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STRUCTURES OF THE PRODUCTS OF CONDENSATION OF PHTHALAZONE HYDRAZONES WITH MESITYL OXIDE

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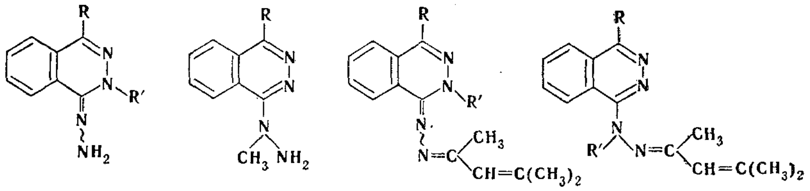
It was established on the basis of data from the UV and PMR spectra, the dipole moments, and the synthesis of fixed structures that the products of the condensation of phthalazone hydrazones with mesityl oxide have the structures of mixed phthalazone azines and mesityl oxide rather than the phthalazinylhydrazone structure that was previously assumed for them.

We have recently shown [1] that the products of condensation of phthalazone and 4-chlorophthalazone hydrazones (Ia, b) (they were previously assigned 1-hydrazinophthalazine structures IIa, b [2]) with aliphatic and aromatic aldehydes and ketones have phthalazone alkyl(aryl) ylidenehydrazone structures (mixed azines of the phthalazone and carbonyl compound). We then proposed [1] that the product of condensation of Ia with mesityl oxide also has a mixed azine structure (IIIa) rather than the mesityl oxide phthalazinylhydrazone structure (IVa), which was established for it by Moroi and co-workers [3, 4].

In order to confirm this assumption and to ascertain the reasons for the discrepancies in the conclusions drawn in [1] and [3, 4] we used the fixed-structure method. By condensation of mesityl oxide with hydrazones Ia, b we obtained a product described in [3] as hydrazone IVa (the hypotensive preparation "budralazine") and its 4-chloroderivative (in correspondence with [3, 4] it should have the IVb structure), whereas with hydrazones Ic, d we obtained 2-methyl- and 2-methyl-4-chlorophthalazone (1,3-dimethyl-bunten-2-ylidene)hydrazones (IIIc, d), and with 1-methyl-1-(4-R-phthalazin-1-yl)hydrazines (IIc, d) [2, 5] we obtained mesityl oxide N-methyl-N-(4-R-phthalazin-1-yl)hydrazones (IVc, d); we studied their IR, UV, and PMR spectra and measured their dipole moments. We isolated the more stable A isomer,



Ia-d IIa-d IIIa-d IVa-d

I-IV a R=R'=H; b R=Cl, R'=H; c R=H, R'=CH$_3$; d R=Cl, R'=CH$_3$

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TABLE 1. UV and IR Spectra of Azines IIIa-d and Hydrazones IVc, d

Compound	λ_{max}, nm (log ε)		ν_{max}, cm^{-1} (petrolatum)	
	CH_3OH	CH_3CN	NH	C=N and C=C
IIIa	211 (4,38); 240 (3,97)[a]; 270 (4,21); 289 (4,30); 360 (4,16)	207 (4,47); 242 (3,88)[a]; 271 (4,23); 288 (4,30); 367 (4,16)	3310	1643 1602 1587
IIIb	213 (4,45); 242 (3,95)[a]; 283 (4,11); 292 (4,28); 367, (4,13)	212 (4,52); 244 (4,00)[a]; 283 (4,20); 292 (4,42); 369 (4,22)	3368	1646 1608 1583
IIIc	213 (4,51); 244 (3,97)[a]; 286 (3,81); 293 (4,02); 368 (4,09)	211 (4,54); 245 (3,98)[a]; 286 (3,95)[a]; 294 (4,04); 370 (4,11)	—	1643 1604 1570
IIId	215 (4,56); 247 (4,00)[a]; 288 (3,93); 298 (4,06); 371 (4,09)	214 (4,50); 246 (3,95)[a]; 287 (3,90); 295 (4,00); 371 (4,06)	—	1640 1585 1565
IVc	220 (4,56); 244 (4,08)[a]; 333 (3,90)	—[b]	—[b]	—[b]
IVd	218 (4,60); 247 (4,08)[a], 343 (3,92)	217 (4,59); 244 (4,06)[a]; 350 (3,88)	—	1615 1580

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[a] Shoulder. [b] Not determined.

TABLE 2. PMR Spectra of Azines IIIa-d and Hydrazone IVd

Compound	Solvent	4-H[a]	5-H—7-H[b]	8-H	NCH_3[a]	$N=CCH_3$[a]	HC=C[b]	$C=C(CH_3)_2$[c]
IIIa[d]	$CDCl_3$	7,71	7,50	8,34	10,30[д]	2,31	5,93	2,10; 1,93
IIIb	CCl_4	—	7,52	8,22	10,00[д]	2,20	5,76	2,06; 1,89
IIIc (A)[f]	CCl_4	7,42	7,33	9,36	3,68	2,12	5,83	2,05; 1,90
IIIc (B)[g]	CCl_4	—[h]	—[h]	—[h]	3,63	2,23	6,28	1,84; 1,76
IIIc (A)[f]	d_6-DMSO	7,84	7,61	9,36	3,65	2,12	5,95	2,03; 1,88
IIId (A)[f]	CCl_4	—	7,47	9,39	3,63	2,09	5,78	2,03; 1,90
IIId (B)[g]	CCl_4	—	—[h]	—[h]	3,59	2,23	6,28	1,85; 1,77
IIId (A)[f]	d_6-DMSO	—	7,75	9,42	3,62	2,13	5,97	2,05; 1,92
IVd[i]	CCl_4	—	7,73 (4H)	(A+B)	3,27 (A+B)	2,28 (A) 2,23 (B)	5,77 (A) 6,23 (B)	1,89[b] and 1.82 (A+B)

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[a] Singlet. [b] Multiplet. [c] Doublet, $J^4_{CH_3H}$ = 1.1 Hz. [d] Identical to that presented in [3, 4]. [e] NH, broad singlet; it depends on traces of moisture. [f] The individual isomer. [g] In a mixture with the A isomer. [h] Not identified. [i] A mixture of A and B isomers.

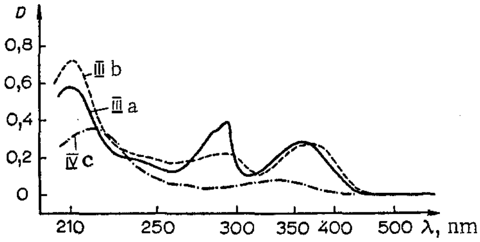


Fig. 1. UV spectra of budralazine IIIa, azine IIIc, and hydrazone IVc in acetonitrile (c = $1 \cdot 10^{-5}$ mole/liter).

with mp 132-133°C, in chromatographically pure form from the two known geometrical isomers of budralazine [3]. 4-Chlorobudralazine was also obtained in the form of one geometrical isomer A. Azines IIIc, d are obtained in the form of a mixture of two geometrical isomers; the A isomers prevail in both cases and were isolated in individual form. The B isomers of azines IIIc, d were not isolated and were characterized only by the PMR spectra. Hydrazones IVc, d are also produced in the form of two geometrical isomers and cannot be separated even by column chromatography.

TABLE 3. Experimental (in Dioxane at 25°C) and Calculated Dipole Moments

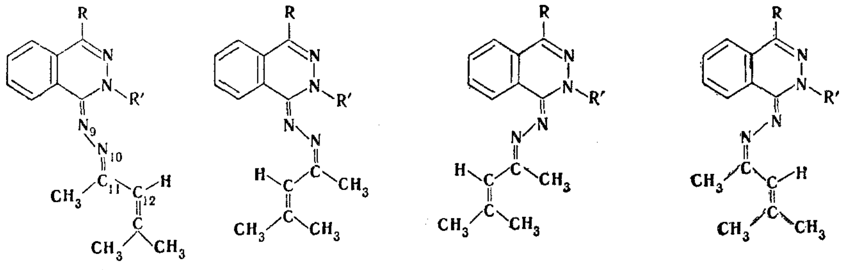
Compound	μ_{exp}, D[a]	μ_{calc}, D			
		ZE′	ZZ′	EE′	EZ′
IIIa	1,97	1,56	0,63	0,63	1,56
IVa	—	7,17	6,70	4,50	4,91
IIIb	2,49	2,69[b]	2,46	2,46	2,69
IVb	—	7,58	7,13	5,13	5,49
IIId	2,28	3,20	2,79	2,79	3,20
IVd[c]	6,40	6,38	6,70	4,78	5,23

[a] With an accuracy of ±0.05 D. [b] All four conformers with $Z_{11,12}$ have μ_{calc} = 2.17 D. [c] A mixture of geometrical A and B isomers.

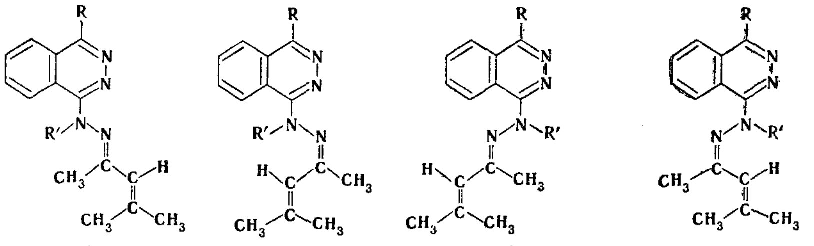
The UV spectra of budralazine and 4-chlorobudralazine are very similar to the spectra of phthalazone arylidenehydrazones [1] and model azines IIIc, d with respect to the form of the absorption bands and their position and intensities but differ markedly from the spectra of hydrazones IVc, d (Fig. 1). The spectra of IIIa, b have characteristic absorption at 275-295 nm in the form of doubled bands; this is peculiar only to compounds with a phthalazone structure but not to those with a phthalazine structure [6]. Consequently, budralazine and 4-chlorobudralazine have azine structures, viz., 4-R-phthalazone (1,3-dimethylbuten-2-ylidene)hydrazones (IIIa, b). The data in Table 1 indicate that the stability of the azine structure does not depend on the polarity of the solvent.

A weak-field shift of the signal of the 8-H proton relative to the signals of the 5-H—7-H protons due to an anisotropic effect of the exocyclic C=N bond is observed in the PMR spectra of azines IIIa, b; this is also characteristic for other phthalazone hydrazones ($\Delta\delta$ = 0.7-1.0 ppm) [1, 2, 6]. As in the spectra of other N-methyl-N-phthalazinylhydrazones [7], the signals of all of the aromatic protons are recorded in the form of a single multiplet in the spectrum of hydrazone IVd (Table 2).

In the spectra of azines IIIc, d the weak-field shift of the 8-H signal is considerably greater than in the spectra of azines IIIa, b (Table 2), and this indicates a change in the configuration relative to the $C_1=N_9$ bond and is due to additional deshielding of 8-H by the unshared pair of the N_{10} atom and the $N_{10}=C_{11}$ bond. A similar effect from the introduction of a CH_3 group in the 2 position is characteristic for all types of phthalazone hydrazones [1, 2, 6].



IIIa-d ZE′* ZZ′ EE′ EZ′



IVa-d ZE′ ZZ′ EE′ EZ′

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*In [1, 2] and other papers the benzene ring was incorrectly adopted as the "more significant" group.

A comparison of the experimental data and the calculated values of the four azine and four hydrazone forms (by the vector additivity method) unambiguously indicates the azine structure of budralazine and 4-chlorobudralazine (IIIa, b) (Table 3). The conformers with a cis orientation of the fragments relative to the N_9—N_{10} and C_{11}—C_{12} bonds (this conformer was preferred in [4]) are sterically strained (from an analysis of Stuart—Briegleb models) and, in our opinion, cannot be realized.

The selection of three-dimensional structures for the two geometrical isomers (A and B) of azines IIIa, b is difficult because of the mutually equal μ_{calc} values of the possible forms (Table 3). With allowance for the data from the PMR spectra (the position of the 8-H signal, and the absence of splitting of the NCH_3 signals), one should prefer the ZZ' form for the stable (A) isomers of azines IIIa, b (additional stabilization due to N_2—H...N_{10} and C_{12}—H...N_9 interactions is possible) and the ZE' form for their B isomers, the EZ' form for the isolated isomers (A) of azines IIIc, d, and EE' form for their B isomers. Isomerization occurs relative to the N_{10}=C_{11} bond; this was previously observed for 2-methyl-4-chlorophthalazone ethylidenehydrazone [1]. The structure of hydrazones IVc, d is most likely nonplanar [7].

The dipole moments of the isomeric (with respect to the CH_3 group) IIId and IVd differ by more than 4 D. In order to confirm the possibility of the dipole moment method for the determination of the tautomers in series of 1-hydrazinophthalazine derivatives we additionally determined the μ_{exp} values of phthalazone isopropylidenehydrazones (Va: 1.99 D, μ_{calc} = 1.73 D), 4-chlorophthalazone (Vb: 2.62 D, μ_{calc} = 2.71 D), 2-methyl-4-chlorophthalazone (Vc: 2.36 D), 4-chlorophthalazone benzylidenehydrazone (1.74 D), 2-methyl-4-chlorophthalazone (2.49 D), as well as acetone N-methyl-N-(4-chloro-1-phthalazinyl)hydrazone (VI: 6.36 D, μ_{calc} = 6.18 D for ZE' and 4.93 D for EE') and benzaldehyde N-methyl-N-(4-chloro-1-phthalazinyl)hydrazone (4.55 D). One should also compare the following μ_{exp} values: Ia, 2.13 D; Ic, 2.19 D; Id, 2.66 D [2]; and IId, 5.38 D [7]. From these data one can clearly trace the tendency of a sharp decrease in μ_{exp} on passing from compounds with a phthalazine ring to isomeric or to similar (with respect to the nature of the substituents) compounds with a phthalazone ring.

Thus azine structure IIIa for budrazine is confirmed by an analysis of data from the UV and PMR spectra, by a comparison of these data with the data for tautomerically-fixed structures and 4-chloro-containing analogs, and twice by the dipole moment method (a comparison of μ_{exp} with μ_{calc} and by analysis of the μ_{exp} values for phthalazine and phthalazone systems). The IR spectra are less informative in this case but do not contradict the III structure (compare Table 1 with [2]).

The reason for the discrepancies in the conclusions drawn in [3, 4] and in [1] consists of the following: In [3], by way of tradition, the acetone phthalazinylhydrazone structure was incorrectly assigned to the product of condensation of hydrazone Ia with acetone, used as a model compound, whereas it is a mixed azine [1], viz., phthalazone isopropylidenehydrazone (Va); this was confirmed once again by dipole moment data (compare the μ values for Va-c and VI).

The structure assigned to the compound assumed in [3] to be acetone N-methyl-N-(1-phthalazinyl)hydrazone (VII) is also incorrect. In the reaction of 1-chlorophthalazine with methylhydrazine by the method in [3, 8] and different variants of it, instead of the expected hydrazine IIc, we obtained only phthalazone methylhydrazone* (VIII) [2]. In the reaction with acetone hydrazone VIII, as in the case of other cyclic amidrazones [9], one observes the formation of an annelated triazoline, viz., 2,3,3-trimethyl-2,3-dihydro-1,2,4-triazolo[3,4-a]phthalazine (IX), which has the same characteristics as the product described in [3] as hydrazone VII.

The form of the absorption bands in the UV spectrum of triazoline IX is similar to that observed for hydrazones Ia-d and VIII [2] and azines Va-c [1], although the maxima of the bands are shifted bathochromically somewhat and differ from the spectra of N-methyl-N-phthalazinylhydrazones [7]. A weak-field shift of the 10-H signal (in analogy with 8-H of

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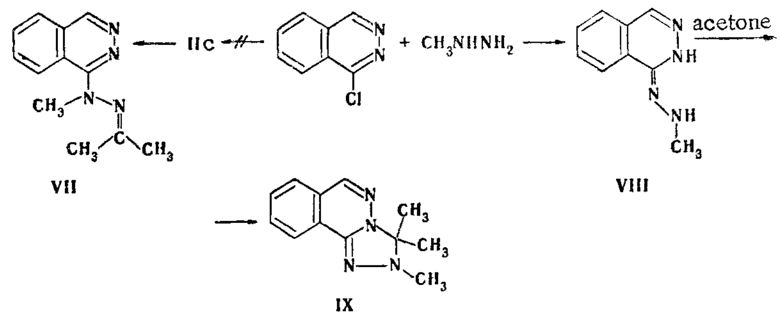
*The difference in the melting point of hydrazone VIII presented in [3] (119-120°C) and in [2] (107-108°C) is evidently explained by the different conditions for its determination, since it melts with decomposition. Recrystallization of it from benzene by the method in [3] does not ensure the chromatographic purity of the product. Isomeric hydrazine IIc (mp 89-91°C) was obtained by electrochemical dechlorination of hydrazine IId [5].

phthalazone compounds) and a singlet signal of two CH_3 groups at 1.43 ppm are observed in the PMR spectrum. In the spectra of acetone hydrazones, including hydrazones Va-c, the $C(CH_3)_2$ fragment is represented by two lines at weaker field (the effect of the N=C bond).



The reason for the discrepancies in the conclusions regarding the azine structure of budralazine (IIIa) and the conclusions in [4], in which the shift-reagent method was used, is difficult to explain without a special study. It may consist in the specific characteristics of the computational method (for example, in [10] it is shown that the calculation of the mean square deviations of the calculated paramagnetic shifts from the experimental values is inadequate and may lead to incorrect conclusions regarding the localization of the lanthanide ion) or in the specific characteristics of the behavior of azine IIIa, the structure of which may undergo a change during the formation of a complex.

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 recorded with a Varian T-60 spectrometer at 36°C with hexamethyldisiloxane as the internal standard; the chemical shifts are presented relative to tetramethylsilane (TMS).* The dielectric permeabilities were measured by the null-beat method at 1 MHz by means of an IDM-1 apparatus at 25°C in dioxane, while the refractive indexes (n_D^{25}) were measured with an IRF-23 refractometer. The melting points were determined with a Boëtius stage. The homogeneousness of the substances was monitored in a thin layer of aluminum oxide on Silufol plates; the eluant was a mixture of low-boiling petroleum ether (40-70°C) with diethyl ether or dioxane, and the chromatograms were developed with iodine vapors.

4-Chlorophthalazone (1,3-Dimethylbuten-2-ylidene)hydrazone (IIIb). A mixture of 3 g (15 mmole) of hydrazone Ib, 2.5 ml of mesityl oxide, and one to two drops of concentrated H_2SO_4 was refluxed for 30-40 min, after which the hot mixture was filtered. The filtrate was cooled to give 3.6 g (87%) of IIIb with mp 138-138.5°C (yellow needles from ethanol) (Tables 1-3). Found: C 61.2; H 5.3; Cl 13.2; N 20.2%. $C_{14}H_{15}ClN_4$. Calculated: C 61.2; H 5.5; Cl 12.9; N 20.4%.

2-Methylphthalazone (1,3-Dimethylbuten-2-ylidene)hydrazone (IIIc). A mixture of 1.74 g (10 mmole) of chromatographically pure hydrazone Ic, and 2 ml of mesityl oxide in 20 ml of ethanol and one to two drops of concentrated H_2SO_4 was refluxed for 3 h, after which the hot mixture was filtered, and the solvent was removed *in vacuo*. The residue was chromatographed with a column [silica gel, petroleum ether—diethyl ether (2:1)] to give 1.2-1.6 g (48-62%) of the A isomer of azine IIIc (R_f $\sim$0.7) as light-yellow crystals with mp 43-43.5°C (Tables 1-3). Found: C 71.3; H 7.0; N 22.2%. $C_{15}H_{18}N_4$. Calculated: C 70.9; H 7.1; N 22.1%.

Subsequent elution gave 0.6-0.75 g (23-30%) of a mixture of the A and B isomers of IIIc in the form of a light-yellow oil (R_f $\sim$0.6).

2-Methyl-4-chlorophthalazone (1,3-Dimethylbuten-2-ylidene)hydrazone (IIId). A mixture of 3.1 g (15 mmole) of chromatographically pure hydrazone Id, 2.5 ml of mesityl oxide, and one to two drops of concentrated H_2SO_4 was heated at 55-65°C for 1.5 h, after which it was filtered. The volatile components were removed *in vacuo*, the residue was transferred to 100 ml of hot water (90-95°C), and the mixture was cooled. The substance in the form of a slab was separated from the suspension and recrystallized from 70-80% ethanol to give 3.0 g

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*The authors sincerely thank A. A. Musinaya for her helpful discussion and assistance in the discussion of the PMR spectra and the data in [4, 10].

(70%) of the A isomer of azine IIId as orange needles with mp 94-95°C (Tables 1-3). Found: C 62.6; H 6.0; Cl 12.2; N 19.5%. $C_{15}H_{17}ClN_4$. Calculated: C 62.4; H 5.9; Cl 12.3; N 19.4%. The solution after crystallization was evaporated to dryness, and the residue was subjected to column chromatography [silica gel, petroleum ether—diethyl ether (1:1)] to give more azine IIId in the form of a mixture of geometrical isomers.

Mesityl Oxide N-Methyl-N-(1-phthalazinyl)hydrazone (IVc). A 0.5-ml sample of mesityl oxide in 2 ml of ethanol and a small drop of concentrated H_2SO_4 were added to 320 mg (1.84 mmole) of hydrazine IIc, and the mixture was maintained at 60-70°C for 3 h, after which the solvent was removed *in vacuo*. The residue was chromatographed with a column [Brockmann II Al_2O_3, petroleum ether—ether—methanol (10:10:1)] to give 300 mg (64%) of IVc as an oil (Tables 1-3). Found: M 254 (by mass spectrometry). $C_{15}H_{17}N_4$. Calculated: M 254.

Mesityl Oxide N-Methyl-N-(4-chloro-1-phthalazinyl)hydrazone (IVd). A suspension of 1.04 g (5 mmole) of hydrazine IId, 1 ml of mesityl oxide, and one drop of concentrated H_2SO_4 in 10 ml of ethanol was heated at 50-60°C for 20 min, after which the solvent was removed. The residual oil was chromatographed with a column [silica gel, petroleum ether—ether (1:1)] to give 1.1 g (76%) of IVd as an oil (a mixture of geometrical A and B isomers, Tables 1-3). Found: C 62.7; H 5.9; Cl 12.0; N 19.5%. $C_{15}H_{17}ClN_4$. Calculated: C 62.4; H 5.9; Cl 12.3; N 19.4%.

2,3,3-Trimethyl-2,3-dihydro-1,2,3-triazolo[3,4-a]phthalazine (IX). A solution of 0.5 g (2.4 mmole) of phthalazone methylhydrazone hydrochloride (hygroscopic; obtained by saturation of a solution of hydrazone VIII in chlorform with dry HCl. A solution of the salt in acetone was prepared in a dry box in an argon atmosphere.) in 2.5 ml of acetone was refluxed for 3 h in a stream of argon, after which the solution was cooled, neutralized with 0.2 g of $NaHCO_3$, and extracted with chloroform. The solvent was removed to dryness, and the oily residue was chromatographed with a column (Brockmann II neutral aluminum oxide, elution with ether) to give 0.22 g (45%) of IX as an oil. UV spectrum (methanol), λ_{max} (log ε): 212 (4.48), 238 (3.70) shoulder, 278 (4.15), and 372 nm (3.52). PMR spectrum, δ: CCl_4: 7.53 (m, 1H, 10-H), 7.13 (m, 4H, 6-H—9-H), 2.68 (s, 3H, NCH_3), and 1.43 ppm [s, 6H, $C(CH_3)_2$]; d_6-DMSO: 7.59 (s, 1H, 6-H), 7.47 (m, 4H, 7-H—10-H), 2.69 (s, 3H, NCH_3), and 1.42 ppm [s, 6H, $C(CH_3)_2$]. Found: C 67.5; H 6.5; N 26.1%. $C_{12}H_{14}N_4$. Calculated: C 67.3; H 6.5; N 26.2%. The product was identical to the product described in [3] as VII.

Subsequent elution of the mixture with ether—alcohol (20:1) gave 0.15 g of starting VIII.

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