THE FIRST THREE AROMATIC TRIBROMIDES OF THE [2.2]PARACYCLOPHANE SERIES

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From the reaction mixtures in the uncatalyzed polybromination of [2.2]paracyclophane by the action of excess Br_2 in CCl_4, there have been found along with the known products — 4,15- and 4,16-dibromo[2.2]paracyclophanes — two new aromatic tribromides of this series, which have been isolated in pure form: 4,12,15- and 4,15,16-tribromo[2.2]paracyclophanes. Special experiments demonstrated that the mixtures of these tribromides are formed as a result of competitive monobromination of 4,15-dibromo[2.2]paracyclophane; the 4,15,16-tribromo[2.2]paracyclophane, together with still another newly isolated isomer of this series — 4,8,12-tribromo[2.2]paracyclophane — is formed as a result of competitive monobromination of 4,16-dibromo[2.2]paracyclophane. As an explanation of the features of the orienting effect of substituents in these competing reactions, a rule was proposed: On the conventional orientation (from the electronic point of view) of entry of the bromine atom into the substituted ring (para > ortho > meta), a steric limitation is imposed on its attack in the pseudo-gem-position, owing to the bulky bromine atom that is transannularly positioned above it in the neighboring aromatic ring. The structures of all of the tribromides were established on the basis of elemental analyses, mass spectrometry, and ^1H NMR spectrometry (including PMR using the homonuclear Overhauser effect). The data obtained in this work indicate that the 4,12,15-tribromo[2.2]paracyclophane and 4,15,16-tribromo[2.2]paracyclophane are predecessors of the two tetrabromides previously obtained by Cram — 4,7,12,15- and 4,5,15,16-tetrabromo[2.2]paracyclophanes; and the 4,8,12-tribromo[2.2]paracyclophane is a possible predecessor of 4,8,12,16-tetrabromo[2.2]paracyclophane, which is unknown up to the present time.

Keywords: *[2.2]paracyclophane, dibromo[2.2]paracyclophane, tribromo[2.2]paracyclophane.*

Interest in the synthetic chemistry of [2.2]paracyclophane (**1**) has increased significantly in recent years. This is a two-layer aromatic system that is distinguished by interesting steric features and unusual electronic properties [1, 2]. Of the starting substances that are used in subsequent chemical transformations in this series, aromatic bromides are among the most important (see Scheme 1 depicting the principal derivatives of this type). Cram [3] has thus far described the following bromides: 4-bromo- (**2**), four dibromides derived from **2** — 4,12- (**3**), 4,15- (**4**), 4,16- (**5**), and 4,7-dibromo- (**6**); and two tetrabromides — 4,5,15,16- (**11**) and 4,8,12,16-tetrabromo[2.2]paracyclophane (**12**), obtained by dibromination of the corresponding dibromides **3-5**. With regard to the aromatic tribromides of the [2.2]paracyclophane series, not one of them had been described up to the present time, even though 4,12,15-tribromo[2.2]paracyclophane (**7**) appears to be the natural intermediate in the synthesis of the tetrabromide **10**, and 4,15,16-tribromo[2.2]paracyclophane **8** in the synthesis of the tetrabromide **11**. True when the dibromination of 4,16-dibromo[2.2]paracyclophane **5** by the action of Br_2 is carried out in the presence of Fe, Cram indicated that along with the main product — the tetrabromide **11** — traces of a tribromoaromatic derivative were formed; however, he did not determine the structure of this tribromide [3] (see Scheme 1 below).

In the course of our systematic studies of [2.2]paracyclophane and its heteroorganic derivatives [4-6], we turned our attention to the fact that in the uncatalyzed bromination of **1** with excess Br_2, the well-known dibromides **4** and **5** are accompanied by trace quantities of two new products, for which it was natural to postulate a tribromoaromatic structure. With

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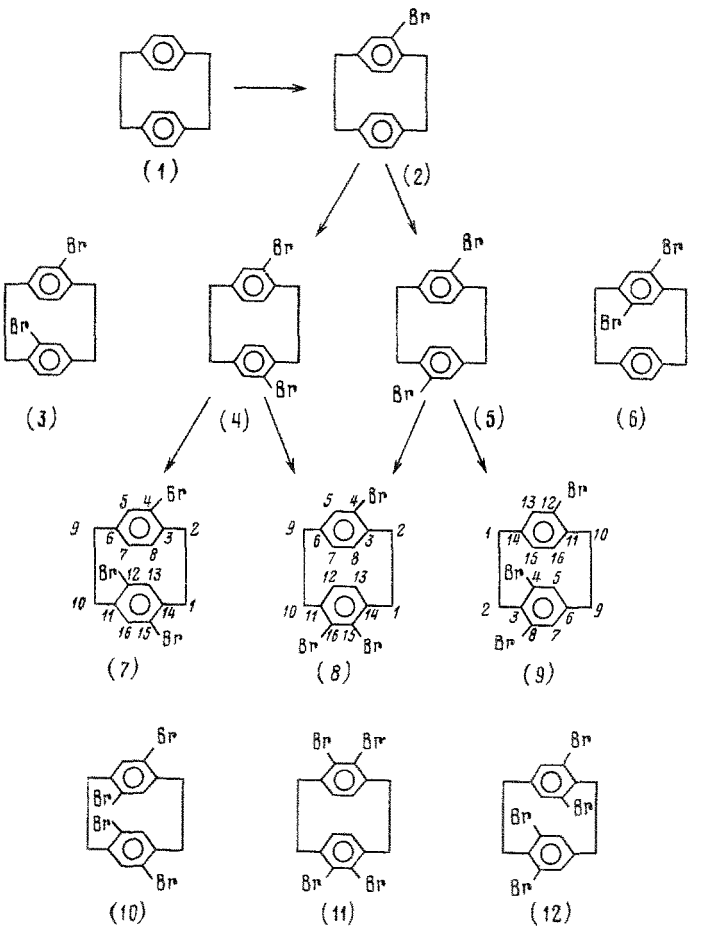
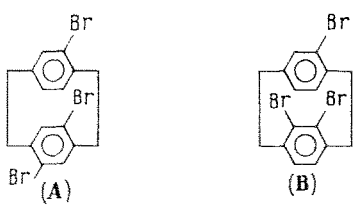
Scheme 1



the aim of confirming the proposed mechanism of bromination (see Scheme 1), in the present work we set ourselves the task of isolating these compounds in individual form and establishing their structures.

^{1}H Spectra of 4,12,15- (7) and 4,15,16-Tribromo[2.2]paracyclophane (8). Compound 7 and 8 were isolated and purified by column chromatography on silica gel. According to elemental analyses and mass-spectrometric and ^{1}H NMR spectrometric data (including the use of double homonuclear resonance and the nuclear Overhauser effect), it was established that 7 and 8 are isomeric tribromo derivatives of [2.2]paracyclophane.*

The main ^{1}H NMR spectral features that distinguish one of these isomeric tribromides from the other are the presence of a well-defined AB quartet of a pair of neighboring protons of the *ortho*-dibromo-substituted aromatic ring in compound 8, and individual singlet signals from two separated protons of the *para*-dibromo-substituted ring in 7.



The theoretically possible pair of 4,5,13- (B) and 4,7,13-tribromoaromatic (A) isomers, representing an alternative from the standpoint of completely analogous multiplicity, can be unambiguously eliminated from consideration when we take into account the mutual influence of atoms in these compounds on their chemical shifts, expressed in a very definite deshielding action (by 0.5-0.7 ppm) of all three of the Br atoms in this case on the aromatic (pseudo-*gem*) protons lying immediately below (or above) the bromine atoms in the neighboring rings (with regard to an analogous influence of Br and F in other

*Both of the compounds that were obtained are chiral; in the scheme, in the interest of conciseness, we have depicted their arbitrary enantiomers.

halocyclophanes; see [5, 7]). With this concerted effect, in the ABX spin systems of the monobromo-substituted rings of the two compounds that we obtained, the A and B components of the spectra proved to be deshielded for compound **8**, and the A and X components for compound **7**, whereas for the alternative structures (B and A) analogous downfield shifts should have been experienced by the signals of the X and B protons, respectively.

Homonuclear Overhauser Effect. We were also able to obtain structural information on these compounds by means of the homonuclear Overhauser effect (NOE), which made it possible for this layers [2.2]paracyclophane ligand, in a number of cases, to make an additional, reliable diagnosis of spin systems lying in the plane of any of the rings (intralayer interaction) and also those located in different rings of the molecule (interlayer interaction). With regard to intralayer interactions, here they are manifested very readily. For example, upon excitation (to complete saturation) of the ^{13}H proton in isomer **8** or the H^7 proton in isomer **7**, we were able to observe distinct NOEs for intralayer *ortho* protons that are adjacent to the irradiated protons (H^{12} and H^8, respectively). This observation, by the way, serves as additional proof that the singlet downfield signal with $\delta = 7.19$ that has remained without change for the second of these compounds pertain specifically to the Br atom located beneath the H^{13} proton. In diagnosing the corresponding interlayer interactions, however, certain complexities appear in connection with the closeness of the chemical shifts of the isolated pair of pseudo-*gem*-positioned protons of the two isomers, and also to their multiplicity, which is "unfavorable" from the standpoint of the NOE. Thus, in compound **8**, when attempting to irradiate the multiplet proton H^5 (doublet 6.55 ppm), we were not able to observe the expected interlayer interaction with the H^{12} proton, the same as that between the H^{16} proton and the multiplet proton H^7 (doublet of doublets with $\delta = 6.48$ ppm) upon irradiation of the latter in the isomer **7**. Nonetheless, we found that when the order of irradiation of the protons in this pair was changed, specifically that of the singlet, with an appropriate selection of the power of the transmitter in the proton decoupling channel in compound **7** with excitation of the singlet proton H^{16} ($\delta = 6.58$ ppm), the NOE could then also be observed (1%) for the interlayer pseudo-*gem*-positioned proton H^7, thus providing final proof of the chemical structure proposed for this isomer.

Paths of Formation of Tribromides 7, 8 and 4,8,12-Tribromo[2.2]paracyclophane (9). After establishing the structure of these isomeric compounds, the next logical question is whether they may be formed as intermediates in the processes of polybromination of the dibromo[2.2]paracyclophanes **4** and **5** that had been investigated previously by Cram [3] (Scheme 1). Since the tribromides **7** and **9** can be formed only from certain specific dibromides (either **4** or **5**, respectively), and the tribromide **8** can be formed at once from both of these dibromides, in order to resolve this problem, in the concluding stage of the present work we carried out model reactions of monobromination of the known individual dibromides **4** and **5**, on the assumption that the results of this study, as a supplement to the now purely chemical method, will prove not only the structure of compounds **7** and **8**, but also the paths of their formation. In investigating his reactions, Cram [3] used a catalyst (Fe), which could affect both the rate and the direction of the bromination processes; therefore, we carried out all of our model processes under analogous conditions, with the presence of 5% iron filings. After chromatographic separation of the product mixtures from these reactions, we found that upon bromination of both of the original dibromides (both **4** and **5**), only the tribromide **8** can be formed; this provides final proof of the chemical structure that we have proposed for **8**. With regard to the tribromide **7**, it is formed only upon bromination of the dibromide **4**, which also proves its structure.

It is interesting to note that in the course of bromination of the dibromide **5**, together with **8** we observed the formation of small quantities of another, previously undescribed aromatic tribromide of the [2.2]paracyclophane series, namely the compound **9**, which has bromine atoms in the 4,8,12 positions. The NMR spectral characteristics of the tribromide **9** fully support the above-stated basic principles (for the isomers **7** and **8**) of the spectral-structural assignments for this class of compounds (Scheme 2). The isolated pair of its pseudo-*gem*-positioned protons H^7 and H^{16} is found in a region corresponding to [2.2]paracyclophane, here undergoing a slight shift, characteristic for isomers **7** and **8**, in the downfield direction (by 0.06-0.15 ppm), owing to the influence of the *ortho*-bromine atom. For the three protons of the aromatic rings that are in the pseudo-*gem* position relative to bromine atoms, this shift is far more significant, so that it is easy to assign the well-defined AB quartet of the pair of protons of the *meta*-dibromo-substituted ring.

Orientation Effects in the Course of Monobromination of Dibromo[2.2]paracyclophanes: Electronic and Steric Factors. Many cases have now been reported of multiple entry of very diverse groupings (NO_2, Br, COR) into the aromatic rings of [2.2]paracyclophane systems in processes of consecutive electrophilic aromatic substitute of the S_EAr type. However, no success have been achieved in constructing a complete theory of orientation for such cases (see, for example, [8]), apparently because of the extremely complex balance of static and dynamic factors that are operative, owing to the influence of both the entering groups and those already present on the ring. In light of this background, compounds **4** and **5** that we investigated in the present work are today the only model objects for which all relationships of the reaction can be formulated

as an extremely simple but rather important rule, which we can state as follows: The orientation of processes of bromination of the regioisomeric 4,15-dibromo[2.2]paracyclophane (**4**) and 4,16-dibromo[2.2]paracyclophane (**5**), from the electronic point of view, is determined by the most ordinary relationships of electrophilic substitution of single-ring polysubstituted aromatic systems (*para* > *ortho* > *meta*), the only difference being that a substituent that is positioned transannularly in relation to the reacting ring provides quantitative steric blocking of an entering bromine atom in the position that is pseudo-*gem* in relation to it.* This rule has the effect that for the 4,15-isomer, the orientation of substitution has the order *para* > *ortho* (there is no substitution in the *meta* position); and for the 4,16-isomer, the order is *ortho* > *meta* (three is no substitution in the *para* position), since both the *meta* position in the first case and the *para* position in the second case are completely shielded by the pseudo-*gem* atom of bromine. From the electronic point of view, this form of orientation is fully consistent with theoretical concepts that were formulated previously in the work of Cram [8]; therefore, the set of data that we obtained indicates that the high-symmetry objects that we investigated are ideal for revealing in pure form the specific steric factor in processes of electrophilic substitution. Comparing our results with the previously observed contrary case [8] of preferential orientation of substitution in the pseudo-*gem* position, the rule that has been formulated will apparently be generalized in the future in that form in which it would be described as the "pseudo-*gem* rule."

The analysis of the first three aromatic tribromides of the [2.2]paracyclophane series that has been thus completed in the present work, in our opinion, can serve as weighty evidence that the reactions of dibromination of the dibromides **3** and **5** that were investigated by Cram [3], these reactions leading to the tetrabromides **10** and **11**, include the intermediate formation of the tribromides that we have isolated, **7** and **8**, respectively. With regard to the tribromide **9**, the fact that it has been found in the reaction products, even though in trace quantities, creates in principle the theoretical possibility of considering this tribromide to be a predecessor of 4,8,12,16-tetrabromo[2.2]paracyclophane (**12**), which has not yet been considered. We can assume, however, that the formation of such a tetrabromide cannot be at all facile, in view of the doubly unfavorable *meta* orientation of the substitution; and, if this compound were nonetheless recovered in reactions of dibromination of **5**, it would be only in trace quantities relative to the main isomer **11** that was obtained in [3].

EXPERIMENTAL

The ^{1}H NMR spectra were recorded in Bruker WP-200 SY (200 MHz) and Varian VXR-400 (400 MHz) instruments in $CDCl_3$ (internal standard TMS). EI mass spectra were obtained in a Kratos MS-890 instrument (70 eV).

Bromination of [2.2]Paracyclophane (1). To a suspension of 25 g (0.12 mole) of **1** in 350 ml of CCl_4, with vigorous stirring and heating, 115 g (0.72 mole) of Br_2 was added dropwise. The stirring was continued to 2 h until the rapid evolution of HBr had ceased and the original **1** no longer appeared in chromatographic tests of the reaction mixture. When the reaction was completed, the solvent was removed under vacuum, and the residue was washed with 50 ml of ethanol and air-dried. Yield of mixed polybromides 33.4 g.

Isolation and Purification of Aromatic Dibromides of the [2.2]Paracyclophane Series. An 11-g quantity of the mixed polybromides was treated successively with ether (solution A) and chloroform (solution B). After driving off the solvent from solution B and recrystallization of the dry residue from ethanol, obtained 1 g of **4**, mp 121-122°C (compare [3]: mp 123.5-125.5°C). From the chloroform in soluble residue, after two recrystallizations from dioxane, obtained 4.4 g of **5**, mp 252-253°C (compare [3]: 248.5-250°C).

Isolation and Purification of Aromatic Tribromides of the [2.2]Paracyclophane Series. After driving off the solvent from solution A, obtained 3.2 g of a mixture of polybromides. A 0.5-g quantity of this mixture was separated by column chromatography (SiO_2, pentane). Fractions were collected (5-7 ml), monitoring the course of the separation by TLC. The fractions with R_f 0.2, containing a single pure substance, were combined; the solvent was driven off, and the residue was recrystallized three times from EtOH. Obtained 0.05 g of **7**.

4,12,15-Tribromo[2.2]paracyclophane (7), mp 118-120°C. Found, %: C 42.51; H 2.98; Br 53.80. $C_{16}H_{13}Br_3$. Calculated, %: C 43.16; H 2.94; Br 53.87. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm; J, Hz): 3.1 m (8H, $-CH_2-CH_2-$); 6.48 d.d (1H, H^7, J = 1.6; J = 7.6); 6.58 s (1H, H^{16}), 7.17 d (1H, H^8, J = 8.0); 7.18 d (1H, H^5, J = 1.6); 7.19 s (1H, H^{13}). Mass spectrum, m/z (I_{rel}, %): 446 (20) $[M]^+$ 262 (20); 184 (100).

*In any detailed theoretical analysis of the problem, the possibility of homolytic contributions to the mechanisms of these processes should apparently be taken into account, and this is a separate analytical problem.

The fractions with R_f 0.18-0.20, containing two substances, were again separated under the same conditions, this time collecting 2-3 ml fractions. From the combined fractions with R_f 0.18, after driving off the solvent and recrystallizing from EtOH, obtained 0.1 g of **8**.

4,15,16-Tribromo[2.2]paracyclophane (8), mp 135.5-136.5°C. Found, %: C 43.78; H 3.34; Br 53.00. $C_{16}H_{13}Br_3$. Calculated, %: C 43.16; H 2.94; Br 53.87. ^{1}H NMR spectrum (δ, ppm; *J*, Hz): 3.1 m (8H, $-CH_2-CH_2-$); 6.49 d (1H, H^{12}, J = 7.6); 6.55 d (1H, H^5, J = 1.6); 6.92 d.d (1H, H^7, J = 1.6; J = 7.6); 6.98 d (1H, H^8, J = 7.6); 7.19 d (1H, H^{13}, J = 7.6). Mass spectrum, *m/z* (I_{rel}, %): 446 (22) $[M]^+$; 262 (35); 184 (100).

Bromination of 4,15-Dibromo[2.2]paracyclophane 4. To a solution of 0.25 g (0.685 mmole) of **4** and 5 ml of absolute CCl_4, 0.1 ml (0.312 g, 1.95 mmoles) of Br_2 and 0.05 g of Fe was added. The reaction mixture was stirred and refluxed for 1 h. After treatment as indicated above, from the fractions with R_f 0.20, after driving off the solvent and recrystallizing, obtained 0.04 g of **7**; from the fractions with R_f 0.18, after driving off the solvent and recrystallizing from EtOH, obtained 0.015 g of **8**, the spectral parameters of which completely matched those listed above for the reference samples. The reaction mixture also contained trace quantities of a fraction with R_f 0.30, apparently corresponding to a tetrabromoaromatic structure.

Bromination of 4,16-Dibromo[2.2]paracyclophane 5. To a suspension of 0.5 g (1.37 mmoles) of **5** in 10 ml of absolute CCl_4, 0.1 ml (0.312 g, 1.95 mmoles) of Br_2 and 0.05 g of Fe was added. The reaction mixture was stirred and refluxed for 10 h and then washed with water and a sodium carbonate solution. The organic layer was dried over $MgSO_4$. After driving off the solvent, the dry residue (0.46 g) was separated by column chromatography (SiO_2, 40-70°C petroleum ether). From the combined fractions with R_f 0.18, after driving off the solvent and recrystallizing from EtOH, obtained 0.15 g of **8**, the spectral parameters of which completely matched the values given above for the reference sample. From the fractions with R_f 0.24, after analogous treatment and recrystallization from EtOH, obtained 0.05 g of **9**.

4,8,12-Tribromo[2.2]paracyclophane (9). ^{1}H NMR spectrum (δ, ppm; *J*, Hz): 3.1 m (8H, $-CH_2-CH_2-$); 6.51 d (1H, H^{16}, J = 7.6); 6.58 d (1H, H^7, J = 1.6); 7.10 d.d (1H, H^{15}, J = 1.6; J = 8.0); 7.16 d (1H, H^5, J = 2.0); 7.17 d (1H, H^{13}, J = 1.6). Mass spectrum, *m/z* (I_{rel}, %): 446 (18) $[M]^+$; 262 (24); 184 (100).

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