BROMINE-SUBSTITUTED 1,2,3,4-TETRAHYDRO-4-METHYLSPIRO[QUINOLINE-2-CYCLOHEXANES]

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The bromination of 1,2,3,4-tetrahydro-4-methylspiro[quinoline-2-cyclohexane] has been carried out under various conditions. Dibromo and monobromo derivatives have been obtained; the monobromo derivatives were synthesized by cyclization of 1-allyl-1-bromophenylaminocyclohexanes.

A preparative method has been developed in our laboratory for the synthesis of 1,2,3,4-tetrahydro-4-methylspiro[quinoline-2-cycloalkanes] (I) [1, 2]. In the present communication we are describing the synthesis of bromine derivatives of compound I. In [3, 4], monobromo derivatives of tetrahydroquinoline were used as starting substances in syntheses of biologically active compounds.

It had been established previously that the main product of electrophilic bromination of compound I by N-bromosuccinimide in an acetic acid/methylene chloride system is 1,2,3,4-tetrahydro-6,8-dibromo-4-methylspiro[quinoline-2-cyclohexane] (II), which was obtained in a 40% yield. The total yield of 1,2,3,4-tetrahydro-4-methyl-6-bromo[quinoline-2-cyclohexane] and the corresponding 8-bromo derivative (III and IV) was 4% [2].

It could be assumed that protonation of the tetrahydroquinoline fragment of compound I by a strong acid would lead to deactivation of the aromatic ring, and this should favor the formation of monobromo derivatives. However, in the bromination of the spiro compound I by N-bromosuccinimide in a system consisting of 80% sulfuric acid and methylene chloride, we found that the dibromo derivative II is obtained in practically the same yield as in the system containing acetic acid. It may be that the free base of compound I is subjected to bromination, analogous to what takes place in the diazotization of primary aromatic amines.

![Diagram of bromine-substituted 1,2,3,4-tetrahydro-4-methylspiro[quinoline-2-cyclohexanes]](image-url)

II \( R = R' = Br \); III \( R = Br \); \( R' = H \); IV \( R = H \), \( R' = Br \)

When compound I is brominated by N-bromosuccinimide in carbon tetrachloride in the presence of azobisisobutyronitrile, no 1,2,3,4-tetrahydro-4-bromo-4-methylspiro[quinoline-2-cyclohexane] is formed. Instead, a mixture of equal quantities of the monobromo derivatives III and IV is obtained with a total yield of 66%. The spectral characteristics of the isomeric bromides III and IV, which were separated chromatographically, correspond to those reported in [2]. Apparently the action of bromosuccinimide, the same as that of ethyleneimines [5], results in N-bromination of compound I. The N-bromo derivative, as a result of a rearrangement similar to the Orton rearrangement [6], is converted to the monobromo derivatives III and IV.

The synthesis of monohalo derivatives of compound I has also been accomplished by means of an intramolecular alkylation reaction [1, 2]. The interaction of N-cyclohexylidene-p-bromo-, -o-bromo-, and -o-chloroanilines (V-VII) with allylmagnesium bromide results in the formation of 1-allyl-1-p-bromo-, -o-bromo-, and -o-chlorophenylaminocyclohexanes (VIII-X) in yields greater than 60%; these undergo cyclization in an acidic medium. Cyclization of the allylarylaminocyclohexane VIII proceeds cleanly with the formation of compound III in a 58% yield. Cyclization of compound IX gives a mixture of bromo derivatives, from which compounds III and IV have been recovered chromatographically (respective yields 19 and 27%), and also a mixture of 1,2,3,4-tetrahydro-4-methyl-5-bromo- and -7-bromospiro[quinoline-2-cyclohexanes] (XI and XII) in a 1:4 ratio with a total yield of 2%. According to PMR spectroscopic data, the cyclization of compound X proceeds unambiguously, forming 1,2,3,4-tetrahydro-4-methyl-8-chlorospiro[quinoline-2-cyclohexane] (XIII).

Here we must note that cyclization of the allylarylaminocyclohexane IX gives a 19% yield of the monobromo derivative III, in which the position of the bromine atom in the phenylene ring is different from that in the phenyl fragment of the original compound IX. Quite probably, an intermediate in the cyclization of compound IX is a cationic σ-complex that is formed as a result of ipso-attack of the carbon atom connected to the bromine atom by a carbocation that has appeared upon protonation of the allyl fragment of compound IX [7]. Upon decomposition of such σ-complexes, it is possible for bromine to split out from the sp3-hybridized ring carbon atom of the cation, a process that will take place more readily than splitting of the alkyl cation [8]; also, intramolecular migration of bromine (1,2-shift) may take place. In order to establish the path of decomposition of these σ-complexes, we have carried out the cyclization of a mixture of the allylarylaminocyclohexane IX and 1-allyl-1-phenylaminocyclopentane [1]. By means of chromatography/mass spectrometry, it has been established that this reaction yields a mixture of 1,2,3,4-tetrahydro-4-methylspiro[quinoline-2-cyclopentane] and bromo derivatives of spiro[quinoline-2-cyclohexanes] III, IV, XI, and XII. No bromine-substituted spiro[quinoline-2-cyclohexanes] were detected, and hence we can postulate intramolecular 1,2-shifts of the bromine in a σ-complex with the formation of the bromine-substituted III, IV, XI, and XII upon cyclization of compound IX.

**EXPERIMENTAL**

The IR spectra were recorded in a Specord IR-75 spectrometer (in a film) and a UR-20 spectrometer (in tablets with KBr). The PMR spectra were obtained in Bruker WP-80 and WM-400 instruments in CDCl3 solutions, with TMS as an internal standard. Mass spectra were measured in an MX-1303 instrument. The chromatographic/mass spectrometric studies were performed in a Finnigan MAT 4615 instrument with a SUPERINKOS automatic data processing system based on a QUEST 1600 computer, quartz capillary column with stationary liquid phase SPB-1 (50 m × 0.33 mm × 0.5 μm), linear flow velocity of helium carrier gas 20 cm/sec, with column temperature program as follows: 1 min at 50°C, then raised at 10°/min to 200°C and at 7°/min to 260°C. Column