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

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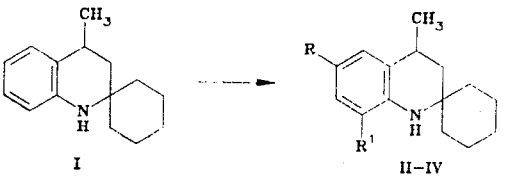
The bromination of 1,2,3,4-tetrahydro-4-methylspiro[quinoline-2-cyclohexane] has been carried out under various conditions. Dibromo and monobromo derivatives have been obtained; the monobromo derivatives were synthesized by cyclization of 1-allyl-1-bromophenylaminocyclohexanes.

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.



I II–IV

II $R=R^1=Br$; III $R=Br$; $R^1=H$; IV $R=H$, $R^1=Br$

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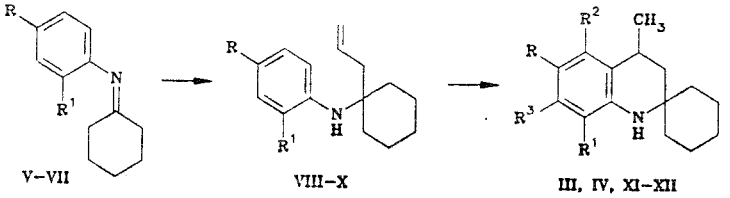
When compound I is brominated by N-bromosuccinimide in carbon tetrachloride in the presence of azobisisobutyronitrile, no 1,2,3,4-tetrahydro-4-bromo-4-methylspiro[quinoline-2-cyclohexane] is formed. Instead, a mixture of equal quantities of the monobromo derivatives III and IV is obtained with a total 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-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).



III, V, VIII R=Br; IV, VI, VII, IX—XIII R=H; IV, VI, IX R^1=Br; VII, X, XIII R^1=Cl; III, V, VIII, XI, XII R^1=H; III, IV R^2=R^3=H; XI R^2=Br; XII, XIII R^2=H; XI, XIII R^3=H; XII R^3=Br

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 sp^3-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-cylohexanes] 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 $CDCl_3$ 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

chromatography of the compounds was performed on silica gel, Grade L 5/40 μm. The course of the reaction was monitored by TLC on Silufol plates with heptane/ethyl acetate (5/1) as the eluent and iodine vapor as the developer.

Elemental analyses for C, H, N, and Br were in agreement with the calculated values.

1,2,3,4-Tetrahydro-4-methyl-6,8-dibromo(II)[6-bromo(III),8-bromo(IV)]spiro[quinoline-2-cyclohexanes] ($C_{15}H_{20}BrN$ and $C_{15}H_{19}Br_2N$). A. A 2-g quantity (0.0102 mole) of the spiro compound I, 1.5 g (0.0102 mole) of N-bromosuccinimide, and several crystals of azobisisobutyronitrile in 30 ml of CCl_4 was refluxed for 12 h. The residue was filtered off. The solvent was driven off from the filtrate, and the residual material was chromatographed in a column (h = 35 cm, d = 3 cm) with heptane/ethyl acetate (25/1) as the eluent. Initially recovered 0.5 g (33%) of compound IV, dark brown oil, R_f 0.83; IR spectrum 3415 cm^{-1} (NH); M^+ 293.295. At the end of chromatographing, recovered 0.9 g of the original compound I. The spectra of compounds III and IV were analogous to those described in [2].

B. To a solution of 1.8 (8.6 mmoles) of the spiro compound I in a mixture of 10 ml of methylene chloride and 10 ml of 80% sulfuric acid, 1.7 g (9.6 mmoles) of N-bromosuccinimide was added in portions. The mixture was refluxed for 10 h, then neutralized with a 25% ammonia solution, extracted with ether (2 × 50 ml), and dried with $MgSO_4$. The residue after driving off the solvents was chromatographed in a column (h = 35 cm, d = 2 cm) with heptane/ethyl acetate (10:1) as the eluent. Initially eluted 1.4 g (43%) of compound II, colorless crystals, mp 61-62°C. A mixed sample with a standard substance melted without depression. Subsequently recovered 0.54 g (21%) of compound III.

1-Allyl-1-(p-bromophenylamino)cyclohexane (VIII $C_{15}H_{20}BrN$). To allylmagnesium bromide obtained from 8.9 g (0.36 mole) of magnesium and 26.5 g (0.22 mole) of allylbromide in 200 ml of ether, 18.5 g (0.073 mole) of N-cyclohexylidene-p-bromoaniline (V) in 50 ml of ether was added at 10°C, and the mixture was then refluxed for 2 h, after which it was cooled and the product was decomposed with a saturated solution of ammonium chloride, extracted with ether (3 × 100 ml) and dried with $MgSO_4$. The residue after driving off the ether was vacuum-fractionated. Obtained 11.6 g (66%) of compound VIII, viscous yellow liquid, bp 160-165°C (8 mm Hg), n_D^{20} 1.5675. IR spectrum: 3370 cm^{-1} (NH). PMR spectrum: 1.46 (10H, m, cyclohexane protons); 2.46 (2H, d, CH_2); 4.87-5.10 (2H, m, CH_2=); 5.60-6.00 (1H, m, CH=); 6.47-7.32 ppm (4H, m, aromatic protons). Found: M^+ 294. Calculated: M 294.

1-Allyl-1-(o-bromophenylamino)cyclohexane (IX, $C_{15}H_{20}BrN$) was obtained similarly from 3.5 g (0.145 mole) of magnesium, 10.5 g (0.087 mole) of allyl bromide, and 7.2 g (0.06 mole) of the imine VI, with a yield of 5.8 g (68%). Viscous yellow liquid, bp 160-167°C (5 mm Hg), n_D^{20} 1.5720. IR spectrum: 3405 cm^{-1} (NH). PMR spectrum: 1.80 and 1.90-2.11 (10H, m, cyclohexane protons); 2.50 (2H, d, CH_2); 4.25 (1H, br.s, NH); 4.85-5.10 (2H, m, CH_2=); 5.52-6.03 (1H, m, CH=); 6.37-6.47 ppm (4H, m, aromatic protons). Found: M^+ 294. Calculated: M 294.

1-Allyl-1-(o-chlorophenylamino)cyclohexane (X, $C_{15}H_{20}ClN$) was obtained similarly from 6.9 g (0.29 mole) of magnesium, 20.6 g (0.17 mole) of allyl bromide, and 11.9 g (0.057 mole) of the imine VII, with a yield of 11.57 g (81%), bp 137-140°C (1 mm Hg); n_D^{20} 1.5610. PMR spectrum: 1.45 and 1.85-2.07 (10H, m, cyclohexane protons); 2.45 (2H, d, CH_2); 4.21 (1H, br.s, NH); 4.80-5.12 (2H, m, CH_2=), 5.50-6.02 (1H, m, CH=); 6.43-7.28 ppm (4H, m, aromatic protons). Found: M^+ 249.251. Calculated: M 249 (calculation based on ^{35}Cl isotope).

1,2,3,4-Tetrahydro-4-methyl-6-bromo(III)[8-bromo(IV),5-bromo(XI),7-bromo(XII)]spiro[quinoline-2-cyclohexanes]. A. A solution of 6.0 g (0.02 mole) of compound VIII in 20 ml of concentrated H_2SO_4 was heated for 6 h at 70-80°C, after which it was cooled, neutralized with a 25% ammonia solution, and extracted with ether (3 × 50 ml), and the ether extract was dried over $MgSO_4$. The residue after driving off the ether was chromatographed in a column (h = 48 cm, d = 2.5 cm) with heptane as the eluent. Obtained 4.1 g (58%) of compound III.

B. By an analogous cyclization of 5.8 g (0.02 mole) of compound IX, the following compounds were recovered chromatographically: 1.6 g (27.4%) of compound IV, 1.1 g (18.8%) of compound III, and 0.1 g (~2%) of a mixture of compounds XI and XII (according to PMR spectrum, a 1/4 mixture).

1,2,3,4-Tetrahydro-4-methyl-8-chlorospiro[quinoline-2-cyclohexane] (XIII, $C_{15}H_{20}ClN$). The cyclization of compound X was performed by the same method used for the cyclization of compounds VIII and IX. From 11.57 g (0.046 mole) of compound X, obtained 5.18 g (45%) of the spiro compound XIII, viscous yellow liquid, bp 171-175°C (8 mm Hg), n_D^{20} 1.5720. PMR spectrum: 1.30 (3H, d, 4-CH_3); 1.50 (10H, br.s, cyclohexane protons); 2.92 (1H, m, 4-H); 4.62 (1H, br.s, NH); 6.52 (1H, t, 7-H); 7.00-7.17 ppm (2H, m, 5-H and 6-H). Found: M^+ 249.251.

Calculated: M 249 (calculation based on ^{35}Cl isotope).

Cyclization of 1-Allyl-1-phenylaminocyclopentane and Compound IX. A mixture of 1.9 g (0.064 mole) of compound IX and 1.4 g (0.069 mole) of 1-allyl-1-phenylaminocyclopentane in 8 ml of concentrated H_2SO_4 was heated for 6 h at 70-80°C. The reaction mixture was worked up in the same manner as in the synthesis of compounds XI and XII. The residue (2.6 g) was chromatographed in a column with No. II activated alumina to remove resinous substances. The fractions that were recovered were analyzed by chromatography/mass spectrometry.

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