SYNTHESIS AND PROPERTIES OF AZOLES AND THEIR DERIVATIVES

XXIII.* PREPARATION OF 3,5-DISUBSTITUTED 1,2,4-OXADIAZOLES FROM 1-CYANOADAMANTANE

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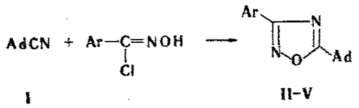
Thermal condensation of 1-cyanoadamantane with arylhydroxamic acid chlorides gave 5-(1'-adamantyl)-1,2,4-oxadiazoles containing aromatic groupings in the 3 position. The same 1,2,4-oxadiazoles were synthesized by reaction of the N-oxides of the appropriate nitriles with adamantane-1-carboxylic acid methyl imino ester obtained from 1-cyanoadamantane. The corresponding 5-(1'-adamantyl)-3-substituted 1,2,4-oxadiazoles were obtained by condensation of the latter with amidoxines.

Oxadiazoles and their derivatives are of interest to researchers as substances that have diverse biological activities.

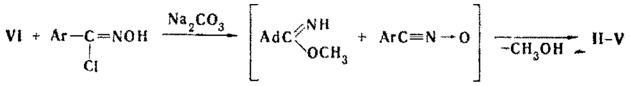
We have studied various methods for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles from 1-cyanoadamantane (I).

Hydrogen chloride evolution is observed when a mixture of I and phenylhydroxamic, m- and p-phenylhydroxamic, and 5-nitrofuryl-hydroxamic acid chlorides is refluxed in toluene. The reaction was complete when hydrogen evolution ceased. The nature of the aromatic residue in the arylhydroxamic acid chlorides affects their reactivities. Thus, 40 h are necessary for completion of the condensation of I with phenylhydroxamic acid chloride, whereas the introduction of a nitrile group into the meta and para positions of the phenyl ring increases the reaction time to 80–112 h.



Where Ad — adamantyl $C_{10}H_{15}$; II $Ar=p\text{-}NO_2\text{—}C_6H_4$; III $Ar=C_6H_5$; IV $Ar=m\text{-}NO_2\text{—}C_6H_4$; V $Ar=5\text{-}NO_2\text{—}C_4H_2O$

The same 1,2,4-oxadiazoles were synthesized by reaction of the N-oxides of the nitriles and methyl iminoester of adamantane-1-carboxylic acid:



$$\text{VI} + \underset{\text{Cl}}{\text{Ar—C=NOH}} \xrightarrow{Na_2CO_3} \left[\text{AdC}\begin{smallmatrix}\text{NH}\\ \text{OCH}_3\end{smallmatrix} + \text{ArC≡N}\rightarrow\text{O} \right] \xrightarrow[-CH_3OH]{} \text{II-V}$$

The nitrile N-oxides were obtained in situ by the action of sodium carbonate on the chlorides of the appropriate arylhydroxyamic acids. Adamantane-1-carboxylic acid methyl iminoester was also obtained in situ from its hydrochloride (VI), which was synthetized by the Pinner reaction from 1-cyanoadamantane:

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*See [1] for communication XXII.

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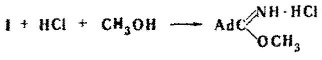


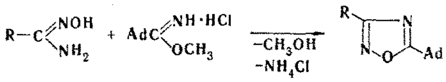
$$\text{I} + \text{HCl} + \text{CH}_3\text{OH} \longrightarrow \text{AdC}\begin{matrix}\nearrow \text{NH}\cdot\text{HCl} \\ \searrow \text{OCH}_3\end{matrix}$$

VI

The yields of 1,2,4-oxadiazoles are higher in the case of thermal condensation than in the reaction of nitrile N-oxides with adamantane-1-carboxylic acid methyl iminoester. The presence of an adamantane residue in the compounds obtained was proved by IR spectroscopy. The nature of the substituent in the 3 position of the oxadiazole ring has practically no effect on the frequencies of the vibrations both as a whole for the oxadiazole ring and for the individual fragments of this ring.

It is known [2] that 1,2,4-oxadiazoles can be obtained by the reaction of amidoximes with the hydrochlorides of carboxylic acid iminoesters.

It was found that the corresponding 3,5-disubstituted 1,2,4-oxadiazoles (VII-IX) (see Table 1) containing the adamantyl grouping are formed when mixtures of equimolecular amounts of the amidoximes of some carboxylic acids and VI are refluxed in absolute methanol.



VII-IX

VII $R=C_6H_5CH_2$—; VIII $R=C_{10}H_{15}$—; IX $R=CH_3$—

The structures of the compounds obtained were confirmed by IR and UV spectroscopy.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer. The UV spectra were recorded with a Unicam SP 800A spectrophotometer. Monitoring of the reaction and determination of the purity of the products were accomplished by thin-layer chromatography (TLC) on activity I aluminum oxide [benzene–methanol (25 : 1)]. The chromatograms were developed in iodine vapors.

The arylhydroxamic acid chlorides were obtained by the method in [3, 4]. The amidoximes of carboxylic acids were obtained by the method in [5].

Preparation of 1,2,4-Oxadiazoles. A) By Thermal Condensation of 1-Cyanoadamantane with Arylhydroxamic Acid Chlorides. A mixture of 0.05 mole of arylhydroxamic acid chloride and 0.05 mole of I in 30 ml of toluene was refluxed until hydrogen chloride evolution ceased. The solvent was then removed by distillation at reduced pressure. The physical constants and the yields of the compounds obtained are presented in Table 1.

B) By 1,3-Dipolar Cycloaddition. A solution of 0.008 mole of arylhydroxamic acid chloride in 15 ml of ether was added to a solution of 0.008 mole of VI in 20 ml of water. After this, a 5% aqueous solution (0.008 mole) of sodium acetate was added dropwise at 5° in the course of 1 h. The mixture was stirred at this temperature for 1 h and at room temperature for 3 h. The ether layer and the ether extracts were combined and dried with Na_2CO_3, and the solvent was removed by distillation at reduced pressure to give II-V (see Table 1).

C) By Condensation of Amidoximes with Adamantane-1-Carboxylic Acid Methyl Iminoester Hydrochloride. A mixture of 0.01 mole of the amidoxime and 0.01 mole of VI in 40 ml of absolute methanol was

TABLE 1. 3-Substituted 5-(1'-Adamantyl)-1,2,4-oxadiazoles

Compound	R	mp, °C*	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
II	*p*-NO_2—C_6H_4—	213—214	$C_{18}H_{19}N_3O_3$	66,8	6,1	13,0	66,5	5,9	12,9	56
III	C_6H_5—	184—185	$C_{18}H_{20}N_2O$	77,3	7,2	9,0	77,1	7,2	9,1	89
IV	*m*-NO_2—C_6H_4—	145—146	$C_{18}H_{19}N_3O_3$	66,7	5,8	12,4	66,5	5,9	12,9	97
V	5-NO_2—C_4H_2O—	170—171	$C_{16}H_{17}N_3O_4$	61,1	5,2	13,3	60,9	5,3	13,4	98
VII	$C_6H_5CH_2$—	194—195	$C_{19}H_{22}N_2O$	77,6	7,8	9,3	77,2	7,5	9,5	40
VIII	(1'-Adamantyl)	118—119	$C_{22}H_{30}N_2O$	78,1	8,9	8,5	77,8	8,9	8,3	88
IX	CH_3—	165—166	$C_{13}H_{18}N_2O$	70,3	8,9	13,6	70,0	8,7	13,5	70

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* The compounds were crystallized as follows: II and III from ligroin, IV and V from methanol, VII from cyclohexane, and VIII from aqueous methanol.

refluxed for 2 h. The resulting precipitate was removed by filtration, and the filtrate was evaporated at reduced pressure to give VII-IX (see Table 1).

Absorption bands at 705-710 cm^{-1} (stretching vibrations of the oxadiazole ring), 910-930, 1315, 1415-1420 cm^{-1} (=N—O—), and 1600-1605 cm^{-1} (C=N) are observed in the IR spectra of all of the compounds.

The UV spectra of heptane solutions of the compounds contain absorption maxima at 255-280 nm, and an absorption maximum at 320 nm (in acetonitrile) is characteristic for V.

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