RING-CHAIN TAUTOMERISM OF SUBSTITUTED HYDRAZONES

V.* DERIVATIVES OF 2-(ARYLHYDRAZINO)ETHANOLS

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The products of the condensation of 2-(N-phenylhydrazino)-, 2-(N-p-tolylhydrazino)-, and 2-(N-p-nitrophenylhydrazino)ethanols with acetaldehyde, acetone, and pinacone exist in tetrachloroethylene solution in the form of tautomeric mixtures of N-aryl-N-(2-hydroxyethyl)-hydrazones and 4-arylperhydro-1,3,4-oxadiazines. For the case of the pinacone derivatives, it has been shown that the equilibrium concentration of the cyclic form rises with an increase in the electron-accepting nature of the substituent in the para position of the aromatic radical.

The position of the equilibrium between the tautomeric 4-alkylperhydro-1,3,4-oxadiazines and the corresponding N-alkyl-N-(2-hydroxyethyl)hydrazones depends fundamentally on the spatial requirements of the N-alkyl substituent [2, 3]. Continuing our investigation in this field, we have turned to a study of the structure of derivatives of β-(N-arylhydrazino) alcohols. Interest in these derivatives was due to the fact that in this case it was possible to determine whether the position of the equilibrium was influenced by the polar effects of substituents on the nitrogen atom, i.e., substituents not bound directly to the reaction center. It is known that in similar ring–chain tautomeric systems – products of the condensation of substituted benzaldehydes of β- and γ-amino alcohols – the equilibrium is shifted in the direction of the cyclic form with a rise in the electron-acceptor capacity of the substituent in the aldehyde fragment [4-6].

2-(N-Phenylhydrazino)- and 2-(N-p-tolylhydrazino)ethanols (I and II) were obtained by the nitrosation of 2-(N-arylamino)ethanols [7] followed by the reduction of the nitrosamines with lithium tetrahydroaluminate. The reduction of these compounds with zinc dust in acid [8, 9] or weakly alkaline [10] media

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* For communication (IV) see [1].

TABLE 1. Products of the Condensation of 2-(N-Arylhydrazino)-ethanols with Carbonyl Compounds

Compound	Mp, °C	R_f*	Empirical formula	N, %		Yield, %
				found	calculated	
IV	58—60	0,17; 0,40	$C_{10}H_{14}N_2O$	15,5; 15,2	15,7	35
V	Oil	0,13; 0,57	$C_{11}H_{16}N_2O$	14,4; 14,7	14,6	40
VI	Oil	0,14	$C_{14}H_{22}N_2O$	11,9; 11,5	11,9	57
VII	44—45	0,16; 0,39	$C_{11}H_{16}N_2O$	14,4; 14,9	14,6	58
VIII	Oil	0,15; 0,66	$C_{12}H_{18}N_2O$	13,7; 13,8	13,6	29
IX	Oil	0,13	$C_{15}H_{24}N_2O$	11,6; 11,7	11,3	49
X	129—130	0,09; 0,37	$C_{10}H_{13}N_3O_3$	18,4; 18,5	18,8	30
XI	94,5—96	0,03; 0,38	$C_{11}H_{15}N_3O_3$	18,0; 18,1	17,7	67
XII	Oil	0,06; 0,64	$C_{14}H_{21}N_3O_3$	14,7; 14,8	15,0	60

* On alumina of activity grade II with the solvent system benzene–ether (1:3); spots revealed in UV light.

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TABLE 2. Spectral Characteristics of the Equilibrium Mixtures of 4-Arylperhydro-1,3,4-oxadiazines and the Corresponding Hydrazones (IV-XII)*

Compound	IR spectrum: ν, cm^{-1}			PMR spectrum, δ, ppm (J, Hz)								Molar ratio, A : B
	C=N	N—H	O—H	CH_3		R		protons of the aromatic ring		OCH_2CH_2N	X	
				A	B	A	B	A	B			
IV	—	3183	—	1,21 d (5,8)	1,93 d (6,6)	4,46 m (J_{H, CH_3}=5,8, $J_{H, NH}$=12,0)	—	6,6—7,3 m		2,5—3,9 m	—	~95 : 5
V	—	3185	3460	1,33 s	1,98 s	1,33 s	1,65 s	6,6—7,1 m		2,8—3,9 m	—	85 : 15
VI	1625	3135	3450	1,40 s	1,66 s	1,02 s	1,16 s	6,6—7,2 m		3,5—3,7 m	—	24 : 76
VII	—	3148	—	1,18 d (5,6)	1,89 d (6,6)	4,46 m (J_{H, CH_3}=5,6; $J_{H, NH}$=11,5)	—	6,7—6,9 m		2,4—3,8 m	2,17 s	~95 : 5
VIII	1642	3176	3440	1,40 s	1,96 s	1,40 s	1,63 s	6,6—6,9 m		2,8—3,7 m	2,18 s	81 : 19
IX	1642	3125	3450	1,41 s	1,65 s	1,02 s	1,15 s	6,6—7,0 m		3,3—3,7 m	2,14 s	13 : 87
X†	—	3208	—	1,33 d (6,0)	2,06 d (6,0)	4,53 m (J_{H, CH_3}=6,0; $J_{H, NH}$=12,0)	—	8,03 d (9,0) 7,03 d (9,0)	—	3,3—4,4 m	—	~95 : 5
XI†	—	3205	—	1,40 s	2,22 s	1,40 s	1,92 s	8,07 d (9,0) 6,95 d (9,0)	—	3,2—4,1 m	—	90 : 10
XII	1617	3205	3480	1,28 s	1,82 s	1,05 s	1,22 s	7,88 d (9,4) 6,80 d (9,4)	7,92 d (9,4) 6,57 d (9,4)	3,5—3,9 m	—	40 : 60

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*Abbreviations: s) singlet, d) doublet, m) multiplet.

† YaMR-5535 (40 MHz) spectrometer; 15-20% solutions in $CHCl_3$ were used because of low solubility in C_2Cl_4. Because of the greater polarity of the solvent, the equilibrium concentration of the hydrazone here may be somewhat higher than in tetrachloroethylene (see [12]).

led mainly to the initial amino alcohols, in spite of existing information [9] on the formation of the hydrazino alcohol (I) by the reduction of the nitrosamine in acetic acid [in this work [9], the hydrazine (I) was not isolated in the individual state]. Reduction with lithium tetrahydroaluminate was also accompanied by denitrosation. The reversed order of mixing the reactants recommended for the reduction of aromatic and aliphatic-aromatic nitrosamines [11] did not lead to the desired result. 2-(N-p-Nitrophenylhydrazino)-ethanol (III) was prepared by the arylation of 2-hydrazinoethanol with p-bromonitrobenzene.

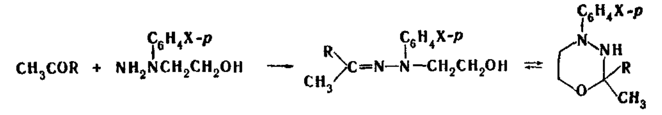
$$p\text{-}XC_6H_4NHCH_2CH_2OH \rightarrow p\text{-}XC_6H_4N(NO)CH_2CH_2OH \rightarrow p\text{-}XC_6H_4N(NH_2)CH_2CH_2OH$$

I X=H; II X=CH_3 I, II

$$p\text{-}O_2NC_6H_4Br + H_2NNHCH_2CH_2OH \rightarrow p\text{-}O_2NC_6H_4N(NH_2)CH_2CH_2OH$$

III

The hydrazino alcohols (I-III) were condensed with acetone, pinacone, and acetaldehyde. The characteristics of the compounds obtained, the majority of which were isolated by preparative TLC are given in Table 1.



I-III IVB-XIIB IVA-XIIA

IV R=X=H; V R=CH_3, X=H; VI R=$t\text{-}C_4H_9$, X=H; VII R=H, X=CH_3; VIII R=X=CH_3; IX R=$t\text{-}C_4H_9$, X=CH_3; X R=H, X=NO_2, XI R=CH_3,X=NO_2; XII R=$t\text{-}C_4H_9$, X=NO_2.

The structures of the crystalline condensation products were shown by IR spectroscopy. The spectra of the p-nitrophenyl derivatives (X) and (XI) showed the bands of stretching vibrations of the N−H bonds (3230-3300 cm^{-1}), and the bands of $\nu_{C=N}$ and ν_{O-H} were absent. Consequently, compounds (X) and (XI) in the crystalline state have the cyclic structures (XA) and (XIA). In the crystalline products of the reaction of acetaldehyde with the phenyl- and p-tolyl-substituted hydrazines [compounds (IV) and (VII)], in addition to a band of medium intensity of ν_{N-H} (3180 cm^{-1}) a very weak band of ν_{O-H} (3440-3650 cm^{-1}) is observed which shows the presence in these materials of small amounts of the hydrazones (IVB) and (VIIB).

In solutions, all the condensation products (VI-VII) exist in the form of tautomeric mixtures. This was deduced even during their chromatographic separation: on the chromatograms two spots were usually found with considerably different R_f values, and the rechromatography of the substances corresponding to each of these two spots, separated preparatively, led to chromatograms completely identical with the original ones.

The assumption of the presence of tautomeric mixtures was confirmed completely by a consideration of the PMR spectra of solutions of these substances in tetrachloroethylene (Table 2). With the exception of the products of the reaction with pinacone (VI, IX, and XII), the main component of the mixture is the cyclic tautomer. Evidence in favor of this is the position and, in some cases, the shape of the signals of the protons of the alkylidene grouping.

Thus, the spectra of the acetaldehyde derivatives (IV, VII, and X) have doublet signals (δ 1.20-1.35 ppm) of the 2-CH_3 groups and quadruplet signals of the 2-H protons (4.45-4.7 ppm) of the cyclic form. The equilibrium concentration of the hydrazones is low, so that it is possible to detect only the doublet of the methyl group on the azomethine carbon atom (1.95-2.05 ppm). The $\nu_{C=N}$ and ν_{O-H} bands characteristic for hydroxyethylhydrazones are not observed in the IR spectra of solutions of these compounds.

As in the cases investigated previously [2, 3], the products of condensation with acetone (V, VIII, and XI) are enriched with the hydrazone form as compared with the acetaldehyde derivatives. A comparison of the intensities of the signals of the gem-dimethyl grouping of the cyclic form (singlet in the δ 1.3-1.4-ppm region) and the chain form (two singlets in the 1.9-2.2-ppm region) shows that in these cases the equilibrium concentration of the hydrazone is 15-25%.

As was expected, the greatest tendency to the formation of the chain tautomer is observed for the pinacone derivatives (VI, IX, and XII). The product of the condensation of pinacone with 2-(N-p-nitrophenylhydrazino)ethanol proved to be particularly interesting. In the PMR spectrum of a freshly prepared sample of (XII) there are the singlets of the methyl group (1.78 ppm) and of the tert-butyl group (1.05 ppm) of the cyclic form, and also the signals of these groups in the syn and anti stereoisomeric hydrazones (1.22, 1.82 and 1.12, 2.06 ppm, respectively). In the spectrum of the equilibrium condensation product (XII) the signals of the anti form of the hydrazone have disappeared and the relative intensities of the signals corresponding to the perhydrooxadiazine (XIIA) have increased. In the IR spectrum of (XII) on passing from the liquid to the equilibrium solution in tetrachloroethylene the $\nu_{C=N}$ band (1616 cm^{-1}) weakens considerably, while the ν_{O-H} band shifts in the short-wave direction (from 3400 to 3485 cm^{-1}) and becomes narrower. Obviously, in this case the equilibrium concentration of the hydrazone in the condensed phase is considerably higher than in solution, and the equilibrium is established comparatively slowly. In the two other pinacone derivatives (X) and (XI) it was possible to observe only the syn stereoisomer of the chain form.

As can be seen from Table 2, a variation in the substituents in the benzene ring does not lead to any appreciable change in the composition of the equilibrium mixtures whatever for the acetaldehyde derivatives. For the acetone derivatives, a slight rise in the equilibrium concentration of the hydrazone is found with an increase in the electron-donating nature of the substituent, but this increase only slightly exceeds the experimental error. However, for products of the condensation of substituted hydrazines with pinacone, in which the equilibrium concentrations of the two forms are comparatively close, this dependence becomes quite clear: the ratio of the equilibrium concentrations of the chain and cyclic forms is 60 : 40 for the p-nitrophenyl derivative and 85 : 15 for the p-tolyl derivative.

The causes of the change in the equilibrium composition must undoubtedly be sought in the polar effects of the substituents, since the steric requirements of the p-substituted aryl groupings are similar. One of the factors stabilizing the hydrazone form is the existence of p,π conjugation in the C=N–N bond system. This conjugation is particularly characteristic for aldehyde hydrazones [13-15]; it is feebler but, nevertheless, apparently still exists in disubstituted ketone hydrazones. With the introduction of an aromatic substituent, the p,π conjugation is disturbed because of the delocalization of the free electron pair of the amine nitrogen atom in the nucleus, the degree of delocalization being the greater the greater the electron-accepting nature of the substituent. Another consequence of this type of delocalization is the weakening or complete destruction of the intramolecular hydrogen bond between the alcoholic group and the amine nitrogen atom in the hydroxyalkylhydrazones. In actual fact, the short-wave displacement of the ν_{O-H} band in the IR spectra of the hydrazone (XIIB) mentioned above on passage into dilute solutions shows the intermolecular nature of the hydrogen bond.

Apparently, these two factors destabilizing the chain tautomeric form also lead mainly to an increase in the equilibrium concentration of the cyclic tautomer with a strengthening of the electron-accepting nature of the substituent in the para position of the aromatic radical.

EXPERIMENTAL

The PMR spectra were obtained on an HA-100-D-15 instrument using ~10% solutions in tetrachloroethylene with HMDS as internal standard. The IR spectra of 1-5% solutions in tetrachloroethylene were taken on UR-10 and UR-20 instruments. Alumina of activity grade II was used for chromatographic analysis and separation.

2-(N-Nitroso-p-toluidino)ethanol. With stirring and cooling to –10 to –15°C, a saturated aqueous solution of 10.3 g (0.15 mole) of sodium nitrite was added dropwise to a solution of 21.5 g (0.14 mole) of p-toluidinoethanol in 21.5 ml of concentrated hydrochloric acid. The mixture was stirred for another 1 h, the temperature being raised to that of the room. The nitrosamine was extracted with ether, and the extract was dried with sodium sulfate and the ether was distilled off. This gave 25 g (98%) of the nitrosamine in the form of an oil crystallizing on cooling. For analysis, it was chromatographed on a column of alumina and was eluted with benzene–ether–methanol (5 : 3 : 1). Mp 39-40°C. IR spectrum, cm^{-1}: 1647 ($\nu_{N=O}$), 3635 (ν_{O-H}). Found, %: N 15.3; 15.1. $C_9H_{12}N_2O_2$. Calculated, %: N 15.5.

2-(N-Nitrosoanilino)ethanol [9] was obtained similarly in the form of a noncrystallizing oily liquid. These nitrosamines were used for subsequent reduction without additional purification.

2-(N-Phenylhydrazino)ethanol (I). A solution of 53 g (0.3 mole) of N-nitroanilinoethanol in 50 ml of ether was added to a solution of 0.43 mole of lithium tetrahydroaluminate in 300 ml of ether. The mixture was boiled with stirring for 2 h and was left at room temperature for 12 h. Then, with cooling to –25°C, 300 ml of a 25% solution of caustic soda was slowly added. The ethereal layer was separated off and the aqueous layer was extracted with ether (4 × 50 ml). After drying and the evaporation of the ether, 35 g of an oily residue was obtained from which by means of preparative TLC [benzene–ether–methanol (25 : 25 : 3)] the liquid hydrazine (I) was isolated with a yield of 18%; R_f 0.28. Found, %: N 18.3; 18.5. $C_8H_{12}N_2O$. Calculated, %: N 18.4.

2-(N-p-Tolylhydrazino)ethanol (II) was obtained by the same method. It was purified on a column of alumina using as eluent cyclohexane–ether–methanol (12 : 35 : 1). Yield, 23%. Picrate, mp 148.5-149°C (decomp., from ethanol). Found, %: N 17.4; 17.8. $C_9H_{14}N_2O \cdot C_6H_3N_3O_7$. Calculated, %: N 17.7.

2-(N-p-Nitrophenylhydrazino)ethanol (III). A mixture of 29 g (0.39 mole) of 2-hydrazinoethanol and 27 g (0.13 mole) of p-bromonitrobenzene in 70 ml of ethanol was boiled for 9 h. The unchanged bromonitrobenzene was distilled off with steam. With stirring, 7 g of caustic soda was added to the residue and the still hot aqueous layer was decanted from the dark resinous residue. On cooling, the aqueous solution deposited 17 g (61%) of the hydrazine (III). After two recrystallizations from a large volume of water, the hydrazine (III) was obtained in the form of thin bright-yellow needles with mp 85.5°C. Found, %: N 21.5; 21.6. $C_8H_{11}N_3O_3$. Calculated, %: N 21.4.

2-Methyl-4-phenylperhydro-1,3,4-oxadiazine (IVA). A solution of 0.55 g (0.013 mole) of acetaldehyde in 15 ml of ethanol was added to a solution of 1.9 g (0.013 mole) of the hydrazino alcohol (I) in 20 ml of ethanol. The mixture was heated at 40-45°C for 1 h, and the ethanol was distilled off in vacuum. The yield of the crude oxadiazine (IVA) was 2 g. It was purified by preparative TLC [cyclohexane–ether–methanol (5 : 2 : 1) system], the zone with R_f 0.5-0.9 being isolated.

2-Methyl-4-(p-tolyl)perhydro-1,3,4-oxadiazine (VIIA) and 2-methyl-4-(p-nitrophenyl)perhydro-1,3,4-oxadiazine (XIIA) were obtained similarly, the first being chromotographed in the cyclohexane–ether–methanol (7 : 7 : 1) system with collection of the zone with R_f 0.4-0.85, and the second being purified by crystallization from 30% ethanol.

2,2-Dimethyl-4-(p-nitrophenyl)perhydro-1,3,4-oxadiazine (XIA). A mixture of 2.1 g (0.11 mole) of the hydrazino alcohol (III), 0.7 g (0.012 mole) of acetone, and 50 ml of ethanol with the addition of a few drops of acetic acid was heated at 50°C. Then the ethanol was distilled off in vacuum and the residue was crystallized from 25% ethanol. The yield of (XIA) was 1.7 g.

The other products of condensation with acetone (V and VIII) were prepared similarly. They were isolated by means of preparative TLC [for (V) using the cyclohexane–ether–methanol (4 : 2 : 1) system, R_f 0.6-0.85, and for (VIII) the ether–benzene (3 : 2) system with the addition of 0.5% for ethanol, R_f 0.55-0.75)].

Condensation of the Hydrazino Alcohols (I-III) with Pinacone. A mixture of 0.004 mole of a hydrazino alcohol and 0.012 mole of pinacone was boiled in 20 ml of benzene in the presence of 20 mg of p-toluenesulfonic acid in flask fitted with a Dean–Stark trap. After the end of the reaction (monitoring by the TLC method), the benzene was distilled off and the residue was separated by preparative TLC [for (VI) the eluent was benzene–ether–ethanol (25 : 25 : 2), R_f 0.65-0.9; for (IX) ether–benzene (3 : 1) with the addition of 0.5% of ethanol, R_f 0.65-0.85; and for (XII) cyclohexane–ether–methanol (8 : 8 : 1), R_f 0.55-0.9].

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