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REACTION OF SUBSTITUTED 7-CYCLOPROPYL-1,4-BENZODIOXANES WITH DINITROGEN TETRAOXIDE

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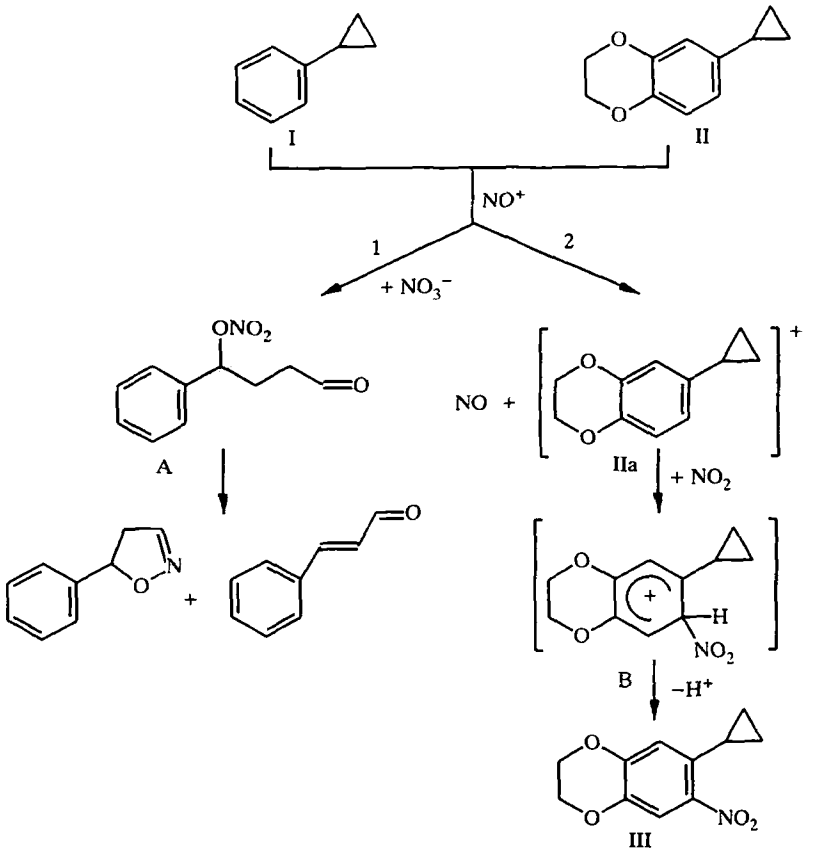
The reaction of 6-bromo-7-cyclopropyl-1,4-benzodioxane with N_2O_4 in methylene chloride does not affect the cyclopropane ring and forms the nitrodebrominated product (ipso-substitution). The same reaction of 6-nitro- and 5,6-dinitro-7-cyclopropyl-1,4-benzodioxanes produces only the products with an modified three-membered ring. The difference in the reaction paths of the studied cyclopropylbenzodioxanes with N_2O_4 is explained by the different ratio of substrate to one-electron oxidant, the nitrosyl cation.

Previous studies [1, 2] have demonstrated that alkyl-substituted analogs of phenylcyclopropane and 1,2-diarylcyclopropanes, in contrast with phenylcyclopropane, react with dinitrogen tetroxide to form exclusively

Scheme 1



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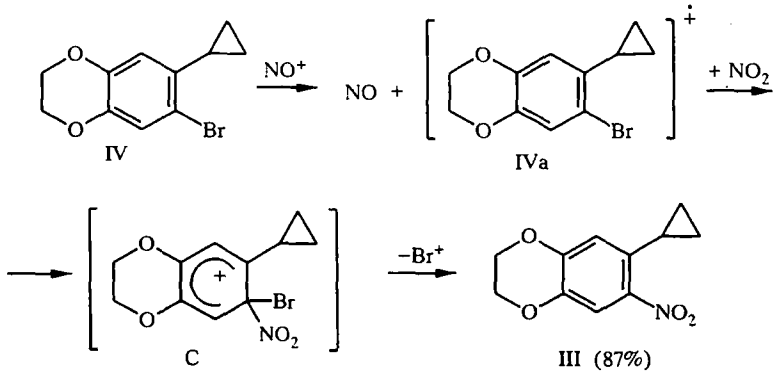
products with an opened ring. The reaction of 6-cyclopropyl-1,4-benzodioxane with N_2O_4 leads to formation of only the nitroaromatic derivative in which the cyclopropane ring is retained. It was proposed that the different behavior of these cyclopropyl-containing reactants is related to the occurrence of processes caused by the different reactivity of the starting materials with respect to one-electron oxidation initiated by the nitrosyl cation [1] (Scheme 1).

In one instance the first ionization potential (FIP) of the cyclopropane substrates is relatively high and the reaction occurs only as electrophilic addition (path 1, scheme 1). In another instance the FIP is sufficient for one-electron transfer to occur and the process occurs in general as aromatic SET nitration (path 2, scheme 1).

In the present work, we attempted to explain the influence of the substituents at the aromatic ring of cyclopropylbenzodioxanes on the paths of the reaction with N_2O_4. Thus, we synthesized 6-bromo-, 6-nitro-, and 5,6-dinitro-7-cyclopropyl-1,4-benzodioxanes and studied their behavior under the reaction conditions described in the literature [1, 2].

We have found that in reaction of 6-bromo-7-cyclopropyl-1,4-benzodioxane (IV) with N_2O_4 the same as for the unsubstituted compound II (Scheme 1), the cyclopropane ring is retained and the nitro group is introduced to the aromatic nucleus of the starting compound. The only difference was that nitro-derivatives corresponding to replacement of the hydrogen atom in the 5- or 8-positions of compound IV did not form, but the *ipso*-substitution product, 6-nitro-7-cyclopropyl-1,4-benzodioxane (III) (Schemes 1 and 2), was obtained. The yield of nitrodebrominated III was even greater than its yield in the reaction of bromide IV with concentrated HNO_3 in acetic anhydride [3], which also occurs according to the *ipso*-substitution mechanism.

Scheme 2

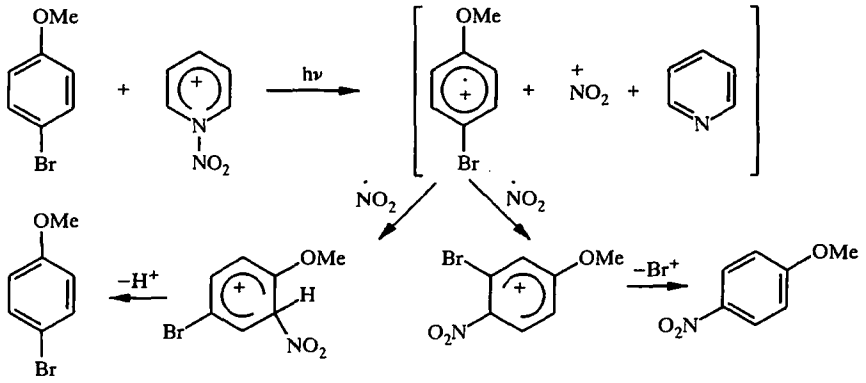


The preservation of the cyclopropane moiety and formation of the nitroaromatic derivative in the reaction of IV with N_2O_4 under normal conditions indicates that the mechanisms for conversion of IV and unsubstituted cyclopropylbenzodioxane II (Scheme 1) are identical. This is as expected if it is recalled that a halogen atom introduced into the aromatic substrate practically does not change the FIP of the substrate [4]. It is important to emphasize that the arenonium cation radical and NO_2 radical pairing is regioselective for the reaction of both 6-cyclopropyl-1,4-benzodioxane (II) and compound IV. Evidently the spin density of the carbon atom bonded to the bromine atom and the energy of formation of the *ipso*-σ-complex C (Scheme 2) assist the attack of the NO_2 radical at the *ipso*-position of the cation radical IVa (Scheme 2).

It is noteworthy that until now examples of nitrodehalogenation of halogenated anisoles and their analogs from reaction with N_2O_4 were unknown. However, under condition of electrophilic nitration [5] this type of transformation has been observed (especially nitrodebromination).

An example of nitrodebromination of 4-bromoanisole that accompanies its photochemically induced nitration by N-nitropyridinium cation ($PyNO_2^+$) has been reported [4]. The process is described by a scheme that supports the probable formation in our case of 7-nitro-6-cyclopropyl-1,4-benzodioxane (III) by *ipso*-substitution through the SET mechanism (see Scheme 3).

Scheme 3



The facts that the reaction of 4-bromoanisole with nitropyridinium cation does not occur without photoinduction and that arenonium cation radicals appear (established by UV spectroscopy) after induction of the reaction are consistent with the proposed scheme.

It can be seen that only the steps generating the arenonium cation radicals in the instance described [4] and in our instance are different whereas the last steps are identical.

Then it turned out that introducing even a single nitro group (compound III) to the aromatic system of cyclopropylbenzodioxane II directed the attack of the nitrosyl cation exclusively at the three-membered ring. The reaction occurs with the same characteristics (intense bluish-green colored reaction mixture at -27°C and irreversible color change to light yellow at elevated temperature) that are observed for the reactions of phenyl- and 1,2-diphenylcyclopropanes with the same reagent [1, 2]. It is important to note that the reactivity of III was so much less than the phenyl- and diphenylcyclopropanes reacting by the same scheme [1, 2] that it is completely converted to the final products after only 16 h. It is interesting that standard treatment of the reaction mixture produces a single product, 5-(7-nitro-1,4-benzodioxan-6-yl)isoxazoline (XIV), in 55% yield. However, PMR spectra indicate that α,β-unsaturated aldehyde XVI is in all probability also present in the mixture in small quantities (7-9%). This was determined from the characteristic doublet at 9.38 ppm (J = 7.8 Hz) (Scheme 4).

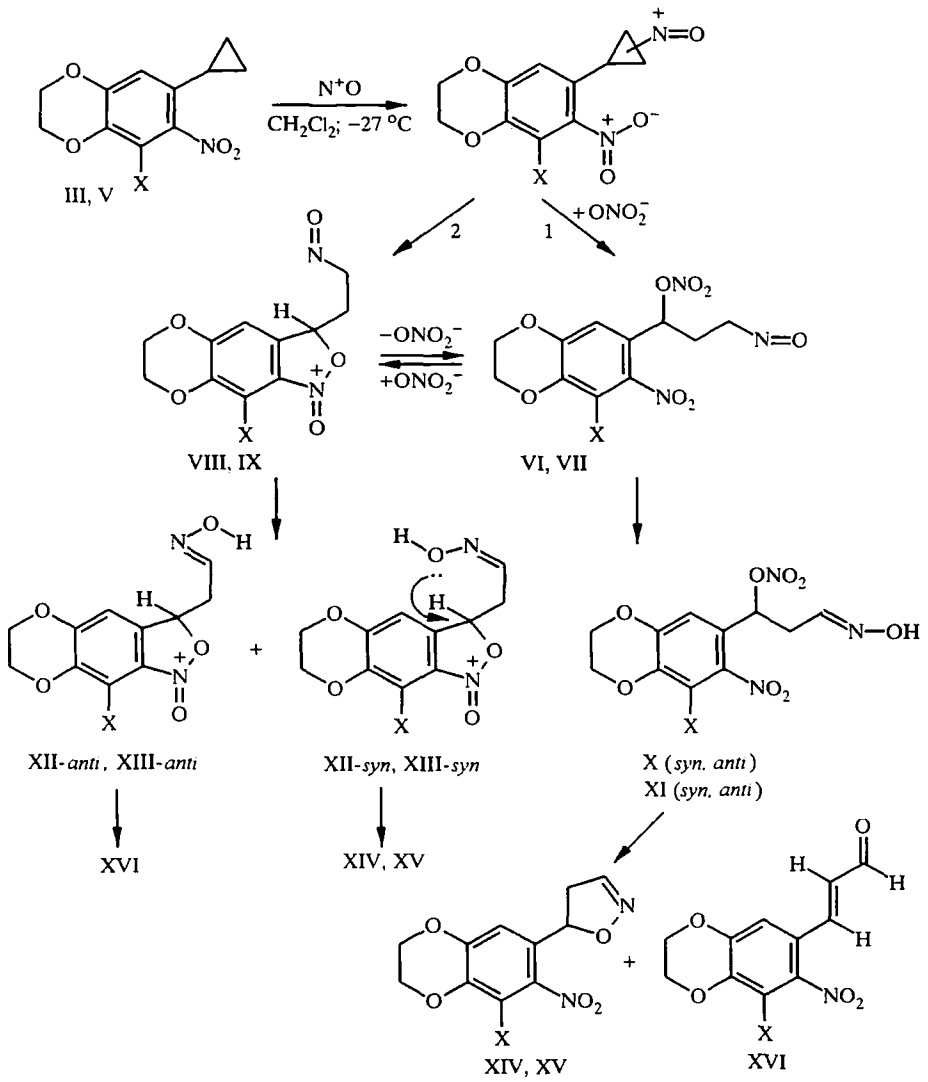
It was also determined that 5,6-dinitro-7-cyclopropyl-1,4-benzodioxane (V), although it reacts by the same scheme as the mononitrocompound III, reacts so slowly that most of it (~60%) is unreacted even after 24 h at -27°C. As a result, only 5-(5,6-dinitro-1,4-benzodioxan-7-yl)izoxazoline (XV) has been isolated (Scheme 4).

It seems reasonable to conclude that the change in the reaction course for nitrocompounds III and V may be related to the higher FIP for these compounds compared with the FIP for 7-cyclopropyl-1,4-benzodioxane (II) or its bromo-substituted analog IV since it is known [6] that introducing a nitro group into the aromatic system significantly increases FIP. Therefore, the nitrosyl cation is unable to oxidize nitrocompounds III and V to the corresponding cation radicals (IIIa and IVa in Schemes 1 and 2), which are responsible for the aromatic substitution.

It should be emphasized that products of modification of the three-membered rings may be formed by two independent pathways during the reaction of III and V with N_2O_4, in contrast with the *p*-alkylphenyl- and 1,2-diarylcyclopropanes [1, 2]. One of these pathways (path 1, Scheme 4) assumes that the reaction occurs with external stabilization of the benzyl-type cations that are generated (as a result of opening of the cyclopropane ring). This was proposed previously [1, 2] for describing the reactions of arylcyclopropanes discussed above. The other pathway (path 2, Scheme 4) is a version of the reaction that proceeds with nucleophilic opening of the small ring by nitrosyl cation (e.g., see [7, 8]), nitrosyl-containing cyclic ions VIII and IX being formed. The latter obviously can form the same isoxazolines XIV and XV and α,β-unsaturated compounds XVI after isomerization into the corresponding oximes XII and XIII.

We note that the yield of dinitrobenzodioxanylisoxazoline XV was greater (79% calculated on the basis of the reactant dinitrocompound V) than for the mononitrocompound III regardless of the low per cent conversion of V. It is still not possible to determine unambiguously why primarily the isoxazolines XIV and XV are formed under the given conditions from the reaction of III and V. It can only be assumed that holding the reaction mixture

Scheme 4



X = H (III, VI, VIII, X - *syn*, *anti*, XII - *syn*, *anti*, XIV, XVI)
X = NO_2 (V, VII, IX, XI - *syn*, *anti*, XIII - *syn*, *anti*, XV)

at low temperature (16-24 h, -27°C) and, therefore, at a slow rate of isomerization of the nitroso compounds VI-IX into the oximes X-XIII (Scheme 4) and that preventing the hydrolysis of the oximes in the *anti*-configuration and the formation from them of α,β-unsaturated compounds in significant quantities leads to a series of reversible reactions of intermediates (e.g., VI and VII into VIII and IX and *vice versa*). This enhances the accumulation of isoxazolines XIV and XV, which are formed under the given conditions by cyclization of oximes X-XIII in the *syn*-configuration.

EXPERIMENTAL

PMR spectra were taken on a Varian VXR-400 spectrometer in $CDCl_3$ with HMDS as standard. Mass spectra were recorded on an MX-1321A instrument at 70 eV ionization energy. The purity of the products was monitored by TLC on Silufol and Alufol plates.

6-Bromo-7-cyclopropyl-1,4-benzodioxane (IV) was prepared by the literature method [3]; bp 136-138°C (3 mm Hg), n_D^{20} 1.5890. Yield 64%.

7-Cyclopropyl-6-nitro-1,4-benzodioxane (III), 80% yield, mp 82°C and **7-cyclopropyl-5,6-dinitro-1,4-benzodioxane (V)**, 84% yield, mp 131°C, were synthesized by the literature method [9].

7-Cyclopropyl-6-nitro-1,4-benzodioxane (III). To solution of bromobenzodioxane IV (2 g, 7.8 mmol) in dry CH_2Cl_2 (10 ml) cooled to -27°C solution of N_2O_4 (1.4 g, 15.6 mmol) in the same solvent (5 ml) cooled to the same temperature was added. The reaction mixture was maintained for 1 h at -27°C. Cold water (40 ml) was added. The organic layer was separated, washed with 3% $NaHCO_3$ and water, and dried over $MgSO_4$. The solvent was evaporated. The residue was chromatographed on a silica gel column (5/40, eluent THF–CCl_4 1:2). Yield 1.5 g (87%), mp 81-82°C. According to literature data mp 82°C [9].

5-(7-Nitro-1,4-benzodioxan-6-yl)isoxazoline (XIV). The reaction was carried out as described above except the reaction mixture was held at -27°C for 16 h. Mixture of nitro compound III (1.7 g, 7.8 mmol) and N_2O_4 (1.4 g, 15.6 mmol) after separation on a silica gel column (40/100, eluent petroleum ether–THF 3:2) yields 1.06 g (55%) of XIV; mp 142°C. PMR spectrum: 3.38 (2H, m, CH_2 isoxazole), 4.39 (4H, s, OCH_2CH_2O), 6.13 (1H, m, 5-H isoxazole), 7.09 (1H, t, 3-H isoxazole), 7.14 (1H, s, 5-H, Ar), 7.71 ppm (1H, s, 8-H, Ar). Mass spectrum: 250 (12, M), 249 (2, M - 1), 235 (9), 234 (14), 233 (74), 232 (18), 220 (29), 206 (100), 205 (39), 204 (20), 203 (24). Found, %: C 52.63; H 3.92; N 10.88. $C_{11}H_{10}N_2O_5$. Calculated, %: C 52.80; H 4.03; N 11.20.

5-(5,6-Dinitro-1,4-benzodioxan-7-yl)isoxazoline (XV) prepared by analogous method. Mixture of dinitro compound V (0.64 g, 2.4 mmol) in CH_2Cl_2 (5 ml) and N_2O_4 (0.45 g, 4.8 mmol) in CH_2Cl_2 (2 ml) held at -27°C for 24 h yielded after separation on a silica gel column (40/100, eluent ether–petroleum ether 5:1) 0.38 g (59%) of starting material (V), mp 131°C, and 0.23 g (79% calculated on the basis of V) of XV. PMR spectrum: 3.16 (1H, dd, J_1 = 6.0 Hz, J_2 = 1.84 Hz) and 3.66 (1H, dd, J_1 = 10 Hz, J_2 = 1.8 Hz, CH_2 isoxazoline); 4.48 (4H, br. s, OCH_2CH_2O); 5.73 (1H, m, 5-H isoxazoline); 7.07 (1H, s, 8-H, Ar); 7.24 ppm (1H, t, J = 1.8 Hz, 3-H of isoxazoline). Mass spectrum: 295 (10, M), 294 (6, M - 1), 265 (16), 251 (15), 250 (100), 249 (50), 248 (19), 236 (15), 235 (17), 234 (15), 221 (40), 220 (19). Found, %: C 44.54; H 2.86; N 14.01. $C_{11}H_9N_3O_7$. Calculated, %: C 44.75; H 3.07; N 14.23.

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