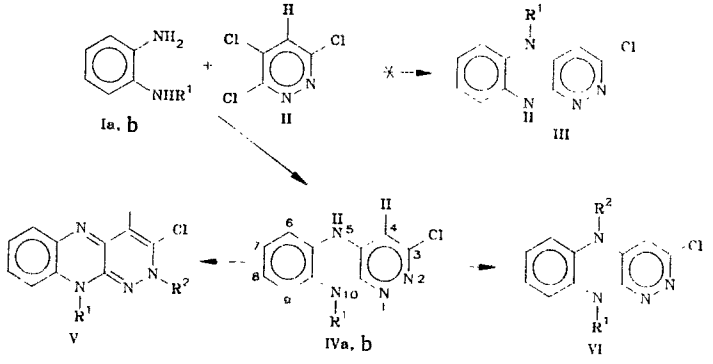
On the basis of the spectral data (^1H and ^{13}C NMR, measurements of the nuclear Overhauser effect (NOE) and T_1, UV spectra), the structure of tricyclic compounds formed in the condensation of substituted o-phenylenediamines with 3,4,6-trichloropyridazine, as well as two types of isomeric products of their alkylation, was established; tautomerism and protonation of the compounds obtained were studied.

Earlier we described some tricyclic compounds formed in the condensation of substituted o-phenylenediamines (I) with 3,4,6-trichloropyridazine (II) and two types of products obtained in alkylation of the indicated compounds [1, 2]. In this work, on the basis of a measurement of the nuclear Overhauser effect (NOE) η and the spin-spin relaxation time T_1 in the ^1H NMR spectra and using the ^{13}C NMR spectra, it was shown that the synthesized compounds are derivatives of pyridazino[3,4-b]quinoxaline; the tautomerism and protonation of these compounds were studied.

As was reported earlier [1], the main condensation products of 3,4,6-trichloropyridazine with N-methyl-o-phenylenediamine (and its N-alkyl analogs) is a green crystalline substance, poorly soluble in water and most organic solvents but rather readily soluble in DMSO and DMFA. In the ^1H NMR spectrum of the condensation product, possessing the structure III or IV, multiplets of four protons of the benzene ring (in the region of δ 6.4-6.75) the singlet of one proton of the pyridazine ring (in the region of δ 5.90), a broadened singlet of the proton of the NH group (at δ 9.3-9.4), and the signal(s) of the protons of substituent R^1 are observed (Table 1).



I a, IVa, V, VI $R^1=CH_3$; I, IV b $R^1=Bu$; V, VI $R^2=Bu$

Considering only two parameters of the spectrum — the chemical shifts (CS) and the SSCC — this spectrum could correspond both to structure III and to IV. To select between these structures we measured two other parameters of the spectrum — the nuclear Overhauser effect η and the spin-lattice relaxation time T_1. In an experiment on the NOE, when the signal of the protons of the N-methyl group in the condensation product was saturated, a substantial increase in the intensity of the signal of one of the protons of the benzene ring was detected (at δ = 6.61, η = 15%), evidently a proton in direct proximity to the N-CH_3 group (in the peri-position to it). For the remaining protons in the indicated product,

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TABLE 1. Parameters of the ^1H NMR Spectra of Pyridazino[3,4-b]quinoxalines[a]

Compound	Solvent	Parameter	4H	5H	6H	7H	8H	9H	NCH_3	α-CH_2	β-CH_2	γ-CH_2	δ-CH_3
IVa	DMFA -D_7	δ	5,92, s	9,32, s	6,40, q	6,65—6,75		6,60	3,13, s				
	DMFA -D_7	η{NCH_3}						15					
	DMFA -D_7	T_1	5,4 (0,3)		2,5 (0,3)		2,5—3,0		1,7 (0,1)				
	b	T_1	19,7 (0,9)		4,7 (0,3)		2,5—3,0		1,7 (0,1)				
IVb	DMFA -D_7	δ	5,92, s	9,40, s	6,42, q		6,55—6,75			3,75, t	1,40—1,65		0,96, t
	DMFA -D_7	T_1	3,7 (0,2)	1,5 (0,1)	1,6 (0,1)		1—1,5						
	CD_3OD	δ	5,67, s		6,20 q	6,50—6,60		6,43		3,61, t	1,30—1,50		0,92, t
	CD_3OD	T_1	8,2 (0,9)		3,5 (0,3)		2—2,5	1,4 (0,3)					
	c	δ	6,10, s				6,6—7,0			3,61, t	1,30—1,60		0,99, t
V	$CDCl_3$	δ	5,24, s			6,6—6,7		6,31, q	2,85, s	3,60, t	1,67	1,38	0,97, t
	$CDCl_3$	η{NCH_3}[d]						18					
	$CDCl_3$	T_1	17,0 (0,8)			3,4—4,5		2,0 (0,1)	1,9 (0,1)	1,0 (0,1)	1,2	1,6	2,1 (0,1)
	1 N. DCl	δ	5,94, s				6,55—6,90		2,89, s	4,02, t	1,68	1,38	0,94, t
VI	$CDCl_3$	δ	5,71, s		6,41, q	6,65—6,75		6,49, q	3,19[e]	3,28, t	1,58	1,47	1,03, t
	$CDCl_3$	η{NCH_3, α-CH_2N}[f]	12		10			10					
	$CDCl_3$	T_1	1,8 (0,2)		1,4 (0,1)	2,9—3,2		2,4 (0,2)	1,5 (0,1)	0,5 (0,1)	0,8—1,2		1,8 (0,1)
	1 N. DCl[g]	δ	6,17		6,70			7,05	3,00	3,46	1,35—1,55		0,94

[a]Units of measurement: δ in ppm, T_1 in sec, η (NEO) in %; s) singlet; t) triplet; q) quartet; absence of letter denotes a multiplet; the mean square error for the value of T_1 is cited in parentheses. [b]A 4:1 mixture of DMFA-D_7—CD_3OD. [c]A 0.5 M solution of DCl in CD_3OD. [d]For all the protons η{α-CH_2} ≤ 3%. [e]The signal is a doublet with SSCC $^6J_{H_6,NCH_3} \approx 0.35$ Hz. [f]The NEO was measured with simultaneous saturation of both signals. [g]All the signals are greatly broadened ($W_{1/2} \geqslant 20$ Hz).

including the pyridazine proton, this effect was absent. Since the pyridazine proton is also in the peri-position to the N-methyl group in structure III, the absence of the NOE for this proton refutes our hypothesis of structure III for the condensation product [1] and confirms structure IV for it.

This conclusion is confirmed by a measurement of the NOE of protons in the alkylation products of compounds IV and a comparison of the relaxation times T_1 in all the compounds studied.

As was reported earlier [2], the alkylation of the condensation products of compound IV by alkyl halides in alcohol solution in the presence of potassium hydroxide leads to the formation of two monoalkyl isomers — red (V) and yellow (VI) forms, isolated in the form of individual compounds. Despite the fact that differences in the CS of analogous protons in the ^{1}H NMR spectra of isomers V and VI exceed 0.3 ppm in certain cases (for example, 4H, N–CH_3, α–CH_2), these differences cannot be used to establish the structure of the isomers, in view of which a measurement of the parameters η and T_1 was undertaken. In the experiment on the NOE, in the case of saturation of the signal of the protons of the N-methyl group in compound V, a significant increase in the signal intensity of the C_9H proton of the benzene ring was noted (η = 20%), which, just as in the case of compound IV, was evidence of a peri-arrangement of these groups. In the case of saturation of the signal of the α–CH_2 protons of the butyl radical, the NOE was not manifested for any of the protons, which was evidence of the addition of the n–C_4H_9 group in compound V to the $N_{(2)}$ nitrogen atom of the pyridazine ring. In the case of compound VI the CS of the protons of the NCH_3 and α–CH_2 groups were so close ($\Delta\delta \approx 0.09$) that saturation of one of them causes a partial saturation of the other; in this case a significant Overhauser effect is detected for three protons — 4-H, 6-H, and 9-H. To separate the contributions of the N–CH_3 and α–CH_2 groups to the NOE, the two dimensional ^{1}H NMR spectrum of compound VI was taken for each of the indicated protons with correlation according to the NOE (Fig. 1). In spectra of this type the presence of nondiagonal signals is evidence of a noncoherent transfer of magnetization (in particular, that responsible for the NOE) between the nuclei whose CS are plotted along the coordinate axes.*

According to Fig. 1, this effect and, consequently, a mutual approach in space occur between the protons 9-H and N–CH_3, 4-H and α–CH_2, 6-H and α–CH_2. Thus, the substituent n–C_4H_9 in the isomer VI, which was incorporated in the alkylation of compound IV, lies between the protons 4-H and 6-H, i.e., at $N_{(5)}$. The data on the spin-lattice relaxation times T_1 (Table 1) agree with this conclusion on the arrangement of the substituents at the nitrogen atoms in compounds IV-VI. A comparison of the values of T_1 of the 4-H proton provides evidence of a substantial decrease in this value in compound VI in comparison with V or IV (under conditions of deuteroexchange). This is evidently explained by the presence of a proton-containing α–CH_2 group (the substituent n–C_4H_9) in the isomer VI close to 4-H (i.e., at $N_{(5)}$), which makes the main contribution to the relaxation of this proton.† The proton of the benzene ring C_6H, the value of T_1 is lowered in comparison with the isomer V, also experiences an appreciable influence of the indicated group.**

For a more complete spectral characterization of the tricyclic system we studied the ^{13}C NMR spectra of compounds IVa, b, V, VI, and trichloropyridazine IIa (Table 2).

The assignment of the signals in the ^{13}C NMR spectra of compounds V, VI, and II, recorded without uncoupling from protons, was performed considering the values of the indirect SSCC, $^2J_{CH}$ and $^3J_{CH}$, and using double heteronuclear selective resonance; for the remaining compounds the assignment of the signal was based on the spectra recorded with incomplete uncoupling from protons and on a comparison of the spectra of all the compounds studied with one another. An analysis of the data of Table 2, pertaining to compounds V and VI, shows that in addition to the two quaternary carbons of the benzene ring, there are three more quaternary carbons, one of which ($C_{(10a)}$) interacts through three bonds with the protons of the P–CH_2 group of the butyl residue.*** Since it was

*For more details on two-dimensional spectra of this type, see [3].

†Here and henceforth we have in mind the spin-lattice relaxation.

**The neighboring protons of the benzene ring make a substantial contribution to the relaxation of the 6-H proton. For the 4-H proton, the neighbor along the pyridazine ring is chlorine, the nuclei of the isotopes of which possess a small magnetic moment and make a negligible contribution to the relaxation of 4-H.

***The observed values of these SSCC are 2.5 Hz or more, which permits us to consider the possibility of their assignment to the long-range constants (through four or more bonds) relatively improbable [4].

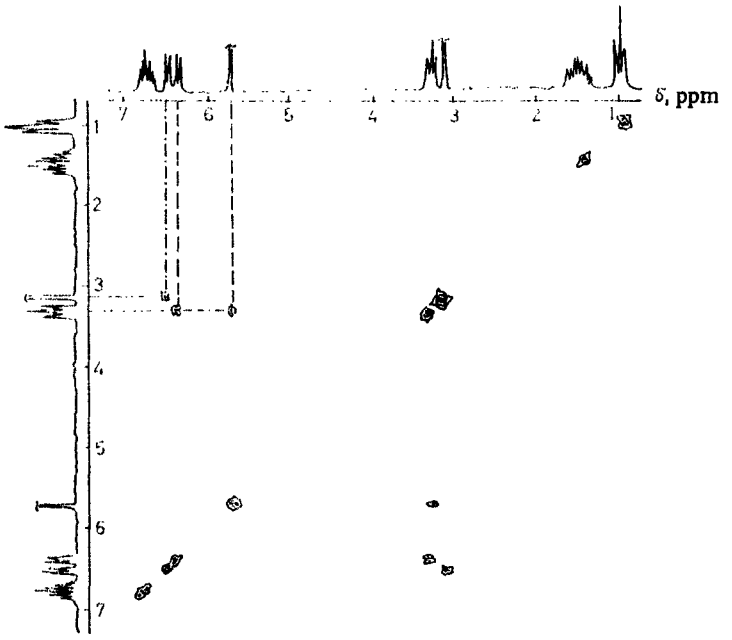


Fig. 1. Spectrum of compound VI correlated according to the NOE. The diagonal region of the spectrum is written with a fourfold weakening of the signals.

TABLE 2. Parameters of the ^{13}C NMR Spectra of Pyridazino[3,4-b]quinoxalines IV-VI and 3,4,6-Trichloropyridazine II[a]

Compound[a]	3	4	4a	5a	6	7	8	9	9a	10a	α	β	γ	δ	NCH_3
IVa	150,2[b]	101,7	138,3	133,5[c]	113,3[d]	123,2[e]	122,4[e]	112,8[d]	130,2[c]	150,0[b]					29,1
IVb	150,1[b]	101,4	138,0	132,4[c]	113,5[d]	123,1[e]	122,1[e]	112,5[d]	130,0[c]	149,4[b]	41,0	26,8	19,6	13,9	
V[f]	141,4	103,8	150,0	138,7	124,9[b]	124,5[b]	122,8[b]	111,1	135,6	149,5	54,2	30,5	19,5	13,7	28,6
		(173,6			159,2[b]	163,3[c]	161,2[c]	160,5[b]			140,0	130,2	125,1	124,2	139,5)
VI[g]	151,1	101,6	138,4	134,8	112,6[b]	123,8[c]	122,1[c]	111,9[b]	131,3	149,9	44,1	29,6	20,0	13,7	29,7
		(170,0			160,0	164,0	163,2	158,0			137,0	124,0	126,0	124,5	139,8)

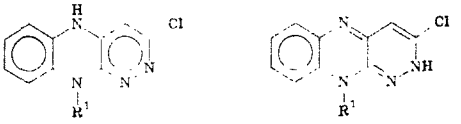
II δ, ppm: $C_{(3)}$ 155,2; $C_{(4)}$ 131,0; $C_{(5)}$ 138,7; $C_{(6)}$ 154,3; J_{CH} (Hz): C_3H_4 (2); C_4H_4 (183,6); C_6H_4 (4,5); C_6H_4 (6,0).

[a]The solvent for compounds II and IVa, b was DMSO-D_6, the signal of which was used as a standard (δ = 39.6 ppm), for V and VI it was $CDCl_3$, with standard TMS. The lines in parentheses correspond to the direct SSCC $^1J_{CH}$ of the corresponding carbon atoms. [b-e]Possibly reversed assignment of the signals marked by the same letters. [f]J_{CH} (Hz): C_3H_4 (<1); C_3NCH_2 (4); $C_{4a}H_4$ (<1); $C_{5a}H_7$ (6.5); $C_{5a}H_9$ (6.5); C_6H_8 (7.5); C_7H_9 (8); C_8H_6 (8); C_9H_7 (6.5); $C_{9a}NCH_3$ (3). [g]J_{CH} (Hz): C_3H_4 (2.5); $C_{4a}H_4$ (<1); $C_{4a}NCH_2$ (4.5); C_6H_8 (8); C_7H_9 (7.5); C_8H_6 (7.5); C_9H_7 (8.5).

established above that alkyl substituents in the compound VI are at the $N_{(5)}$ and $N_{(10)}$ nitrogen atoms of the central ring, the presence of different neighboring carbons for each of these nitrogens demonstrates a six-membered (pyrazine) structure of the central ring. From this it follows that the third ring is also six-membered (pyridazine). This conclusion is confirmed by the presence of a characteristic SSCC in the spectrum of compound VI, of the type of "meta-interaction": $^3J_{C(10a)H_4} \approx 5.5$ Hz; an analogous SSCC is observed in compounds V ($^3J_{C(10a)H_4} \approx 5.5$ Hz) and II ($^3J_{C_6H_4} \approx 6$ Hz). Differences in the values of the SC of the carbons in the 3-, 4a-, and 5a-positions, which, next to a "pyridine"-type nitrogen, are in a weaker field than when they are next to a "pyrrole" nitrogen, agree with the presumed structure of compounds V and VI. An analogous effect is also experienced by one of the carbon atoms of the benzene ring distant from the $N_{(5)}$ nitrogen (evidently $C_{(6)}$).

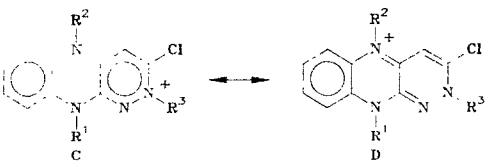
Thus, on the basis of the data of the ^1H and ^{13}C NMR spectra, a tricyclic structure of compounds IV-VI was confirmed, and the positions of the substituents at the nitrogen atoms were determined.

In connection with the alkylation of pyridazino[3,4-b]quinoxalines at two sites, $N_{(5)}$ and $N_{(2)}$, noted, it was of interest to establish at which of the nitrogen atoms there is a proton in compounds IV, for which tautomeric forms with "aromatic" (A) and "quinoid" (B) pyridazine rings are possible.



A B

As it follows from Table 1, the relaxation time T_1 of the protons 4-H and 6-H in compounds IV depends on the solvent (or additives to the solvent), increasing greatly in cases when deuteroexchange is possible. Evidently this is explained by disappearance of the contribution to T_1 by the proton exchanged for deuterium and the nitrogen atom closes to 4-H and 6-H, i.e., at $N_{(5)}$, which agrees with the tautomeric structure A. The data of the ^{13}C NMR spectra confirm this conclusion, since the CS of all the carbons of the tricyclic nucleus in compounds IVa, b are close to the corresponding values in compound VI and differ from those in its isomer V; the last two compounds can be considered as a model with fixed "aromatic" and "quinoid" structures of the pyridazine ring. Convincing evidence in support of the existence of pyridazinoquinoxaline IV in the form of the tautomer A is provided by the similarity of the spectrum of this compound to the spectrum of the N_5-alkyl derivative VI, in contrast to the spectrum of the N_2-alkyl isomer V [compound IVa, C_2H_5OH: 246* (4.68) 368 (3.90), 400 sh (3.78); compound V, C_2H_5OH: 260 (4.46), 278 (4.25), 290 sh (4.10), 316 (3.60), 332 (3.58), 382 (3.99), 400 sh (3.91), 435 sh (3.78), 455 (3.85), 484 sh (3.73), 520 sh (3.32); compound VI, C_2H_5OH: 247 (4.63), 360 (3.90), 400 sh (3.74)]. It is interesting to note that in acid media the UV spectra of all the pyridazinoquinoxalines studied, IV-VI, are close to one another [compound IVb, C_2H_5OH—1 n HCl (1:1): 213 (4.21), 252 (4.60), 258 sh (4.54), 282 (4.26), 291 sh (4.18), 315 sh (3.84), 370 (3.84), 474 (3.64); compound V, C_2H_5OH—1 N HCl (1:1): 212 (4.22), 252 (4.54), 258 sh (4.50), 280 (4.23), 292 sh (4.15), 315 sh (3.90), 372 (3.78), 470 (3.73); compound VI, C_2H_5OH—1 N HCl (1:1): 212 (4.18), 252 (4.52), 260 sh (4.45), 280 (4.18), 290 sh (4.15), 315 sh (3.90), 370 (3.78), 468 (3.56)]. This is independent evidence of the identity of the tricyclic framework in pyridazinoquinoxalines IV-VI and suggests that compound IV and VI are protonated at $N_{(2)}$, while compound V is protonated at $N_{(5)}$; in this case the presence of a substituent has little effect on the localization of the charge in monocations of the indicated compounds.



C D

IVa·H+ $R^1=CH_3$, $R^2=H$, $R^3=H$; IVb·H+ $R^1=n$-Bu, $R^2=H$, $R^3=H$; V·H+ $R^1=CH_3$, $R^2=H$, $R^3=n$-Bu; VI·H+ $R^1=CH_3$, $R^2=n$-Bu, $R^3=H$

*Here and henceforth, the first number represents λ_{max} in nm; sh is a shoulder; log ε is given in parentheses.

The structure of monocations of the pyridazinoquinoxalines studied was confirmed by the data of the ^{1}H NMR spectra, taken in 1 N DCl (compounds V, VI†) or in a mixture of CD_3OD—DCl (compound IV). A characteristic of the ^{1}H NMR spectra of monocations of the isomers V and VI is a weak-field shift of the protons of the α-CH_2 group of the butyl substituent relative to the signal in the bases V and VI, which is evidence of migration of the positive charge from the site of protonation to the nitrogen atom in the other ring (i.e., from $N_{(2)}$ to $N_{(5)}$, and vice versa); the possibility of such migration is illustrated by the limiting resonance structures of the monocations C and D.

On the basis of the greater closeness of the UV spectra of compound V to the spectra of the monocations, it can be considered that the charge in the latter is localized to a greater degree on the $N_{(5)}$ atom, and thus the structure D is represented with greater weight.

For the CS of the protons of the substituents at $N_{(10)}$, protonation either has no effect (compounds IVb, V) or induces a strong-field shift of the signal (compound VI). This permits us to exclude the possibility of protonation at $N_{(1)}$, which would induce a weak-field shift of the protons of the $N_{10}CH_3$ group (in compounds V and VI) or the $N_{10}CH_2$ group (in compound IVb) as a result of migration of the positive charge to $N_{(10)}$. We should mention that protonation of any of the compounds IV-VI (or all of them) at $N_{(1)}$ would lead to monocations differing in the number of σ-bonds at the analogous nitrogen atoms; in this case the similarity of the UV spectra of the indicated compounds in acid medium noted above would scarcely be possible.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were taken on a Varian XL-200 spectrometer (Switzerland) with working frequency 200 MHz for ^{1}H nuclei and 50.3 MHz for ^{13}C nuclei. The solvents and standards are indicated in Tables 1 and 2. In the measurement of the NOE and the relaxation times T_1, samples purged with helium to remove oxygen were used. The NOE was measured by the method of differential spectroscopy — by subtracting the unperturbed spectrum from the spectrum obtained in the case of saturation of a definite signal in the period of the lag between pulses. The measurement of T_1 was performed by the "inversion—reduction" method ($t - 80 - \tau - 90°$). The two-dimensional spectrum with correlation according to the NOE was recorded using the NOE2D program, included in the standard mathematical provisions for the XL-200 NMR spectrometer; resolution 3 Hz per point, time of mixing 0.5 sec. The UV spectra were recorded on a Perkin-Elmer 575 spectrophotometer (Sweden).

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†The signals in the ^{1}H NMR spectrum of compound VI are extremely broad, which may indicate a relatively slow exchange between the protonated and nonprotonated forms of this compound. As was indicated earlier, the hydrochloride of this compound cannot be isolated [2].