RING–CHAIN TAUTOMERISM OF SUBSTITUTED HYDRAZONES.
XI.* SYNTHESIS OF 5,6-DIHYDRO-4H-1,3,4-OXADIAZINES

A. A. Potekhin and N. A. Nikolaeva

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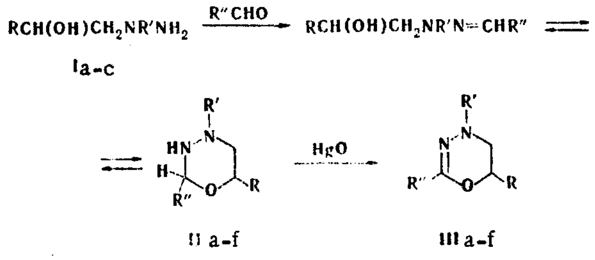
It is shown that 5,6-dihydro derivatives are formed as a result of the oxidation of 2-unsubstituted or 2-monosubstituted perhydro-1,3,4-oxadiazines with yellow mercuric oxide.

As we have shown in a number of papers of this series, β-hydroxyalkylhydrazones are capable of equilibrium isomerization to perhydro-1,3,4-oxadiazines. The structures of the latter were confirmed unambiguously by spectral data (IR and PMR spectroscopy); however, chemical evidence for their presence in an equilibrium mixture has not yet been presented. Since tautomeric perhydro-1,3,4-oxadiazines contain a trisubstituted hydrazine fragment, it might have been expected that when no more than one substituent is present in the 2 position, they would be capable of undergoing oxidation in the same way as the similarly constructed hydrazines [2] to give compounds with a C=N bond — 5,6-dihydro-4H-1,3,4-oxadiazines. Biologically active compounds have been found among representatives of this class of heterocycles (for example, see [3, 4]); however, the methods used to prepare them are not always sufficiently universal.

In order to synthesize dihydro-1,3,4-oxadiazines we studied the oxidation of the products of condensation of aliphatic aldehydes with hydrazino alcohols Ia-c. Judging from the molecular refractions and the PMR spectroscopic data, all of these condensation products have cyclic structure II immediately after distillation (the characteristics of the II obtained for the first time in this research are presented in Tables 1 and 2). The refractometric constants undergo a slight change during storage, and this constitutes evidence for the formation of only small amounts of the acyclic tautomer. It was established by means of the PMR spectra that the equilibrium concentration of the hydrazone at room temperature does not exceed 5% in the case of IIb, c, e, whereas a hydrazone could not be detected at all by means of the PMR spectrum in the case of IIf.



I a R=H, R'=n-C_3H_7; b R=H, R'=i-C_3H_7; c R=CH_3, R'=i-C_3H_7; II, III a R=H, R'=n-C_3H_7, R''=CH_3; b R=H, R'=n-C_3H_7, R''=i-C_3H_7; c R=R''=H, R'=i-C_3H_7; d R=H, R'=i-C_3H_7, R''=CH_3; e R=H, R'=R''=i-C_3H_7; f R=R''=CH_3, R=i-C_3H_7

In general, attempts to oxidize IId with aqueous ferric chloride solution, bromine water, or bromine in hydrobromic acid did not lead to positive results, although these oxidizing agents have been successfully used for the conversion of trisubstituted acyclic hydrazines to hydrazones [2]. In connection with the facile hydrolysis of starting perhydrooxadiazines II under the oxidation conditions and because of the high solubility of the oxidation product in water, it was isolated in low yield and was contaminated. However, we were able to link the presence of a strong band at 1665 cm^{-1} in its IR spectrum and of an intense singlet at δ 1.8 ppm in its PMR spectrum with the formation of dihydrooxadiazine IIId.

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*See [1] for communication X.

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TABLE 1. Perhydro-1,3,4-oxadiazines II

Compound	bp, °C (mm)	d_4^{20}	n_D^{20}	Found			Empirical formula	Calc.			Yield, %
				N, %	E	MR_D		N, %	E	MR_D	
IIb	101—105 (45)	0,9026	1,4450	16,2 16,0	174 174	50,80	$C_9H_{20}N_2O$	16,3	172	51,00	40
IIc	77 (33)	0,9592	1,4564	21,6 21,5	135 130	37,08	$C_6H_{14}N_2O$	21,5	130	37,06	68
IIe	109—111 (52)	0,9104	1,4470	16,1 16,3	172 171	50,70	$C_9H_{20}N_2O$	16,3	172	51,00	70
IIf	79—81 (27)	0,9131	1,4433	17,9 17,6	163 163	45,98	$C_8H_{18}N_2O$	17,7	158	46,35	67

TABLE 2. Parameters of the PMR Spectra of Perhydro-1,3,4-oxadiazines II[a]

Compound	R	R′	R″	δ, ppm (J, Hz)					
				R″	2-H	5-H	6-H	R	R′
IIb[b]	H	n-C_3H_7	i-C_3H_7	0,8—1,0m 1,3—1,8m	4,30 e[c] (5,5)	2,0—2,8 m	3,88 m		0,8—1,0 m 1,3—1,8 m 2,0—2,8 m
IIc[d]	H	i-C_3H_7	H	4,42 e (7,5)		2,3—2,7 m	3,92 t (5,0)		0,99 d (6,5) 2,3—2,7 m
IIe[e]	H	i-C_3H_7	i-C_3H_7	0,8—1,0m 1,59 sept (7,0)	4,21 e[c] (5,5)	2,0—3,0 m	3,83 m		0,8—1,0 m 2,0—3,0 m
IIf	CH_3	i-C_3H_7	CH_3	1,08 d (6,0)	4,27 q[c] (6,0)	5-H_e 2,66 dd 5-H_a 1,65 dd (J_{5e5a} = −10,5, J_{5a6a} = 10,5, J_{5e6a} = 2,2)	3,65 m	1,02 d (6,0)	0,96 d 2,41 sept (6,0)

[a] The spectra of equilibrium mixtures of the perhydrooxadiazines with the hydrazones were investigated. [b] The CH=N signal of the hydrazone form is observed as a doublet at 6.73 ppm (J = 5.0 Hz). [c] The signal is broadened because of coupling with the proton of the NH group. [d] Signals of the hydrazone form, δ: 6.10 and 6.22 (AB system, J = 12.0 Hz, CH_2=N); 3.50 (t, J = 6.0 Hz, CH_2—O); 1.06 ppm (d, J = 7.0 Hz, CH_3). [e] Signals of the hydrazone form, δ: 6.69 (d, J = 5.5 Hz, CH=N) and 1.08 ppm [d, J = 7.0 Hz, $(CH_3)_2C$].

Satisfactory results were obtained when yellow mercuric oxide was used as the oxidizing agent. Dihydro-1,3,4-oxadiazines III were isolated in high yields in all cases (Table 3). Dihydrooxadiazines III have higher densities and refractive indexes than the starting compounds; the molecular refractions are close to the calculated values, and this indicates the absence of p,π conjugation in the "hydrazone" fragment. In contrast to the starting saturated oxadiazines, dihydrooxadiazines III do not display basic properties and are not titrated by mineral acids.

The presence of a C=N bond in the compounds obtained is confirmed by the presence of a strong band at 1650-1660 cm^{-1} (Table 4), which is considerably more intense than the analogous band in the spectra of the starting equilibrium tautomeric mixtures. The structures of the dihydrooxadiazines III are also confirmed by the PMR spectra (Table 4). As compared with the starting perhydrooxadiazines, all of the signals in the spectra of the dihydro derivatives are shifted to the weak-field side and, in addition, frequently differ in intensity. Thus, whereas the signal of the 2-H methylene protons is observed in the spectrum of 4-isopropylperhydro-1,3,4-oxadiazine (IIc) in the form of a doublet at 4.42 ppm, the signal of the 2-H proton in the spectrum of dihydrooxadiazine IIIc is a singlet at 6.58 ppm; the shift of this signal to the low-field side unambiguously indicates that the proton is attached to the azomethine carbon atom. The appearance of a singlet signal of a methyl group at 1.8 ppm in place of the doublet at ∿1.1 ppm in the spectra of the corresponding perhydrooxadiazines is also characteristic for 2-methyldihydrooxadiazines IIIa, d, e. Another peculiarity is the fact that the protons of the methylene groups of IIIa-e give two symmetrical "triplets" (an AA'XX' system), whereas a complex ABMX multiplet is observed in

TABLE 3. 5,6-Dihydro-4H-1,3,4-oxadiazines III

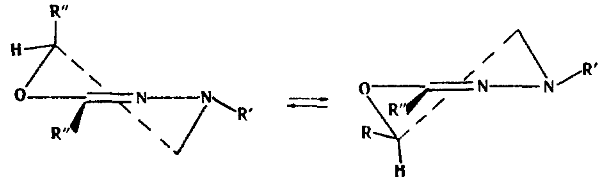
Compound	bp, °C (mm)	d_4^{20}	n_D^{20}	Found		Empirical formula	Calc.		Yield, %
				N, %	MR_D		N, %	MR_D	
IIIa	80—83 (30)	0,9513	1,4552	19,9	40,57	$C_7H_{14}N_2O$	19,7	40,62	62
IIIb	84—89 (20)	0,9189	1,4557	16,4	50,34	$C_9H_{18}N_2O$	16,5	49,91	60
IIIc	71—74 (26)	0,9869	1,4590	21,7	35.51	$C_6H_{11}N_2O$	21,9	35,81	76
IIId	60—63 (11)	0,9657	1,4572	19.9	40,16	$C_7H_{14}N_2O$	19,7	40,16	72
IIIe	87—91 (22)	0,9213	1,4529	16,7	49,94	$C_9H_{18}N_2O$	16.5	49,91	44
IIIf	70—74 (33)	0,9385	1,4536	17,8	45,05	$C_8H_{16}N_2O$	17,9	45,10	66

TABLE 4. Spectral Characteristics of 5,6-Dihydro-4H-1,3,4-oxadiazines III

Compound	R	R′	R″	$\nu_{C=N}$, cm^{-1}	δ, ppm (J, Hz)				
					R″	5-H	6-H	R	R′
IIIa	H	n-C_3H_7	CH_3	1660	1,76 s	2,77 t (4,5)	4,29 t (4,5)		0,87 t (6,5) 1,6 m 2,61 t (7,5)
IIIb	H	n-C_3H_7	i-C_3H_7	1658	1,04 d 2,32 sept (7,0)	2,76 t (4,5)	4,32 t (4,5)		0,89 t (7,0) 1,59 sext 2,65 t (7,5)
IIIc	H	i-C_3H_7	H	1650	6,58 s	2,93 t (5.0)	4.34 t (5,0)		1,04 d (6.0)[a]
IIId	H	i-C_3H_7	CH_3	1664	1,83 s	2,77 t (4,7)	4,21 t (4,7)		1,03 d (6,3) 2,95 sept
IIIe	H	i-C_3H_7	i-C_3H_7	1655	1.03 d 2,32 sept (6,5)	2,80 t (4,5)	4,32 t (4,5)		3.00 sept 1,03 d (6,5)
IIIf	CH_3	i-C_3H_7	CH_3	1660	1,76 s	5-H_e 2,77 dd 5-H_a 2,30 dd ($J_{5a,5e} = -11{,}0$, $J_{5a,6a} = 7{,}5$, $J_{5e,6a} = 2{,}8$)	4,30 m	1,21 (7,0)	1,04 e[b] 1,02 e[b] 3,01 sept (6,5)

[a] The signal of the methylidyne proton is superimposed on the 5-H signal. [b] Diastereotopic methyl groups.

the spectra of the corresponding saturated compounds. This is evidently associated with rapid inversion of two equivalent half-chair conformations. It is apparent from the spin–spin coupling constants (SSCC) that primarily conformation IVb with a pseudoequatorial 6-CH_3 group is realized in the case of dihydrooxadiazine IIIf:



IV a IVb

Thus the oxidation of perhydrooxadiazines may serve as a convenient method for the synthesis of 5,6-dihydro-1,3,4-oxadiazines; it is also a sufficiently general method, since even the presence of branched alkyl groups in the 2 and 4 positions does not hinder oxidation. However, this method cannot be used for the preparation of 4-substituted or 2-aryl substituted dihydrooxadiazines, since the starting compounds from the condensation of the corresponding hydrazino alcohols and carbonyl compounds exist, according to our data, entirely in the acyclic form.

EXPERIMENTAL

The IR spectra of thin layers of the compounds were recorded with a UR-10 spectrometer. The PMR spectra of 20% solutions of the compounds in carbon tetrachloride were obtained with a Varian HA-100D-15 spectrometer with hexamethyldisiloxane as the internal standard. The individuality of the dihydrooxadiazines was confirmed by means of thin-layer chromatography (TLC) on Silufol UV-254 plates.

<u>1-(N-Isopropylhydrazino)-2-propanol (Ic)</u>. A 38.1 g (0.66 mole) sample of propylene oxide was added dropwise with stirring and ice cooling to 48.8 g (0.66 mole) of isopropylhydrazine, and the mixture was stirred at room temperature for 2 h and at 50°C for 3 h.

Distillation yielded 53.2 g (61%) of hydrazino alcohol Ic with bp 98-102°C (16 mm), d_4^{20} 0.9265, and n_D^{20} 1.4497. Found: N 20.7; 21.3%; equivalent weight 134; MR_D 38.32. $C_6H_{16}N_2O$. Calculated: N 21.2%; equivalent weight 132; MR_D 38.82.

2-Alkylperhydro-1,3,4-oxadiazines (IIa, b, d-f). These compounds were obtained by condensation of hydrazino alcohols Ia-c with aliphatic aldehydes by the method in [5]. The characteristics of the new compounds are presented in Tables 1 and 2.

4-Isopropylperhydro-1,3,4-oxadiazine (IIc, Tables 1 and 2). A mixture of 31.7 g (0.27 mole) of 2-(N-isopropylhydrazino)ethanol (Ib) [5], 8.1 g (0.09 mole) of paraformaldehyde, and 30 ml of benzene was refluxed with a Dean—Stark trap until the water was removed completely. The residual mixture was then distilled with a column.

5,6-Dihydro-4H-1,3,4-oxadiazines (IIIa-f, Tables 3 and 4). Perhydrooxadiazines IIa-f were added cautiously to a 10% molar excess of yellow mercuric oxide. The reaction usually began spontaneously when the mixture was stirred; when the reaction was too vigorous, the mixture was cooled with ice water. The mixture was heated on a boiling-water bath for 30-60 min to complete the reaction. The organic layer was separated, dried with potassium carbonate, and distilled.

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REACTIONS OF TELLURIUM TETRAHALIDES WITH 1,5- AND 1,6-DIOLEFINS AND THEIR DERIVATIVES*

Yu. V. Migalina, I. M. Balog,
V. G. Lendel, A. S. Koz'min,
and N. S. Zefirov

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1,4-Dihalo-substituted tellurolanes were obtained by reaction of tellurium tetrabromide and tetrachloride with 1,5-hexadiene, and the corresponding six-membered heterocyclic compounds with a tellurium atom in the ring were obtained with 1,6-diolefins.

A few examples of heterocyclic systems that contain a tellurium heteroatom have been described [2]. Considering the ability of tellurium tetrahalides to add to double bonds (for example, propylene [3]), we decided to extend this reaction to diolefins in order to obtain heterocyclic compounds.

We selected 1,5-hexadiene (I), diallyl ether (IIa), diallyl sulfide (IIb), diallylamine (IIc), and N-methyldiallylamine (IId) as the diolefins. By varying the order of addition, the reagent ratio, the temperature, and the solvent we found conditions under which crystalline substances that do not contain multiple bonds are formed in good yields from tellurium tetrahalides and diolefins. After reaction of 1,5-hexadiene with tellurium tetrabromide and tetrachloride, we were able to isolate 1,1-dibromo-2,5-dibromomethyl- (IIIa) and 1,1-dichloro-2,5-dichloromethyltellurolane (IIIb), respectively, from the reaction mixtures.

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