CHEMICAL PROPERTIES OF N'-CYANODIAZENE N-OXIDES. REACTIONS INVOLVING THE NITRILE GROUP

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The reactivity of the nitrile group in N'-cyanodiazene N-oxides has been examined for the first time. A general approach to the synthesis of nitrogenous functional derivatives of azoxycarboxylic acids by reaction of N'-cyanodiazene N-oxides with nucleophiles (water, alcohol, and hydroxylamine) is described. A method of synthesis of novel azoxy-1,2,4-oxadiazoles and tetrazoles has been developed in which aliphatic, aromatic, or heterocyclic N'-cyanodiazene N-oxides are reacted with benzonitrile N-oxide or sodium azide. Trimerization of N-cyanodiazene N-oxides, catalyzed by anhydrous HCl, has given novel symm-triazines in which the heterocycle bears three diazene N-oxide groups.

Compounds containing the N'-cyanodiazene N-oxide grouping have been found to possess antibacterial [1-4], fungicidal [4-8], and antitumor [9] activity. Although methods of synthesis of these compounds are currently receiving much attention [3, 5, 6, 9-13], there has been little work on their chemical properties. The only such reports describe the hydrolysis of cyanoazoxyarenes to N'-carbamoyldiazene N-oxides on treatment with HCl [2, 3], and the cleavage of the N'-cyanodiazene N-oxide group by acids and bases [6]. Nevertheless, the presence of a cyano-group activated by the diazene N-oxide group in N'-cyanodiazene N-oxides suggests that they could undergo reactions characteristic of nitriles, namely addition and cyclization to give azoxycarboxylic acids and unsymmetrical heterocyclic azoxycompounds, which might be of practical value.

The aim of this investigation was to examine the reactions of N'-cyanodiazene N-oxides with acids, nucleophiles, and 1,3-dipolar compounds to give products with a range of functional and heterocyclic groupings at the terminal nitrogen of the diazene-N-oxide group.

Taking compounds (I)-(IV) as examples, we have now shown that the nitrile group in aliphatic, aromatic, and heterocyclic N'-cyanodiazene N-oxides is highly reactive toward addition and cyclization. For example, (I) and (IV) react smoothly with the dilute HCl, methanol, and hydroxylamine at 0-20°C, to give high yields of the addition products, namely azoxyamides (V) and (VI), the azoxyiminoester (VII), and the azoxyamidooximes (VIII) and (IX) (Table 1). The reaction of (I) with methanol was carried out by adding a catalytic amount of sodium methoxide to the reaction mixture.

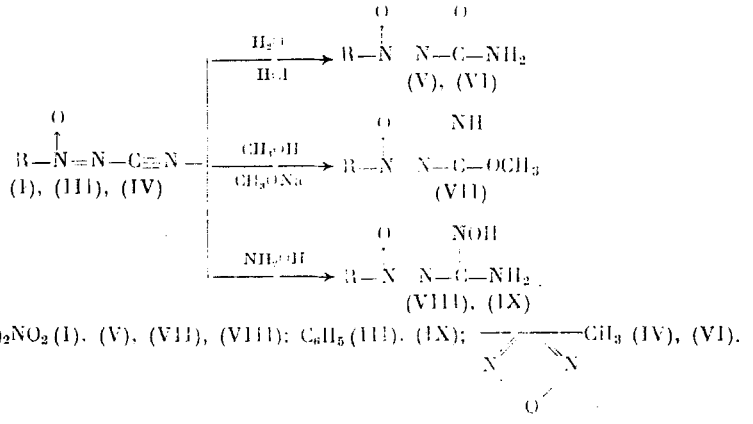

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TABLE 1. Yields and Physicochemical Properties of (V)-(XXV)

Compound	Yield, %	Mp, °C (solvent)	IR spectrum (ν, cm^{-1})	PMR spectrum (δ, ppm)	Found/Calculated, %			
					C	H	N	Br
(V)	82	117–118 ($CHCl_3$)	1510, 1570, 1685, 3215, 3362	2,10 s (6H), 7,13 br.s (2H)	27,80 27,27	4,34 4,55	31,92 31,82	
(VI)	54,5	87–88 ($CHCl_3/CCl_4$)	1505, 1595, 1720, 3200	2,55 s (3H), 7,20 br.s (2H)	27,68 27,07	2,98 2,92	40,83 40,94	
(VII)	92	50–51 (ether/hexane)	1500, 1570, 1668, 3315, 1075	2,16 s (6H), 3,73 s (3H), 7,62 s (1H)	32,03 31,58	5,25 5,26	29,20 29,47	
(VIII)	92	97–102 (decomp.)	1500, 1570, 1620, 2700–3300, 3390, 3500	2,10 s (6H), 4,0 br.s (3H)				
(IX)	89	128–130 (ether/heptane)	1485, 1530, 1645, 2800–3300, 3380, 3500	8,30–7,80 m (5H), 6,40 br.s (3H)	46,77 46,67	4,77 4,44	31,27 31,11	
(X)	75/90 *	198–200 (alcohol)	1350, 1400, 1495, 1565	2,33 s (18H)	30,88 30,38	4,10 3,80	34,91 34,44	
(XI)	80	200–202 (*i*-PrOH)	1370, 1495, 1545	2,32 s(18H)	25,00 25,24	3,13 3,52	21,88 22,22	41,67 41,22
(XII)	61	244–246 (MeOH/acetone)	1350, 1440, 1475, 1525		57,67 57,14	3,56 3,40	28,64 28,57	
(XIII)	63	165–166 (*i*-PrOH/acetone)	1310, 1355, 1385, 1435, 1480, 1530, 1585	2,67 s (9H)	31,14 31,37	2,38 1,97	45,94 45,75	
(X V)	63	69–71 (hexane)	1500, 1580	2,30 s (6H), 7,30; 7,80 m (5H)	47,75 47,65	4,08 3,97	25,15 25,27	
(XV)	71	85–86 (hexane)	1330, 1445, 1500, 1530	2,30 s (6H), 7,43; 8,05 m (5H)	42,44 43,17	3,54 4,08	18,01 17,75	25,72 25,86
(XVI)	78	138–140 (ether/hexane)	1325, 1350, 1435, 1490, 1525	7,63; 8,37 m (10H)	63,08 63,16	3,90 3,76	20,98 21,05	

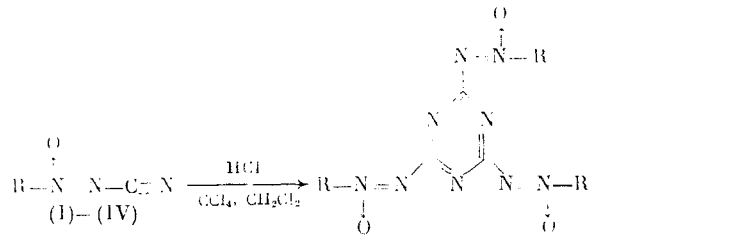
TABLE 1 (continued)

Compound	Yield, %	Mp, °C (solvent)	IR spectrum (ν, cm^{-1})	PMR spectrum (δ, ppm)	Found/Calculated, %			
					C	H	N	Br
(XVII)	70	111–114 (hexane/chloroform)	1500, 1585	2,73 s (3H), 7,42; 8.15 m (5H)	48,59 / 48,53	2,99 / 2,94	31,06 / 30,88	
(XVIII)	94	155–156 (H_2O)	1480, 1520, 1580, 2500–3200	2,35 s (6H)	24,38 / 23,88	3,55 / 3,48	48,94 / 48,75	
(XIX)	83	137–138 ($CHCl_3/CCl_4$)	1380, 1510, 2600–3100	2,40 s (6H)	20,43 / 21,06	2,98 / 3,14	35,74 / 36,31	34,04 / 33,89
(XX)	88	197–198 ($CHCl_3/CCl_4$)	1300, 1360, 1420, 1440, 1485, 1515, 1520	7,70; 8,38 m (5H)	44,37 / 44,21	3,40 / 3,16	43,88 / 44,21	
(XXI)	78	147–150 (H_2O)	1475, 1485, 1585, 2590–2960	2,75 s (3H)	24,45 / 24,48	2,09 / 2,04	57,02 / 57,14	
(XXII)	27.5	74–75 (hexane/chloroform)	1520, 1570	2,35 s (6H), 4,15 s (3H)	28,42 / 27,91	4,16 / 4,19	45,39 / 45.58	
(XXIII)	66	51–53 (hexane/chloroform)	1520, 1570	2,32 s (6H), 4,48 s (3H)	28,22 / 27,91	4,15 / 4,19	45.27 / 45.58	
(XXIV)	26	117–120 (acetone/hexane)	1525, 1590	2,80 s (3H), 4,20 s (3H)	28,89 / 28,57	2,96 / 2,86	52,58 / 53,33	
(XXV)	42	oil	1525, 1590	2,73 s (3H), 4,48 s (3H)	29,00 / 28,57	3,11 / 2,86	52,99 / 53,53	

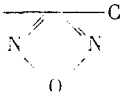
*Yield in the reaction of 2,4,6-tris(dibromoamino)-1,3,5-triazine with 2-nitro-2-nitrosopropane.

It is important to note that these reactions occur with retention of the diazene N-oxide group, and provide convenient methods for the preparation of difficultly accessible and novel nitrogenous functional derivatives of azocarboxylic acids.

The high chemical reactivity of the nitrile group in N'-cyanodiazene N-oxides is shown by their ability to undergo cyclotrimerization and cycloaddition reactions under mild conditions. Cyclotrimerization of (I)-(IV) occurs on treatment with anhydrous HCl in an inert organic solvent (dichloromethane or chloroform) to give the 2,4,6-tris(azoxy)-1,3,5-triazines (X)-(XIII). The reaction probably proceeds via the formation of adducts of HCl with (I)-(IV), followed by addition of these compounds to the C≡N group in the starting compounds [14]. The triazine ring is formed at temperatures as low as −10 to 20°C, which by comparison with the severe conditions required for the trimerization of most organic cyano-compounds [14] indicates that the nitrile group in (I)-(IV) is highly reactive. The yields of (X)-(XIII) ranged from 61 to 90%.



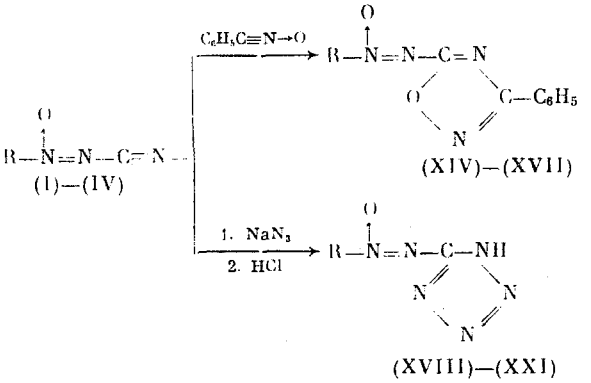
(I)–(IV) → (X)–(XIII)

R = $C(CH_3)_2NO_2$ (I), (X); $C(CH_3)_2Br$ (II), (XI); C_6H_5 (III), (XII);  (IV), (XIII).

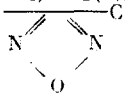
The ability of N'-cyanodiazene N-oxides to undergo 1,3-dipolar cycloaddition is well shown by the reactions of (I)-(IV) with benzonitrile oxide and sodium azide. Addition of (I)-(IV) to benzonitrile oxide takes place readily at 0°C to give 63-78% of the 1,2,4-oxadiazoles (XIV)-(XVII). The competitive dimerization of benzonitrile oxide to diphenylfuroxan takes place to a significant extent only in the case of (III), 50% of which failed to react and was recovered unchanged.

The differing reactivities of N'-cyanodiazene N-oxides toward 1,3-dipoles are apparent in the reactions of (I)-(IV) with sodium azide. In all cases, the sole reaction product was the corresponding tetrazole (XVIII)-(XXI), but although (I), (II), and (IV) reacted readily with NaN_3 at temperatures as low as -20°C, the reaction with (III) required temperatures of 70-80°C. The use of water or aqueous dioxane as solvent enabled the isolation of (XVIII)-(XXI) to be greatly simplified, requiring merely acidification of the reaction mixture followed by isolation of the solid products by filtration. The yields of (XVIII)-(XXI) were 78-94%.

Azoxy-derivatives of 1,2,4-oxadiazole and tetrazole, and triazines bearing three diazene N-oxide groups, have not been reported. The structures of (X)-(XXI) were established by

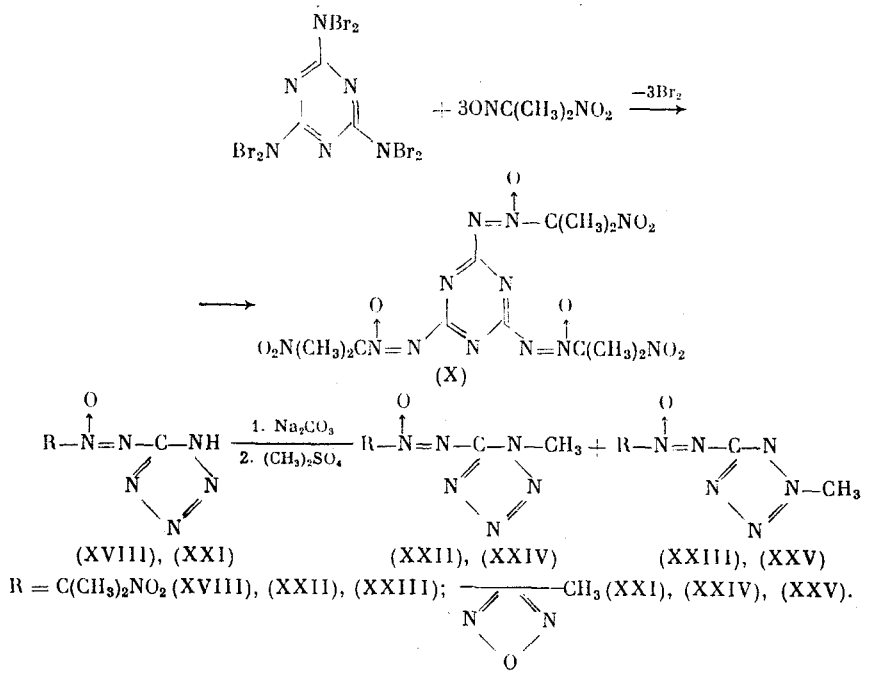


(I)–(IV) → (XIV)–(XVII) and (XVIII)–(XXI)

R = $C(CH_3)_2NO_2$ (I), (XIV), (XVIII); $C(CH_3)_2Br$ (II), (XV), (XIX); C_6H_5 (III), (XVI), (XX);  (IV), (XVII), (XXI).

their elemental composition, IR, PMR and [in the cases of (XII) and (XIII)] mass spectra (Table 1). Further confirmation of the structures of the 2,4,6-tris(azoxy)triazines (X)-(XIII) was provided by the direct synthesis of (X) from 2,4,6-tris(dibromoamino)triazine and 2-nitro-2-nitrosopropane, by the method reported in [15]. The structures of the azoxytetrazoles (XVIII) and (XXI) were confirmed by the preparation of their N-methyl derivatives (XXII)-(XXV) by reacting (XVIII) and (XXI) with dimethyl sulfate in the presence of base. The isomeric alkylation products of (XXII)-(XXV), bearing methyl groups at N^1 and N^2 of the tetrazole ring, were separated by TLC and characterized in the pure state (Table 1).

The products (XXII) and (XXIV), which had higher melting points and smaller chemical shifts (δ) of the N-methyl group protons, were assigned the 1-methyltetrazole structure in accordance with literature data [16], and the isomeric compounds (XXIII) and (XXV) the 2-methyl structure.



This study of the reactivity of N'-cyanodiazene N-oxides has thus afforded convenient synthetic routes to difficultly-accessible and novel functional derivatives of azoxycarboxylic acids and unsymmetrical heterocyclyldiazene N-oxides of varying structure, by reaction of N'-cyanodiazene N-oxides with nucleophiles and dipoles, and acid-catalyzed cyclotrimerization of N'-cyanodiazene N-oxides.

EXPERIMENTAL

The IR spectra of (V)-(XXIV) were obtained in KBr disks, and that of (XXV) in a thin layer, on a Specord 75 JR spectrometer. The PMR spectra of the compounds were recorded in fully deuterated solvents (acetone, chloroform, and DMSO) on a Tesla BS 467, internal standard HMDS, mass spectra (m/z) were obtained on a Varian MAT CH-6 with direct introduction of the sample into the ion source, ionizing electron energy 70 eV, accelerating voltage 1.75 kV, emission current 10 mA.

Compounds (I)-(IV) were obtained as in [13], dibromoisocyanurate (DBI) as in [17], 2-nitro-2-nitrosopropane as in [18], and 2,4,6-tris(dibromoamino)-1,3,5-triazine as in [19].

The yields and properties of the products are shown in Table 1. The melting points were not corrected, and the yields were not optimized.

N-(R)-N'-(Carbamoyl)diazene N-Oxides (V) and (VI). An emulsion of (I) or (IV) (1.27 mmoles) in 15% HCl (8 ml) was stirred for 2 h at 20°C, until a homogeneous solution was formed. The solvent was removed under reduced pressure, and the residue crystallized.

N-(1-Methyl-1-nitroethyl)-N'-(methoxyiminomethyl)diazene N-Oxide (VII). To a solution of (I) (1.27 mmoles) in dry methanol (5 ml) was added three drops of $NaOCH_3$ solution (~0.05 mmole) in dry methanol, and the mixture kept for 15 min at ~20°C. The solvent was removed,

the residue extracted with ether, the ether solution evaporated, and the product crystallized.

N-(R)-N'-(Hydroxyiminoaminomethyl)diazene N-Oxides (VIII) and (IX). To a solution of hydroxylamine hydrochloride (1.5 mmoles) in dry methanol (5 ml) were added successively with stirring at 0°C a solution of $NaOCH_3$ in dry methanol (1.5 mmoles of sodium in 2 ml of dry methanol), and a solution of (I) or (III) (1.27 mmoles) in dry methanol (2 ml). The mixture was kept for 30 min at 0°C and 1 h at 10-15°C. The methanol was then removed under reduced pressure, and the residue extracted with ether. The ether solution was evaporated to give (VIII) or (IX) as a crystalline solid. The product (VIII) was of low stability, decomposing on crystallization from organic solvents, but (IX) was more stable, allowing it to be isolated in an analytically pure state.

2,4,6-Tris[N-(R)-N-oxidodiazene-N'-yl]-1,3,5-triazines (X)-(XIII). A solution of (I)-(IV) (3.79 mmoles) in dry CCl_4 (or CH_2Cl_2) (30 ml) was saturated with dry HCl, and kept for 12 h at −10°C and 8 h at 20-23°C. The solvent was removed under reduced pressure. Compound (X) was isolated by two crystallizations from alcohol.

Products (XI)-(XIII) were extracted with boiling 2-propanol (15 ml), and the solutions cooled and evaporated, and the residue crystallized. Mass spectra, m/z: M^+ 441 (XII), M^+ 459 (XIII). From the mother liquors after evaporation there were extracted unreacted (III) and (IV) (23 and 29%, respectively). The yields of (X)-(XIII) given are calculated in the (I)-(IV) reacted (Table 1).

2,4,6-Tris[N-(1-methyl-1-nitroethyl)-N-oxidodiazene-N'-yl]-1,3,5-triazine (X). A solution of 2-nitro-2-nitrosopropane (3.5 mmoles) and 1,3,5-tris(dibromoamino)-2,4,6-triazine (1 mmole) [19] in dry CH_2Cl_2 (10 ml) was stirred for 20 h at 20°C, then the solid was filtered off, the filtrate evaporated, and the residue recrystallized.

3-Phenyl-5-[N-(R)-N-oxidodiazen-N'-yl]-1,2,4-oxadiazoles (XIV)-(XVII). To a solution of chlorobenzaldoxime (1.63 mmoles) in dry ether (10 ml) was added triethylamine (1.63 mmoles) at −20°C. After 15 min, a solution of (I)-(IV) (1.63 mmoles) in dry ether (2 ml) was added. The mixture was kept for 24 h at −15 to −20°C, 24 h at 5°C, and 24 h at 20-23°C. The solid was filtered off, washed with ether, and the filtrate evaporated. The products (XIV)-(XVIII) were isolated by TLC (Silpearl, benzene) and recrystallized. In the case of (XVI), in addition to the reaction product, 50% of the starting material (III) was isolated [the yield of (XVI) in Table 1 is calculated on (III) reacted].

5-[N-(R)-N-Oxidodiazen-N'-yl]tetrazoles (XVIII)-(XXI). A mixture of the appropriate N'-cyanodiazene N-oxide (I), (II), or (IV) (1.27 mmoles), sodium azide (1.54 mmoles), and water (3 ml) was stirred vigorously for 3 h at ~20°C. The resulting homogeneous solution was acidified with conc. HCl to pH 1, and the products (XVIII), (XIX), and (XXI) filtered off and crystallized. Compound (XX) was obtained similarly, using aqueous dioxane (50:50) (6 ml) as solvent, the reaction being carried out for 4 h at 70-80°C.

Alkylation of (XVIII) and (XXI) with Dimethyl Sulfate. A mixture of the azoxytetrazole (XVIII) or (XXI) (1.19 mmoles), dimethyl sulfate (1.35 mmoles), Na_2CO_3 (1.10 mmoles), and acetone (7 ml) was stirred for 40 h at ~20°C. The solid was filtered off, and the filtrate evaporated. The products (XXII)-(XXIV) were isolated by TLC (Silpearl, eluent ether), and recrystallized.

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