3. V. P. Chernetskii, N. A. Petrusha, and I. V. Alekseeva, in: Physiologically Active Substances [in Russian], Naukova Dumka, Kiev (1973), p. 121.
4. Ya. L. Povolotskii, I. V. Bagdasarova, and V. P. Chernetskii, Pediatriya, 39 (1972).
5. T. A. Bektemirov, G. L. Linitskaya, V. P. Chernetskii, and G. A. Galegov, Vopr. Med. Khim., 20, 50 (1974).
6. P. Calabresi and W. Turner, Ann. Int. Med., 64, 352 (1966).
7. U. Niedballa and H. Vorbrüggen, Angew. Chem., 82, 449 (1970).
8. E. R. Garrett, J. K. Seydel, and A. J. Sharpen, J. Org. Chem., 31, 2219 (1966).
9. M. Prystas and F. Sorm, Coll. Czech. Chem. Commun., 34, 1104 (1969).
10. A. Dipple and C. Heidelberger, J. Med. Chem., 9, 715 (1966).
11. M. Bobek, J. Farkas, and F. Sorm, Coll. Czech. Chem. Commun., 32, 3581 (1967).
12. M. W. Winkley and R. K. Robins, J. Org. Chem., 35, 491 (1970).
13. G. T. Rogers and T. L. V. Ulbricht, Europ. J. Biochem., 22, 457 (1971).
14. Z. Smiatacz and J. Sokolowski, Rocz. Chem., 44, 757 (1970).
15. L. Gatterman and H. Wieland, Practical Research in Organic Chemistry [Russian translation], Goskhimizdat, Moscow–Leningrad (1948), p. 436.
16. R. H. Ness, N. N. Diehl, and H. G. Fletcher, J. Am. Chem. Soc., 76, 763 (1954).
17. P. A. Levene and R. S. Tipson, J. Biol. Chem., 92, 109 (1931).

SYNTHESIS AND SOME PROPERTIES OF 2-METHYLPHTHALAZONE HYDRAZONES*

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The reaction of 1-chloro- and 1,4-dichloro-2-methylphthalazinium salts with hydrazine leads to the formation of hydrazones and azines of the corresponding 2-methylphthalazones, the ratio of which depends on the reaction conditions. Symmetrical azines of 4-substituted phthalazones exist in the EE'E" form, while azines of 2-methyl-4-substituted phthalazones exist in the ZE'Z" form.

During a study of the structure of 1-hydrazinophthalazines [2] it was found necessary to synthesize model compounds having a fixed hydrazone structure – 2-methyl- and 2-methyl-4-chlorophthalazone hydrazones (Ia,b). Hydrazones Ia,b and phthalazones IIIa,b in close ratios were obtained from the hygroscopic 1-chloro- (IIa) and 1,4-dichloro-2-methylphthalazinium (IIb) chlorides and 1,4-dichloro-2-methylphthalazinium methylsulfate (IIc) (the analogous 3,6-dichloro-4-methylpyridazinium methylsulfate is stable in water [3]) under the influence of aqueous hydrazine solution. In the reaction of salts IIa-c (without isolation after synthesis) with aqueous hydrazine solution we isolated, in addition to hydrazones Ia,b and phthalazones IIIa,b, azines of 2-methyl-4-substituted phthalazones (IVa,b), the ratio of which depends on the hydrazine concentration. An increase in the hydrazine concentration increases the yield of the hydrazone, whereas a decrease in its concentration raises the yields of phthalazones IIIa,b and azines IVa,b. The use of anhydrous hydrazine in organic solvents raises the yields of hydrazones Ia,b considerably.†

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* Communication LII of the series "Hydrazones." See [1] for communication LI.

† The synthesis of 2-methyl-4-chlorophthalazone dimethylhydrazone in low yield by reaction of methylsulfate salt IIc with aqueous 1,1-dimethylhydrazine solution was described in [2]. The yield increases to 85-90% in anhydrous methanol.

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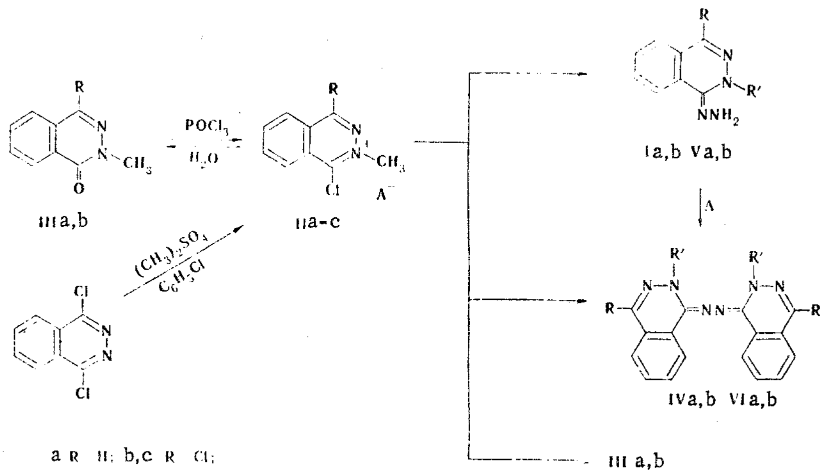
TABLE 1. Spectral Characteristics of Symmetrical Azines IVa,b and VIa,b

Compound	R	R'	UV spect., λ_{max}, nm (log ε), in dioxane	IR spect., ν_{max}, cm^{-1} (mineral oil)	δ, ppm (hexametapol)			
					H-5 H-7	H-4	H-8	NH
VIa	H	H	415 (4,18); 285 (4,58)	3335	7,76m	8,05 s	8,98m	12,05 br, s
IVa	H	CH_3	435 (4,27); 296 (4,27)	—	7,91m	8,05 s	9,86m	—
VIb	Cl	H	419 (4,20); 290 (4,43)	3395	7,77m	—	9,21 m	12,73 br, s
IVb	Cl	CH_3	440 (4,35); 296 (4,32)	—	—	—	—	—



a R H; b,c R Cl;

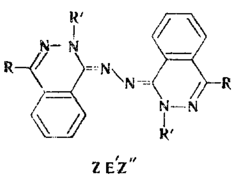
I and IV a,b R' CH_3; V and VI a,b R' = H

We were unable to carry out the transhydrazonation of azines IVa,b, under the influence of a large excess of the hydrazine in dimethylformamide (DMF) solution by heating for 12 h; the starting azines were isolated in quantitative yields.

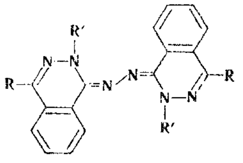
When hydrazones Ia,b are heated, they quite readily undergo disproportionation to the corresponding azines IVa,b. The hydrochlorides of hydrazones Ia,b are converted in water to azines IVa,b at room temperature after 2 days, as compared with 10–20 min in dimethyl sulfoxide (DMSO). The disproportionation of phthalazone Va and 4-chlorophthalazone hydrazone Vb to phthalazone azine VIa and 4-chlorophthalazone hydrazone VIb proceeds with greater difficulty. The hydrochlorides of phthalazone hydrazones Va,b are stable compounds.

The side product isolated in the synthesis of hydrazone Va, for which the 1,2-di(1-phthalazinyl)hydrazine structure has been proposed [4, 5], was identical to the compound obtained by disproportionation of hydrazone Va. Similarly, the disproportionation of hydrazone Vb gives VIb. A comparison of the UV spectra of VIa,b with the spectra of azines IVa,b, which have a fixed structure (Table 1), demonstrate their identical character and indicates that the investigated compounds have phthalazone azine structures rather than the structure of hydrazine derivatives. In addition, the UV spectra of 1,2-di(1-phthalazinyl)hydrazines should have on absorption band close to the band of 1-(α-methylhydrazino)-4-chlorophthalazine [2]. The stretching vibrations of the NH groups in the IR spectra of VIa,b are represented by one band. In the PMR spectra the signals of the aromatic protons in the 8 position of both phthalazone rings are represented by one multiplet, the intensity of which corresponds to two protons. These facts indicate the symmetrical structure of the VIa,b molecules, and the phthalazone (1-phthalazinyl)hydrazone is consequently excluded as an alternative structure.

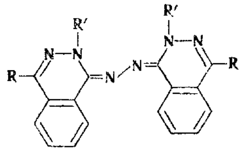
In view of the pronounced steric hindrance in the s-cis conformations (the Z' conformers relative to the N–N bond), only three conformers can be considered for symmetrical azines IVa,b and VIa,b [6]. It is known [2]



ZE'Z''



EE'E''



EE'Z''

TABLE 2. Characteristics of the Products of the Reaction of Salts IIa,b,c with Hydrazine

Starting salt	Reaction prod.	Yield, %, by method			mp, °C	Found, %				Empirical formula	Calculated, %			
		A[a]	B[b]	C		C	H	Cl	N		C	H	Cl	N
IIa	Ia	27	32	84	86—88[c]	61,8	5,6	—	32,2	$C_9H_{10}N_4$	62,1	5,8	—	32,2
	IIIa	28	20—24	3—6	112[7]	—	—	—	—	—	—	—	—	—
	IVa	—	44	5—10	190—192	68,3	5,1	—	26,9	$C_{18}H_{16}N_6$	68,4	5,1	—	26,6
IIb(IIc)	Ib	10 (15)	15 (23)	75 (80)	106—108[c]	51,7	4,2	16,9	26,7	$C_9H_9ClN_4$	51,8	4,3	17,0	26,9
	IIIb	25 (22)	18 (44)	5 (6)	128—130[8]	—	—	—	—	—	—	—	—	—
	IVb	—	65 (33)	20 (14)	258—260	56,7	3,9	21,5	18,2	$C_{18}H_{14}Cl_2N_6$	56,3	3,7	21,4	18,2

[a] The indicated yields are based on phthalazones IIIa,b (for salts IIa,b) and 1,4-dichlorophthalazine (for salt IIc); the hydrazine hydrate concentration was 60-70% in the reactions with salts IIa,b and 40% in the reaction with salt IIc.

[b] The hydrazine hydrate concentration in the reactions with salts IIa,b was 50%, as compared with 40% in the reaction with salt IIc.

[c] These compounds melt with decomposition.

that the chemical shift of the 8-H proton should be different for the Z and E isomers (relative to the $C_{phth}{=}N$ bond). For the EE'Z" form, in view of the nonequivalence of the 8-H protons of the phthalazone rings, their chemical shifts should be different; this is not in agreement with the experimental data for azines IVa* and VIa,b. In the ZE'Z" form the deshielding of the 8-H protons of the phthalazone ring should be greater, and the position of the resonance signals should consequently be shifted to weaker field than in the spectrum of the EE'E" form.

A comparison of the PMR spectra shows (Table 1) that a considerable shift of the signal of the 8-H protons to weak field (Δδ 0.88 ppm) is observed on passing from azine VIa to azine IVa. Consequently, the introduction of a methyl group in the 2 position of the phthalazone ring of symmetrical azines VIa,b leads to a change in the geometrical structure of the molecule, which is similar to the change observed for phthalazone hydrazones [2]. The data presented above make it possible to assign the EZ'E" form to azines VIa,b and the ZE'Z" form to azines IVa,b. The high λ_{max} value of the long-wave band and its high intensity in the UV spectra of azines IVa,b and VIa,b (Table 1) make it possible to assume that a planar conformation is realized for them. In the case of a nonplanar conformation the UV spectrum should approach the spectra of phthalazone hydrazones [2].

Symmetrical azines IVa,b and VIa,b remain unchanged under the influence of refluxing 90% AcOH (for up to 5 h), although azines IVa,b are quite readily (after 1 h) hydrolyzed to the corresponding phthalazones IIIa,b when they are heated with 18% HCl.

EXPERIMENTAL

The UV spectra were recorded with a Specord UV-Vis spectrophotometer. The IR spectra were recorded with a UR-20 spectrometer. The PMR spectra were obtained with a BS-467 spectrometer with an operating frequency of 80 MHz and tetramethylsilane as the internal standard. The melting points were determined with a Boetius microscope stage. The individuality of all of the compounds was monitored by chromatography on Silufol plates by elution with a mixture of petroleum ether with dioxane or benzene and development with iodine vapors.

1-Chloro- (IIa) and 1,4-Dichloro-2-methylphthalazinium (IIb) Chlorides. A mixture of 0.02 mole of phthalazone IIIa or IIIb, 9 ml of $POCl_3$, and 0.34 ml of 98% H_2SO_4 was refluxed for 3 h, after which it was allowed to stand at −5 to −10°C for 3-5 h. The resulting precipitate was removed by filtration, washed one to two times with cold dry benzene, and vacuum dried. The yield of salts IIa,b, with mp > 300°C (in a sealed capillary), was 50-70%. Salts IIa,b are extremely hygroscopic and are rapidly (5-10 min) hydrolyzed to 2-methyl- (IIIa) and 4-chloro-2-methylphthalazone (IIIb), respectively, when they are allowed to stand in air.

2-Methylphthalazone Hydrazone (Ia) and Azine (IVa). Method A. A 2.14-g (0.01 mole) sample of salt IIa was dissolved rapidly in 30 ml of water, and the solution was immediately poured into 20-30 ml of 60-70% hy-

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* The low solubility of azine IVb makes it impossible to record its PMR spectrum, but its IR and UV spectra are similar to the spectra of azine IVa.

drazine hydrate solution. After 10 min, precipitated hydrazone Ia was removed by filtration and recrystallized from 2-3% hydrazine hydrate solution to give yellow needles. During recrystallization of hydrazone Ia the solution should not be heated above 70°C, since azine IVa is formed in this case. The mother liquor was evaporated, and the residue was crystallized from ether to give white crystals of phthalazone IIIa.

Method B. A solution of salt IIa (0.02 mole of phthalazone IIIa, 9 ml of $POCl_3$, and 0.34 ml of 98% H_2SO_4) was added dropwise at 0°C with vigorous stirring to 60-80 ml of 50% hydrazine hydrate solution, and the mixture was maintained at room temperature for 10 min, after which it was heated to 80-90°C, and the precipitated azine IVa was removed by filtration. Recrystallization from DMF gave bright-red crystals. Cooling the mother liquor to 0-5°C gave hydrazone Ia. Evaporation of the solution remaining after separation of hydrazone Ia gave phthalazone IIIa.

Method C. A solution of salt IIa (from 0.02 mole of phthalazone IIIa) was added dropwise with vigorous stirring at 0-5°C to 80 ml of a 15% solution of anhydrous hydrazine in absolute methanol, after which stirring continued at room temperature for another 30 min. The mixture was filtered, and the solid was washed two to three times with methanol to give azine IVa. The methanol washings were combined and vacuum evaporated to dryness to give hydrazone Ia. Evaporation of the mother liquor after recrystallization of hydrazone Ia gave phthalazone IIIa.

2-Methyl-4-chlorophthalazone Hydrazone (Ib) and Azine (IVb). Method A. The reaction of 1,4-dichloro-2-methylphthalazinium chloride (IIb) and methylsulfate (IIc) [2] with hydrazine hydrate was carried out as in the case of chloride IIa. Hydrazone Ib was extracted with chloroform, the extract was dried with Na_2SO_4, and the chloroform was removed in vacuo to dryness. Recrystallization of the residue from methanol gave yellow needles.

Evaporation of the mother liquor after recrystallization of hydrazone Ib gave phthalazone IIIb as a pale-yellow crystalline powder (from methanol).

Methods B and C. The reaction of solutions of salts IIb and IIc with hydrazine was carried out in the same way as in methods B and C in the case of chloride IIa. Hydrazone Ib and phthalazone IIIb were isolated as in method A. Recrystallization of the chloroform-insoluble substance from DMF yielded red filamentary crystals of azine IVb.

The yields, melting points, and the results of elementary analysis of the products of the reaction of salts IIa-c with hydrazine by methods A, B, and C are presented in Table 2.

Phthalazone Azine (VIa). A 1.6-g (0.01 mole) sample of phthalazone hydrazone Va was dissolved in 50 ml of xylene, and the solution was refluxed for 5 h. Half the solvent was then removed by vacuum evaporation, and the concentrate was cooled and worked up to give 1.1 g (76%) of azine VIa as an orange crystalline powder with mp > 280°C (dec., from dioxane). Azine VIa was also obtained in the synthesis of phthalazone hydrazone [4, 5]. The spectral characteristics of azine VIa are given in Table 1.

4-Chlorophthalazone Azine (VIb). This compound was obtained in 30-45% yield by disproportionation of 4-chlorophthalazone hydrazone Vb in xylene in the course of 5 h. The orange crystalline powder melted above 300°C (dec., from xylene). Found: C 54.1; H 2.8; Cl 19.7; N 23.7%. $C_{16}H_{10}Cl_2N_6$. Calculated: C 53.9; H 2.8; Cl 19.7; N 23.6%. The spectral characteristics of azine VIb are presented in Table 1.

LITERATURE CITED

1. B. I. Buzykin, L. P. Sysoeva, and Yu. P. Kitaev, Zh. Org. Khim., 12, 1676 (1976).
2. B. I. Buzykin, N. N. Bystrykh, A. P. Stolyarov, S. A. Flegontov, V. V. Zverev, and Yu. P. Kitaev, Khim. Geterotsikl. Soedin., No. 3, 402 (1976).
3. G. Kremer and R. Surean, Belgian Patent No. 669609 (1965); Chem. Abstr., 64, 2198 (1966).
4. J. Druey and B. H. Ringier, Helv. Chim. Acta, 34, 195 (1951).
5. A. Murray and D. A. Williams, Syntheses of Organic Compounds with Carbon Isotopes [Russian translation], Part II, Inostr. Lit., Moscow (1962), p. 214.
6. Yu. P. Kitaev and B. I. Buzykin, Hydrazones [in Russian], Nauka, Moscow (1974), p. 60.
7. S. Gabriel and F. Müller, Ber., 28, 1830 (1895).
8. Ysao Satoda, Niro Yashida, and Kazuo Nori, Yakugaku Zasshi, 77, 703 (1957); Chem. Abstr., 51, 17927i (1957).