STRUCTURES AND SOME PROPERTIES OF THE PRODUCTS OF CONDENSATION OF PHTHALAZONE HYDRAZONES WITH ALDEHYDES AND KETONES*

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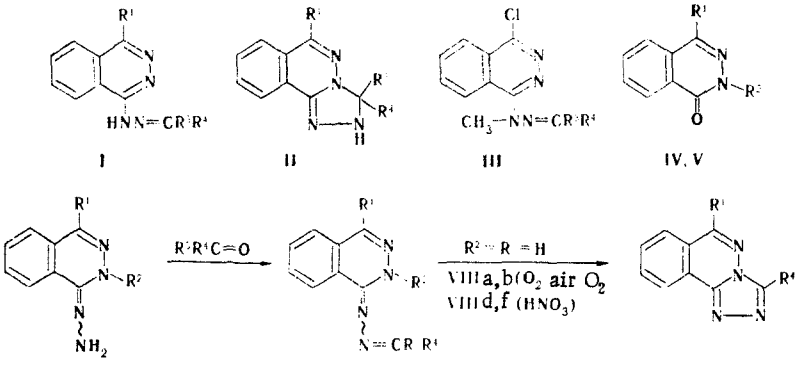
The products of condensation of 2-H-phthalazone hydrazones with carbonyl compounds in solution and in the crystalline form have phthalazone ylidenehydrazone (unsymmetrical azine) rather than phthalazinylhydrazone I structures, as has previously been assumed. 2-H-Phthalazone arylidenehydrazones exist in the EE' form, and their analogs methylated in the 2-N position of the phthalazone ring exist in the ZE' form. Facile ZE' → ZZ' isomerization was noted for 2-methyl-4-chlorophthalazone ethylenehydrazone in halogen-containing solvents. Its unmethylated analog — 4-chlorophthalazone ethylenehydrazone (VIIIb) — is a mixture of geometrical isomers (EE'/EZ' = 3:1).

The products of the reaction of hydrazine with 1-chloro- and 1,4-dichlorophthalazines have 4-substituted hydrazone or azine structures [2, 3]. Like phthalazone hydrazone (the hydrochloride of which is known as "apressin" [4]), its aldehyde and ketone derivatives have been proposed as hypotensive (for example, preparation DI-1461, which later was called "budralazin") [5-8] or antihelmintic substances [9]. The corresponding phthalazinylhydrazone structure (I) was assigned to these compounds [5-8, 10-12], although Druey and Ringier [10] assumed the possibility of their existence in the tautomeric phthalazone ylidenhydrazone form (VIII) (a mixed azine of phthalazone and a carbonyl compound). One also cannot exclude the probability of the cyclic form II and tautomeric equilibrium between the three forms.

To study this problem we obtained the products of the condensation of phthalazone hydrazone VIa and 4-chlorophthalazone hydrazone VIb with carbonyl compounds and compared the data from their IR, UV, and PMR spectra (Tables 1 and 2) with the analogous data for their analogs methylated in the 2-N position of the phthalazone ring (IXa-h) and at the nitrogen atom of the hydrazone fragment (III) [13]. Unsymmetrical azines IXa-h (2-methyl- and 2-methyl-4-chlorophthalazone alkyl- and arylidenehydrazones) were obtained by condensation of 2-methylphthalazone and 2-methyl-4-chlorophthalazone (VIIb) hydrazones with the same aldehydes and



I II III IV, V

VI, VII VIII, IX X, XI

II R^1=Cl; R^3=R^4=H; IV R^1=H, a R^2=H, b R^2=CH_3; V R^1=Cl, a R^2=H, b R^2=CH_3; VI R^2=H, a R^1=H, b R^1=Cl; VII R^2=CH_3, a R^1=H, b R^1=Cl; VIII a—and R^2=H; IX a—h R^2=CH_3; See Table 1 for R^1-R^4 values. X R^1=Cl, a R^4=H, b R^4=CH_3, c R^4=C_6H_5, d R^4=4-$NO_2C_6H_4$; XI R^1=OH, R^4=C_6H_5

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TABLE 1. UV and IR Spectra of Azines VIIIa-i and IXa-h

Compound	R^1	R^2	R^3	R^4	λ_{max}, nm (lg ε)			ν_{max}, cm^{-1} (mineral oil)	
					dioxane	acetonitrile	crystal	NH	C=N and C=C
VIIIa	Cl	H	H	H	345 (3,98); 282 (4,38)	342 (3,94); 281 (4,32); 212 (4,54)	350, 285, 215	3145	1634, 1594
VIIIb	Cl	H	H	CH_3	345 (3,96); 282 (4,42)	343 (3,93); 281 (4,29); 212 (4,51)	350, 284, 212	3278 3308[a]	1581, 1594[a] 1629, 1614[a]
VIIIc	Cl	H	CH_3	CH_3	350 (4,08); 282 (4,48)[b]	355 (4,02); 281 (4,30); 212 (4,57)	350, 285, 214	3323	1638, 1612 1594, 1576
VIIId	Cl	H	H	C_6H_5	370 (4,40); 290 (4,28)	371 (4,34); 292 (4,30); 211 (4,53)		3395	1628, 1587
VIIIe	Cl	H	CH_3	C_6H_5	374 (4,27); 293 (4,27)	369 (4,26); 291 (4,30); 211 (4,55)		3407	1612, 1574
VIIIf	Cl	H	H	4-$NO_2C_6H_4$	418 (4,36); 285 (4,26)			3404	1635, 1602 1588
VIIIg	Cl	H	H	2-$NO_2C_6H_4$	390 (4,11); 286 (4,18)			3389	1629, 1581
VIIIh	H	H	CH_3	CH_3	350 (4,08); 280 (4,53)	344 (3,94); 279 (4,46); 207 (4,56)		3262	1648, 1630 1590
VIIIi	H	H	H	C_6H_5	377 (4,23); 292 (4,13)	372 (4,24); 293 (4,15); 210 (4,43)		3397	1620, 1581 1574
IX[a]	Cl	CH_3	H	H	355 (3,95); 287 (4,09)			—	1606 (w) 1544
IXb	Cl	CH_3	H	CH_3	358 (4,00); 287 (4,22)	350 (4,02); 285 (4,24); 213 (4,56)	351, 286, 214	—	1560 (w)
IXc	Cl	CH_3	CH_3	CH_3	359 (4,02); 288 (4,28)[c]	349 (3,95); 281 (4,38); 212 (4,55)	360, 288, 214	—	1557 (w)
IXd	Cl	CH_3	H	C_6H_5	384 (4,38); 303 (4,06); 280 (4,04)	378 (4,26); 300 (4,10); 279 (4,04); 217, 203[a]	392, 307, 282, 218, 204[a]	—	1604 (w) 1574 (w)
IXe	Cl	CH_3	CH_3	C_6H_5	377 (4,27); 300 (4,04); 281 (4,11)	374 (4,22); 298 (4,00); 280 (4,04); 215 (4,56); 203 (4,49)[a]	386, 303, 284, 218, 206[a]	—	1594 (w) 1568 (w)
IXf	Cl	CH_3	H	4-$NO_2C_6H_4$	430 (4,26); 291 (4,15)				1589 (w)
IXg	Cl	CH_3	H	2-$NO_2C_6H_4$	410 (4,20); 280 (4,11)				1599 (w) 1567
IXh	H	CH_3	H	4-$NO_2C_6H_4$	435 (4,33); 289 (4,15)				1600 (w) 1580 (w)

a) Shoulder. b) In methanol, λ_{max} (log ε): 355 (4.04), 282 (4.30), and 214 nm (4.57); in CCl_4, λ_{max}: 350 and 284 nm. c) In methanol, λ_{max}: 350 and 286; in CCl_4: 360 and 389 nm.

TABLE 2. PMR Spectra of Azines VIIIa-i and IXa-e

Compound	Solvent	Chemical shift, δ, ppm				
		5-H—7-H	H-3a	NR² b,c	C—CH₃	C—H
VIIIa	DMSO	—	8,26	12,10	—	7,31 d; 6,84 d[d]
VIIIa	Hempa	—	8,28	12,52	—	7,31 d; 6,66 d[d]
VIIIb	CH_2Cl_2	—	8,16	9,61	1,97 d[e] (EE′); 2,07 d[f] (EZ′)	7,75 q[e] (EE′); 7,20 q[f] (EZ′)
VIIIb	$CDCl_3$	—	8,23	10,06	2,00 d[e] (EE′); 2,10 d[f] (EZ′)	7,81 q[e] (EE′); 7,25 q[f] (EZ′)
VIIIb	d_6-DMSO	—	8,21	11,51	2,02 d[e] (EE′); 2,03 d[e] (EZ′)	7,76 q[e] (EE′), 7,23 q[e] (EZ′)
VIIIc	CCl_4	—	8,29	10,36	2,06 s; 2,13 as	—
VIIIc	DMSO	—	8,33	11,38	—	—
VIIId	CH_2Cl_2	7,38 m(3H)	8,38	10,43	-	8,45 s
VIIId	DMSO	7,43 m(3H); 8,28 m(2H)	8,36	12,18	—	8,49 s
VIIId	Hempa	7,37 m (3H); 8,23 m (2H)	8,47	13,28 s	—	8,49 s
VIIIe	CH_2Cl_2	7,42 m (3H)	8,43	10,35	2,57 s	—
VIIIe	d_6-DMSO	7,33 m (3H); 8,06 m (2H)	8,34	11,80 s	2,49 s	—
VIIIf	Hempa	8,23 - 8,85 m (4H, AA′BB′)	8,58	13,52	—	8,78 s
VIIIh	CH_2Cl_2	7,69 s (II-4)	8,29	10,30	2,07 s; 2,16 s	—
VIIIh	d_6-DMSO	7,89 s (II-4)	8,20	11,28	2,01 s; 2,04 s	—
VIIIi	CH_2Cl_2	7,36 m (3H)	8,38	10,43	-	8,45 s
VIIIi	DMSO	7,48 m (3H); 8,05 m (2H)	8,33	12,25	-	8,48 s
VIIIi	Hempa	7,40 m (3H); 8,18 m (2H)	8,45	13,21	—	8,45 s
IXa	CCl_4	—	9,23	3,60	—	7,17 d; 6,60 d[g]
IXa	d_6-DMSO	—	9,23	3,55	—	7,22 d 6,78 d[g]
IXb	$CDCl_3$	—	9,30	3,62	2,08 d[e]	—
IXb	d_6-DMSO	—	9,31	3,56	2,05 d[e]	—
IXb	$C_6H_5NO_2$	—	9,55	3,62	2,06 d[e]	—
IXc	CCl_4	—	9,52	3,68	2,03 s 2,12 s	—
IXd	CH_2Cl_2	7,38 m (3H)	9,55	3,74	-	8,39 s
IXd	d_6-DMSO	7,42 m (3H)	9,42	3,63	-	8,35 s
IXe	CCl_4	7,69 m and 7,30 m (8H)	9,27	3,74	2,41 s	—
IXe	d_6-DMSO	7,43 m (3H)	9,25	3,68	2,12 s	—

a) Multiplet of I. Multiplet of 5-H—7-H protons at 7.80-7.90 ppm. b) The NH group for VIIIa-i gives a broad singlet. c) The NCH_3 group for IXa-e gives a singlet. d) AB system, J_{HH} = 14 Hz; $\Delta\nu_{AB}$ 18.5 Hz (in d_6-DMSO) and 19.27 Hz (in hempa). e) J_{CH_3-H} = 5.6 Hz. f) J_{CH_3-H} = 5.2 Hz. g) AB system, J_{HH} = 15 Hz; $\Delta\nu_{AB}$ = 34.4 Hz (in CCl_4); J_{HH} = 14 Hz, $\Delta\nu_{AB}$ = 35.33 Hz (in d_6-DMSO).

TABLE 3. Characteristics of Unsymmetrical Azines VIIIa,b,d-g and IXa-h

Compound	mp, °C	Crystallization solvent	Found, %				Empirical formula	Calc., %				Yield, %
			C	H	Cl	N		C	H	Cl	N	
VIIIa	122 - 125*	CH₃OH	52,5	3,3	17,3	27,2	$C_9H_7ClN_4$	52,3	3,4	17,2	27,1	40
VIIIb	97 - 100*	CH₃OH	54,5	4,2	16,0	25,3	$C_{10}H_9ClN_4$	54,4	4,1	16,1	25,4	80
VIIId	175—177	DMF	64,0	4,0	12,4	20,0	$C_{15}H_{11}ClN_4$	63,7	3,9	12,6	19,8	93
VIIIe	139—140	C_6H_5OH	64,9	4,3	12,1	18,6	$C_{16}H_{13}ClN_4$	64,8	4,4	12,0	18,9	92
VIIIf	278—280	DMF	54,9	2,9	11,0	21,3	$C_{15}H_{10}ClN_5O_2$	55,0	3,0	10,8	21,4	95
VIIIg	248—250	DMF	55,0	3,2	11,0	21,5	$C_{15}H_{10}ClN_5O_2$	55,0	3,0	10,8	21,4	90
IXa	74,5—75	Pentane	54,0	4,2	16,3	25,1	$C_{10}H_9ClN_4$	54,4	4,1	16,1	25,4	35
IXb	92—93	C_2H_5OH	56,1	4,8	15,3	24,0	$C_{11}H_{11}ClN_4$	56,3	4,7	15,1	23,9	32
IXc	88	C_2H_5OH	58,2	5,2	14,4	22,3	$C_{12}H_{13}ClN_4$	58,0	5,2	14,3	22,5	51
IXd	96 - 97,5	C_2H_5OH	65,0	4,3	11,9	19,1	$C_{16}H_{13}ClN_4$	64,8	4,4	12,0	18,9	19
IXe	115 - 117	C_2H_5OH	62,5	4,6	11,2	18,2	$C_{17}H_{15}ClN_4$	65,7	4,8	11,3	18,0	45
IXf	208 - 210	Dioxane	56,0	3,5	10,3	20,6	$C_{16}H_{12}ClN_5O_2$	56,2	3,5	10,4	20,5	78
IXg	177—178	DMF	56,4	3,6	10,3	20,7	$C_{16}H_{12}ClN_5O_2$	56,2	3,5	10,4	20,5	74
IXh	164—165	C_2H_5OH	62,3	4,3	—	22,7	$C_{10}H_{13}N_5O_2$	62,5	4,2	—	22,8	80

*With decomposition.

ketones. The reaction of hydrazone VIIb with formaldehyde, acetaldehyde, benzaldehyde, and acetone leads to 2-methyl-4-chlorophthalazone (Vb). We were able to prove the formation of acetone azine and benzalazine, as well as small amounts of azines IXa-d, by means of thin-layer chromatography (TLC) and UV spectroscopy. The use of catalytic amounts of the acid increases the yields of IXa-d somewhat (Table 3).

The UV spectra of alkylidenehydrazones IXa-c (Table 1) are similar to the spectrum of hydrazone VIIb [2], but the intensities of the bands are higher. The spectra of VIIIa-c and VIIIh are also similar to the spectra of starting hydrazones VIa,b [2]. The long-wave band is shifted only slightly bathochromically, but its intensity and particularly the intensity of the short-wave band are increased (the effect of replacement of π—n conjugation by π—π conjugation). The spectra of VIIIa-c are similar to the spectra of azines IXa-c but differ markedly from the UV spectra of the N-methyl-N-(4-chloro-1-phthalazinyl)hydrazones of the same carbonyl compounds (II), which have one long-wave absorption band at 325-336 nm [13] (Table 1). A similar result is characteristic for the UV spectra of solutions of the compounds in various solvents (methanol, CCl_4, and acetonitrile) at various concentrations and in the crystalline form (Table 1). Consequently, alkylidene derivatives VIIIa-c and VIIIh exist primarily in the ylidenehydrazone form (VIII) rather than in the tautomeric phthalazinylhydrazone form (I) in solution and in the crystalline form.

Transition from alkylidene derivatives IXa-c to benzaldehyde (IXd) and acetophenone (IXe) derivatives leads to the appearance of a third absorption band in their UV spectra at 300-303 nm. The nonmethylated analogs (azines VIIId,e) also evidently contain a similar band, but it is overlapped by an intense short-wave band. The position of this band in the spectra of IXd,e is close to the position of the long-wave absorption band of benzaldehyde [14] and acetophenone [15] methylhydrazones; this indicates rotation about the N-N bond.

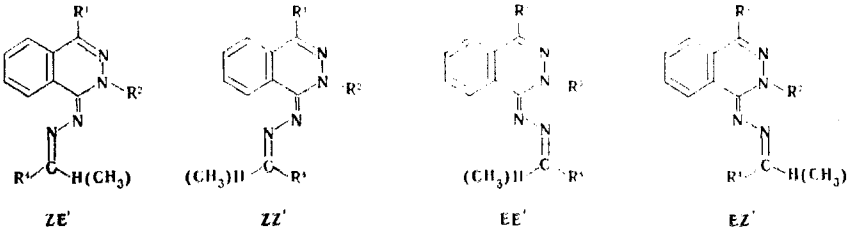
A comparison of the UV spectra of azines IXd-h, VIIId-g, and VIIIi with the spectra of the N-methyl-N-(4-chloro-1-phthalazinyl)hydrazones of the same oxo compounds [13] (Table 1) also indicates unambiguously that VIIId-g and VIIIi exist primarily in arylidenehydrazone form VIII in solution and in the crystalline form.

The closeness of the spectral data for VIIIh (which was selected in [12] as a model in the study of the structures of phthalazinylhydrazones) and VIIIc indicates the similarity in their structures. A comparison of the UV, PMR, and IR spectra of VIIIc, 2-methyl-4-chlorophthalazone isopropylidenehydrazone (IXc) (Tables 1 and 2), and acetone N-methyl-N-(4-chloro-1-phthalazinyl)hydrazone [13] indicates unambiguously that VIIIc and VIIIh have azine structures. Consequently the conclusions [6, 7, 12] regarding the structures of budralazin (mesityl oxide phthalazinylhydrazone) and its analogs are not adequately substantiated.

The weak-field shift of the 8-H proton in the PMR spectra of phthalazones IVa,b and Va,b [2], 2-H-phthalazone hydrazones VIa,b [2], phthalazone azines [3], and ylidenehydrazones VIIIa-i is due to the anisotropic effect of the exocyclic multiple bond (C=O or C=N). In our opinion, the weak-field shift of the 8-H proton in the spectra of the products of condensation of phthalazone hydrazone with tiglaldehyde and mesityl oxide also is a consequence of the anisotropy of the exocyclic C=N bond in the mixed azine structure rather than in the phthalazinylhydrazone structure (I).

The shift of the signal of the NH proton of azines VIIIa-i to weak field as the associating capacity increases in the order CCl_4 < d_6-DMSO < hempa (Table 2) indicates the absence of an intramolecular hydrogen bond.

In view of the pronounced steric hindrance in the s-cis conformations of azines VIII and IX one should consider four s-trans forms [16]: ZE', ZZ', EZ', and EE' (Z and E relative to the C_{phth}=N bond, and Z' and E' relative to the N=CR^3R^4 bond).



ZE' ZZ' EE' EZ'

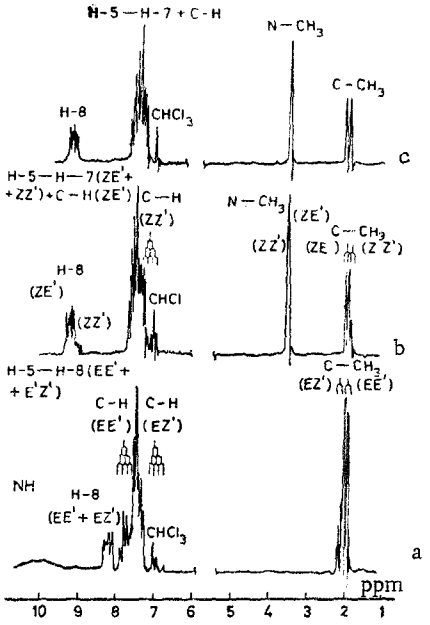


Fig. 1. PMR spectrum in $CDCl_3$ (the amplification was reduced for the methyl groups): a) VIIIb; b) IXb (after 12 h in $CDCl_3$ solution); c) IXb (freshly prepared solution).

It is known [2, 3] that the chemical shift of the 8-H proton differs for the Z and E isomers. The similarity in the forms of the signals of the protons of the phthalazone ring, including the 8-H proton, in the PMR spectra of azines VIIIa-i (Table 2), phthalazones IVa and Va, the E forms of hydrazones VIa,b [2] and 2-H-phthalazone azines [3] (which is an additional confirmation of the azine structures of VIII) makes it possible to conclude that azines VIIIa-i (R^2 = H) exist in the E form. A considerable shift of the signal of the 8-H proton to weak field is observed on passing from azines VIII (R^2 = H) to azines IX (R^2 = CH_3); this makes it possible to assign a Z-isomer structure to them. Consequently, the introduction of a methyl group in the 2 position of the phthalazone ring of unsymmetrical azines leads to a change in the geometrical structure of the molecule, as in the case of the hydrazones and symmetrical azines of the corresponding phthalazones [2, 3].

In addition to signals of aromatic protons, the PMR spectra of azines VIIIa and IXa contain a quartet of the lines of the protons of the methylene fragment (signal of the NH proton in VIIIa and singlet of the CH_3 group in IXa); this indicates realization of one noncyclic monomeric azine form — the E form for azine VIIIa and the Z form for azine IXa. The high value of the geminal spin—spin coupling constant (SSCC) of the protons of the $N{=}CH_2$ group (14.0 Hz) in the spectra of azines VIIIa and IXa is in agreement with the data [17] for the methylene fragment of various formaldehyde hydrazones.

We assigned the CH=N low-field doublet signal at 7.14-7.31 ppm in the spectra of azines VIIIa and IXa to the resonance of the methylidyne proton in the syn position and the doublet signal at 6.60-6.84 ppm to the proton in the anti position (in analogy with the data in [18, 19]). The assignment of the signals of the protons of the CH_3 groups of the ylidene fragment is ambiguous [13, 16, 18-23] and cannot be used independently.

The PMR spectrum of 2-methyl-4-chlorophthalazone ethylenehydrazone (IXb) (Table 2 and Fig. 1) provides evidence that chromatographically purified azine IXb also exists in one geometric form in a freshly prepared solution in $CDCl_3$ or CCl_4. However, new signals appear after 12 h at 15-20°C in $CDCl_3$ (Fig. 1): CCH_3 doublet (2.02 ppm, J_{CH_3-H} = 5.2 Hz), NCH_3 singlet (3.64 ppm), =CH quartet (7.25 ppm), and 8-H multiplet (9.16 ppm). Changes of this type are not observed in nitrobenzene and d_6-DMSO up to 100°C. This is explained by isomerization relative to the C=N bond in the ethylideneimine fragment without a change in the configuration at the exocyclic $C_{phth}{=}N$ bond. The ability of halogen-containing solvents to lower the energy barrier to Z—E isomerization of hydrazones was noted in [16, 20]. The appearance of a quartet of a methylidyne proton at strong field indicates that in the resulting isomer it is trans-oriented relative to the C=N bond of the ylidene residue. Consequently, the starting isomer has the ZE' form, and the resulting isomer has the ZZ' form. On the basis of this, it was concluded (in agreement with the data in [18-21]) that the signal of the CCH_3 group of the ZE' form for azine IXb and, evidently, for isopropylidenehydrazone IXc is found at weaker field than the corresponding signal of the ZZ' form (cis orientation).

The ratio of the isomers of azine IXb in $CDCl_3$ was 4:1 24 h after dissolving the ZE' isomer and 3:2 after 20 days in a sealed ampule.

The samples of 4-chlorophthalazone ethylidenehydrazone VIIIb obtained from the reaction mixture and recrystallized from methanol were found to be mixtures of two geometrical isomers in CH_2Cl_2, $CDCl_3$, and d_6-DMSO; the mixtures cannot be separated with a chromatographic column because of the rapid conversion of the compound to 3-methyl-6-chloro-1,2,4-triazolo[3,4-a]-phthalazine (Xb). The quartet at 7.84 ppm in the PMR spectrum of azine VIIIb in $CDCl_3$ (Table 2 and Fig. 1) was assigned to the signal of the methylidyne proton of the EE' form, and the quartet at 7.20 ppm was assigned to the signal of the methylidyne proton of the EZ' form; judging from the spectrum, the EE' form predominates. The ratio of the isomers of azine VIIIb was 3:1.

The IR spectrum also confirms the presence of geometrical isomers of azine VIIIb: almost all of the absorption bands have additional lines in the form of shoulders.

The position of the signals of the 8-H and CH=N protons in the PMR spectra (Table 2) makes it possible to conclude that azines VIIId,f,i exist in the EE' form in solution and that azine IXd (and apparently azines IXg,h) exist in the ZE' form.

The transition from alkylidenehydrazones VIIIa,b and IXa,b to isopropylidenehydrazones VIIIc and IXc does not give rise to appreciable changes in the position of the absorption bands and their intensities in the UV spectra of solutions and crystalline samples (Table 1). This fact constitutes evidence for similar structures of alkylidenehydrazones VIIIa-c and IXa-c and makes it possible to assume that their molecules are nonplanar.

The transition from benzylidenehydrazones VIIId and IXd to acetophenone derivatives (azines VIIIe and IXe) is accompanied by a considerable decrease in the intensity of the long-wave band; this can be explained by an increase in the angle of rotation about the N-N bond in azines VIIIe and IXe because of steric hindrance [13-16]. The strong-field shift of the signal of the 8-H proton in the PMR spectrum of azine IXe as compared with the position of the analogous signal of azine IXd also constitutes evidence for this.

Alkylidenehydrazones VIIIc, VIIIh, and IXa-c and arylidenehydrazones VIIId-g and IXd-h are quite stable compounds under ordinary conditions, 4-chlorophthalazone methylidene- and ethylidenehydrazones VIIIa,b are readily oxidized both in solution and in the crystalline state to 3-R^4-6-chloro-1,2,4-triazolo[3,4-a]phthalazines [Xa (R^4 = H) and Xb (R^4 = CH_3)]. Triazole Xb was also obtained by refluxing 4-chlorophthalazone hydrazone (VIb) in acetic acid or 1,4-dichlorophthalazine with acetylhydrazine in dioxane.

Brief refluxing of azine VIIIa in ethanol leads to the formation of XII, which is only slightly soluble in most organic solvents. It is also obtained by condensation of 4-chlorophthalazone hydrazone VIb with formaldehyde. This compound is rapidly converted to triazole Xa in nonpolar and low-polarity solvents (CCl_4, $CHCl_3$, dioxane, etc.), whereas its stability is somewhat higher in polar solvents (alcohols, DMSO, DMF, and hempa). Its PMR spectrum contains a multiplet of aromatic protons (4H) and a singlet (2H) at 5.30 ppm, and its UV spectrum is similar to the spectrum of 2-methyl-4-chlorophthalazone hydrazone VIIb with a slight bathochromic shift of the long-wave band. These results are in good agreement with the 2,3-dihydro-6-chloro-1,2,4-triazolo[3,4-a]phthalazine structure (II), but the absence of absorption at 3100-3400 cm^{-1} in the IR spectrum compels us to assume a dimeric structure for it. The determination of the molecular weight was hindered because of its low solubility and easy conversion to triazole Xa.

Arylidenehydrazones VIIId,f remain unchanged after refluxing in alcohols and xylene for 5-7 h; however, they are oxidized to triazoles Xc,d in good yields by 20-25% HNO_3. Triazoles Xc and Xd were also obtained from 1,4-dichlorophthalazine and benzoylhydrazine [24] and 4-nitrobenzoylhydrazine, respectively. Triazole Xc is extremely resistant to the action of acids and remains unchanged after refluxing in 90% AcOH for 6 h. It is saponified to 3-phenyl-6-hydroxy-1,2,4-triazolo[3,4-a]phthalazine (XI) by heating in a solution of KOH in 90% dioxane. The structure of XI was confirmed by the IR spectroscopic data and by the similarity between its UV spectrum and the spectrum of triazole Xd.

When unsymmetrical azines VIIId,f,g are heated with 18% HCl for 15-20 min, they are converted to the hydrochlorides, which are stable on prolonged refluxing. Azines VIIIf,g and IXf,h are also stable in AcOH. When azine VIIId is heated in AcOH for 90 min, a small amount of its acetate salt and an unstable product are formed. The absence of triazoles Xb,c and

XI, the 4-chlorophthalazone, and the benzalazine and azine of 4-chlorophthalazone was demonstrated by thin-layer chromatography.

The different behavior of ylidenehydrazones of the VIII and IX type and N-methyl-N-(4-chloro-1-phthalazinyl)hydrazones of the same carbonyl compounds [13] with respect to the action of acids also confirms the azine structure of VIII.

EXPERIMENTAL*

The conditions under which the spectral measurements were made and chromatographic monitoring was accomplished are presented in [2, 3, 13]. Azine VIIIc was obtained by condensation of 4-chlorophthalazone hydrazone (VIb) with acetone, and azines VIIIh,i were obtained by condensation of phthalazone hydrazone (VIa) with acetone and benzaldehyde, respectively, by the method in [10].

4-Chlorophthalazone Methylidenehydrazone (VIIIa). Excess dry gaseous CH_2O was bubbled through a suspension of 1.96 g (10 mmole) of 4-chlorophthalazone hydrazone (VIb) in 100 ml of absolute methanol at 30-40°C for 20-30 min, after which the mixture was heated to 50°C. The precipitate was removed by filtration of the hot solutions and recrystallized from methanol to give yellow needles of azine VIIIa (Tables 1 and 2).

Compound XII. A) The methanol solution from the preceding experiment after separation of azine VIIIa was evaporated to dryness, and the residue was crystallized from ethanol to give 0.2-0.3 g (10-15%) of orange acicular crystals of XII with mp 133-134°C (dec.). UV spectrum, λ_{max} (log ε) in methanol: 212 (4.65), 287 (4.25), and 354 (3.74); in CH_3CN: 210 (4.65), 293 (4.26), and 362 nm (3.72). PMR spectrum, δ (in hempa): 7.94 (m, 4H, 5-H–8-H), and 5.30 (s, 2H, CH_2). Found, %: C 52.2; H 3.4; Cl 17.3; N 27.0. μ_{exp} in dioxane, 25°; 1.72 ± 0.07D. $C_9H_7ClN_4$. Calculated, %: C 52.3; H 3.4; Cl 17.2; N 27.1.

B) A solution of 0.51 g (2.5 mmole) of azine VIIIa in 100 ml of ethanol was refluxed for 15-20 min, after which it was cooled and worked up to give 0.35 g (68%) of XII.

4-Chlorophthalazone Ethylidenehydrazone (VIIIb). One drop of concentrated H_2SO_4 and 1.5-2 ml of acetaldehyde were added to a suspension of 1.96 g (10 mmole) of hydrazone VIb in 30-40 ml of ether, and the mixture was stirred for 15-20 min. It was then heated to 35°C, and the solution was filtered. The ether was removed in vacuo to give azine VIIIb as a yellow crystalline powder (see Table 3). The dipole moment of a mixture of the geometrical isomers of azine VIIIb in dioxane at 25°C was 2.28 ± 0.3 D.

4-Chlorophthalazone Benzylidenehydrazone (VIIId), (1-Phenylethylidenehydrazone (VIIIe), 4-Nitrobenzylidenehydrazone (VIIIf), 2-Nitrobenzylidenehydrazone (VIIIg), 2-Methyl-4-chlorophthalazone 4-Nitro- and 2-Nitrobenzylidenehydrazones (IXf and IXg), and 2-Methylphthalazone 4-Nitrobenzylidenehydrazone (IXh). One drop of concentrated H_2SO_4 and 10 mmole of the appropriate carbonyl compound in 15-20 ml of ethanol were added to a solution of 10 mmole of hydrazone VIb (for azines VIIId-g), hydrazone VIIb (for azines IXf and IXg), or hydrazone VIIa (for IXh) in 20-30 ml of DMF (for azines VIIId, VIIIf, and VIIIg), or in 100 ml of ethanol, and the mixture was refluxed for 30 min. It was then cooled and worked up to give yellow needles of azines VIIId and VIIIe, orange powdered VIIIf, orange needles of VIIIg, or red needles of azines IXf, IXg, and IXh. Dipole moments (μ_{exp}) in dioxane in 25°C: zine VIIId 1.74 ± 0.04 D, azine VIIIe 2.54 ± 0.16 D, azine VIIIf 5.27 ± 0.03 D, azine IXf 6.05 D, and azine IXh 5.12 D.

2-Methyl-4-chlorophthalazone Methylidenehydrazone (IXa). One drop of concentrated H_2SO_4 was added to a solution of 2.09 g (10 mmole) of hydrazone VIIb in 50-70 ml of absolute methanol, and excess dry CH_2O was bubbled through the solution at 20°C for 30 min. The mixture was then filtered, and the methanol was removed from the filtrate by evaporation to dryness. The residue was chromatographed with a 60 × 2 cm column filled with neutral activity II (Brockmann classification) aluminum oxide [elution with petroleum ether–dioxane (1:1)] to give yellow needles of azine IXa.

2-Methyl-4-chlorophthalazone Ethylidenehydrazone (IXb), Isopropylidenehydrazine (IXc), Benzylidenehydrazone (IXd), and 1-Phenylethylidenehydrazone (IXe). One drop of concentrated H_2SO_4 and 2 ml of acetaldehyde (for azine IXb), 2 ml of acetone (for azine IXc), 10 mmole of

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benzaldehyde (for azine IXd) or acetophenone (for azine IXe) were added to a solution of 2.09 g (10 mmole) of hydrazone VIIb in 100 ml of absolute methanol, and the mixture was stirred at 40°C for 30 min. The solvent was then removed by evaporation to dryness, and the residue was chromatographed with a 60 × 2 cm column filled with neutral activity II (Brockmann classification) aluminum oxide [elution with petroleum ether–diethyl ether (1:1)] to give azines IXb and IXd as yellow crystalline powders or azines IXc and IXe as yellow needles.

6-Chloro-1,2,4-triazolo[3,4-a]phthalazine (Xa). A solution of 1.03 g (5 mmole) of azine VIIIa in 80-100 ml of dioxane was refluxed for 2 h, after which it was evaporated to dryness, and the residue was crystallized from acetone to give 0.85 g (84%) of white needles of Xa with mp 164-165°C. UV spectrum, λ_{max}, nm (log δ), dioxane: 245 (4.53). PMR spectrum, δ ($CDCl_3$): 7.83 (m, 2H) and 8.13 (m, 1H) (7-H–9-H), 8.56 (m, 1H, 10-H), and 8.88 ppm (s, 1H, 3-H).

Triazole Xa was also obtained by alternative synthesis by refluxing hydrazone VIb in HCOOH by the method in [25].

3-Methyl-6-chloro-1,2,4-triazolo[3,4-a]phthalazine (Xb). A) A solution of 1.1 g (5 mmole) of azine VIIIb in 80 ml of dioxane was refluxed for 2 h, after which it was evaporated to dryness to give 0.8 g (79%) of Xb as a pale-green crystalline powder with mp 196°C (from dioxane). UV spectrum, λ_{max} (log ε), dioxane: 249 nm (4.53). PMR spectrum, δ ($CDCl_3$): 7.81 (m, 2H) and 8.11 (m, 1H) (7-H–9-H), 8.54 (m, 1H, 10-H), and 2.78 (s, 3H, CH_3). Found, %: C 60.2; H 3.1; Cl 16.1; N 25.8. $C_{10}H_7ClN_4$. Calculated, %: C 59.9; H 3.2; Cl 16.6; N 25.6.

B) A solution of 1.96 g (10 mmole) of hydrazone VIb in 40 ml of CH_3COOH was refluxed for 2 h, after which it was evaporated to dryness, and the residue was washed with 5% $NaHCO_3$ to give 1.96 g (89%) of triazole Xb.

C) A mixture of 1.99 g (10 mmole) of 1,4-dichlorophthalazine and 1.5 g (20 mmole) of acetic acid hydrazide in 30 ml of dioxane was refluxed for 8 h, after which the solvent was evaporated to give 1.6 g (73%) of triazole Xb.

3-Phenyl-6-chloro-1,2,4-triazolo[3,4-a]phthalazine (Xc). A suspension of 1.4 g (5 mmole) of azine VIIId in 40 ml of 25% HNO_3 was triturated in a porcelain mortar for 40 min, after which the solid was removed by filtration and washed with water to give 1.2 g (86%) of triazole Xc as light white needles with mp 168-170°C (from 70% methanol). The product was identical to the compound obtained in [24]. UV spectrum, λ_{max} (log ε) in dioxane: 270 nm (4.53). PMR spectrum, δ (in $CDCl_3$): 7.88 (m, 2H) and 8.28 (m, 3H) (7-H–9-H plus two aromatic protons), 8.61 (m, 1H, 10-H), and 7.51 (m, 3H, aromatic H).

3-(4-Nitrophenyl)-6-chloro-1,2,4-triazolo[3,4-a]phthalazine (Xd). As in the synthesis of triazole Xc, this compound was obtained by oxidation of azine VIIIf with 25% HNO_3 for 30 min. Workup of the reaction mixture gave yellow needles of triazole Xd (80%) with mp 232°C (from dioxane). UV spectrum, λ_{max} (log ε) in dioxane: 322 (4.33) and 255 nm (4.40). Found, %: C 55.5; H 2.4; Cl 10.8; N 21.7. $C_{15}H_8ClN_5O_2$. Calculated, %: C 55.3; H 2.5; Cl 10.9; N 21.5.

B) A mixture of 1.99 g (10 mmole) of 1,4-dichlorophthalazine and 3.62 g (20 mmole) of 4-nitrobenzoic acid hydrazide was refluxed in 80 ml of dioxane for 8 h, after which it was filtered. The mother liquor was cooled and worked up to give 3.0 g (92%) of triazole Xd.

3-Phenyl-6-hydroxy-1,2,4-triazolo[3,4-a]phthalazine (XI). A solution of 2.8 g (10 mmole) of triazole Xc and 0.56 g (10 mmole) of KOH in 40 ml of 90% dioxane was refluxed for 3 h, after which it was cooled and treated with 40 ml of water. The aqueous mixture was neutralized with dilute HCl, and the precipitate was removed by filtration and washed with water to give 2.25 g (86%) of triazole XI as a white crystalline powder with mp 320°C (dec., precipitated from solution in DMF by the addition of water). UV spectrum, λ_{max} (log ε) in dioxane: 268 nm (4.48). Found, %: C 67.8; H 4.0; N 21.3. $C_{15}H_{10}N_4O$. Calculated, %: C 67.7; H 3.8; N 21.3.

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PHTHALAZONE ARYLHYDRAZONES*

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The products of the reaction of 1-chloro- and 1,4-dichlorophthalazine with nitrophenylhydrazines are the E isomers of the nitrophenylhydrazones of the corresponding phthalazone. 2-Methyl-4-chlorophthalazone 4-nitrophenylhydrazone was found to be a mixture of Z and E isomers (3:2). 1,4-Dichlorophthalazine reacts with 1-methyl-1-phenyl- and 1,1-diphenylhydrazines to give monosubstitution products, for which the phthalazone hydrazone (III) or phthalazinylhydrazine (VI) form or a tautomeric mixture of III and VI is realized, depending on the nature of the solvent and other factors. Some oxidation, reduction, and nucleophilic substitution reactions of the compounds obtained are examined.

In a continuation of our research on the structures, chemical and biological properties, and isomerism of the amidrazone-hydrazinoimine type of hydrazino derivatives of phthalazine [1-6] we investigated the reactions of 1-chloro- and 1,4-dichlorophthalazines (Ia,b) with 4-nitro- (IIa), 2-nitro- (IIb), 2,4-dinitro- (IIc), 2,4,6-trinitro- (IId), 1-methyl-1-phenyl- (IIe), and 1,1-diphenylhydrazines (IIf). Replacements of the chlorine atom in 1-chlorophthalazine Ia by an arylhydrazine group proceeds smoothly and leads to IIIa-c. Both chlo-

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