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BEHAVIOR OF 6-CYCLOPROPYL- AND 6-BROMO-7-CYCLOPROPYL-1,4-BENZODIOXANES UNDER ELECTROPHILIC SUBSTITUTION REACTION CONDITIONS

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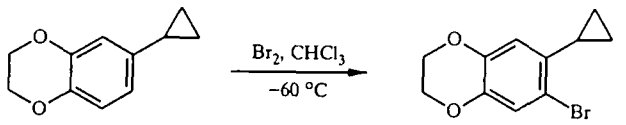
Bromination of 6-cyclopropyl-1,4-benzodioxane occurs with concerted orientation of the ethylenedioxy group and the cyclopropyl radical for the least sterically hindered position of the aromatic ring. Nitration of 6-bromo-7-cyclopropyl-1,4-benzodioxane does not lead to products of substitution of the hydrogen atom in the 5 or 8 position of the 1,4-benzodioxane, but rather to the nitrodebromination product: 7-nitro-6-cyclopropyl-1,4-benzodioxane. The anomalous behavior of the bromo-substituted benzodioxane is explained by the predisposition of the carbon atom bonded to the bromine toward ipso *attack by an electrophile.*

Electrophilic substitution reactions in a number of cyclopropyl-substituted 1,4-benzodioxanes have not been studied up to now; only quite recently [1] did we describe nitration of 6-cyclopropyl- and 6-(1-methyl)cyclopropyl-1,4-benzodioxanes for the first time. Moreover, determining whether it is possible to use the indicated reactions to synthesize functionally substituted cyclopropyl-1,4-benzodioxanes becomes important in connection with prospective study of their intramolecular transformations, cyclizations and rearrangements, such as have been found in a number of functionally substituted phenylcyclopropanes (see, for example, [1-4]).

In this paper, we present the results of bromination of 6-cyclopropyl-1,4-benzodioxane (I) and nitration of its bromo derivative II.

In principle, 6-cyclopropyl-1,4-benzodioxane (I) can be considered as an ether analog of 4-cyclopropylanisole, which we know [5] is brominated under such mild conditions as phenylcyclopropane (Br_2, $CHCl_3$, −65°C, no catalyst) and in this case the bromine atom in practice is only introduced into the aromatic ring of the substrate at the position determined by the methoxy group. It has been found that 6-cyclopropyl-1,4-benzodioxane I also easily reacts under the conditions used for 4-cyclopropylanisole; but in contrast to the latter, compound I is regioselectively brominated at the position corresponding to concerted orientation of the ether moiety and the cyclopropyl radical far from the ether group.



I II

The nature of the substitution in substrate I is easily established based on analysis of the aromatic part of the ^1H NMR spectrum of compound II: the presence of two singlets (6.61 and 7.21 ppm) with integrated intensity for each corresponding to a single proton unambiguously suggests that the bromine atom is introduced into the 7 position of the cyclopropylbenzodioxane I.

Generally speaking, the result of bromination of compound I is consistent with data on electrophilic substitution reactions in the 6-substituted 1,4-benzodioxane series. It follows that the electrophilic substituent introduced into the aromatic ring occupies the 7 position, regardless of the nature of the substituent located in the 6 position of the heterocycle [6]. Never-

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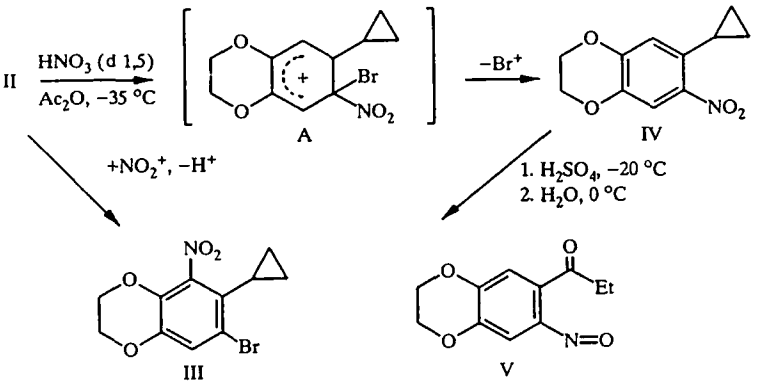
theless, it seems surprising that the bromine atom in practice is not introduced into the 5 position of substrate I, despite the concerted orientation of the ether moiety and a strong electron-donor substituent like the cyclopropyl radical.

Bearing in mind the specific *ortho*-directing effect of the cyclopropyl radical in nitration of phenylcyclopropane [7,8], and also the fact that upon nitration 2-bromophenylcyclopropane yields a significant amount of 2-bromo-6-nitrophenylcyclopropane [9], we hypothesized that nitration of the 6-bromo-substituted cyclopropylbenzodioxane II unambiguously leads to the corresponding 8-nitro derivative III (a system of interest to us in studying acid-catalyzed intramolecular rearrangement). But we found that in this case, the reaction proceeds in an anomalous fashion: the product of substitution of substrate II in the 8 position is generally not observed, but rather only 6-nitro-7-cyclopropyl-1,4-benzodioxane (IV) is formed as a consequence of the nitrodebromination reaction.



The structure of compound IV has been confirmed by comparing its physicochemical characteristics with those of a sample obtained earlier in [1] and by chemical reaction.

We know [10,11] that nitrodebromination rather often is accompanied by nitration of the *ortho*- or *para*-bromo-substituted alkylbenzenes and anisoles, and that it occurs via a step involving formation of the corresponding *ipso*-σ complexes expected for nitrodebromination. Most likely, even in our case nitrodebromination occurs through such complexes (A, see the scheme), and the yield of the end product of the reaction suggests facile formation of the indicated *ipso*-benzenonium ions (A) from compound II under the nitration conditions employed.

We should note that nitrodebromination in a number of 6-substituted 7-bromo-1,4-benzodioxanes has been observed only upon nitration of 6-bromo-7-ethyl-1,4-benzodioxane. In this case, the nitrodebromination product (6-nitro-7-ethyl-1,4-benzodioxane) was obtained in only 20% yield; the major reaction products in this case were 5- and 8-nitro-substituted 6-bromo-7-ethylbenzodioxanes [12]. In our opinion, comparison of the nitrodebromination results for 7-ethyl- [12] and 7-cyclopropyl-6-bromo-1,4-benzodioxanes is convincing evidence in favor of the idea that the cyclopropyl radical promotes electrophilic attack on the carbon atom of the aromatic ring of benzodioxane which is bonded to the halogen atom (*ipso* attack) to a significantly greater degree than the ethyl radical. It is interesting that under the same nitration conditions, the nitrodebromination product is not observed (at least not in appreciable amounts) from 2-bromophenylcyclopropane (a structural analog of compound II) [9].

EXPERIMENTAL

The IR spectra were taken on an IKS-22 spectrometer in Vaseline oil. The ^{1}H NMR spectra were obtained on Tesla BS-467 (60 MHz) and Varian VXR-400 spectrometers in $CDCl_3$; HMDS was used as the standard. TLC on Silufol plates was used to monitor the purity of the compounds obtained.

6-Cyclopropyl-1,4-benzodioxane (I) was obtained in 71% yield, as described in [1]; T_{bp} 138-139°C (8 torr), n_D^{20} 1.5615.

6-Bromo-7-cyclopropyl-1,4-benzodioxane (II). 5.9 g (0.037 moles) bromine in 30 ml chloroform was added slowly to a solution of 6 g (0.034 moles) 6-cyclopropyl-1,4-benzodioxane I in 45 ml chloroform cooled down to −60°C, maintaining that temperature. The reaction mixture was stirred for 3 h at −60°C and poured into a 3% solution of sodium sulfite. The colorless organic solution was separated, washed with water and a 3% K_2CO_3 solution and then again with water, and dried

with anhydrous Na_2SO_4. The solvent was evaporated off and the residue was distilled under vacuum. Obtained: 6.5 g compound II (65%), T_{bp} 130-132°C (2 torr), n_D^{22} 1.5883. ^1H NMR spectrum (400 MHz): 0.48-0.72 (4H, m) and 1.81-1.93 ppm (1H, m) for the cyclopropane protons; 4.23 (4H, s, OCH_2CH_2O); 6.61 (1H, s, Ar, 8-H); 7.21 ppm (1H, s, 5-H). Found, %: C 51.35; H 4.13; Br 31.78. $C_{11}H_{11}BrO_2$. Calculated, %: C 51.76; H 4.31; Br 31.37.

Nitration of 6-Bromo-7-cyclopropyl-1,4-benzodioxane (II). 1.9 g (0.03 moles) HNO_3 (*d* 1.5) was slowly added to 30 ml acetic anhydride at −35°C, the temperature was raised to −5°C, and the solution was held at that temperature for 30 min. The solution of acetylnitrate formed was cooled down to −35°C and 2.5 g (0.01 moles) compound II in 20 ml Ac_2O was added to it, maintaining the initial temperature constant. The reaction mixture was stirred for 2 h at −30°C and poured into a 10% solution of K_2CO_3. The reaction products were extracted with chloroform, then the extract was washed with water and dried with $CaCl_2$. After the solvent was evaporated, the residue was chromatographed on a column with Al_2O_3, 1:5 ether—petroleum ether as the eluent. Obtained: 1.6 g (72%) 6-nitro-7-cyclopropyl-1,4-benzodioxane (IV), T_{mp} 81°C [1]. No depression of the melting point was observed when a sample was mixed with an authentic sample.

6-Nitroso-7-propionyl-1,4-benzodioxane (V). 1.1 g (0.005 moles) compound IV was added slowly with stirring to 8 ml conc. H_2SO_4 cooled down to −20°C. The reaction mixture was stirred for 2 h at the same temperature and poured into water (60 ml) with ice (20 g). The amorphous precipitate was extracted with $CHCl_3$, the chloroform solution was washed with water and dried with $MgSO_4$ and, after the solvent was evaporated off, the residue was recrystallized from alcohol. Obtained: 0.68 g (62%) compound V, T_{mp} 119-120°C (decomp.). ^1H NMR spectrum (60 MHz): 1.14 (3H, t, $\underline{CH_3}CH_2$); 2.29 (2H, q, $CH_3\underline{CH_2}$); 4.14 (4H, s, OCH_2CH_2O); 6.41 (1H, s, Ar, 5-H); 7.16 ppm (1H, s, 8-H). UV spectrum: λ_{max} 742 nm (ε 34, N=O). Found, %: C 59.55; H 4.89. $C_{11}H_{11}NO_4$. Calculated, %: C 59.72; H 5.01.

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