QUININDINES

V.* CHLORINATION OF 2,3-POLYMETHYLENEQUINOLINES WITH PHOSPHORUS PENTACHLORIDE

L. E. Kholodov, N. M. Merzlyakova,
N. P. Kostyuchenko, and M. N. Shchukina

UDC 547.836.3:542.944

β-Quinindane and tetrahydroacridine derivatives are chlorinated at the methylene groups of the hydrogenated ring under the influence of phosphorus pentachloride. Two, three, or five hydrogen atoms are replaced by chlorine, depending on the substituent in the 9 position and the size of the polymethylene chain. The structures of the compounds obtained were confirmed by IR, UV, and PMR spectra.

We previously described several reactions in the β-quinindane series with respect to the active 3 position [1]. It was of interest to study the halogenation of compounds of this series. It was observed that the methylene groups of β-quinindane are chlorinated by PCl_5. For comparison, similar reactions were carried out for 1,2,3,4,-tetrahydroacridine derivatives.

The following compounds were subjected to reaction with PCl_5: β-quinindane (I), 1,2,3,4-tetrahydroacridine (II), β-quinindane-9-one (IIIa), 1,2,3,4-tetrahydro-9-acridone (IIIb), and β-quinindane- and 1,2,3,4-tetrahydroacridine-9-carboxylic acids (IVa and IVb).

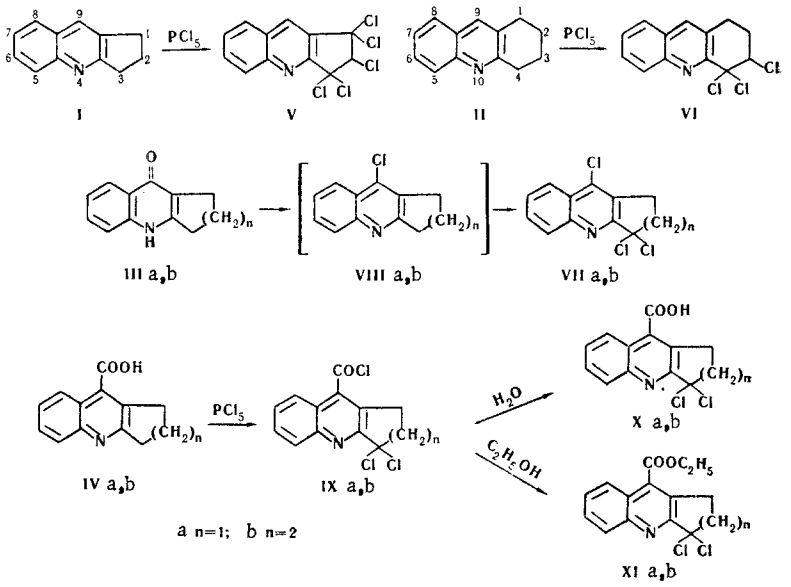
Excess PCl_5 in phosphorus oxychloride chlorinates I to form 1,1,2,3,3-pentachloro-β-quinindane (V). Only three hydrogen atoms are replaced by chlorine during the chlorination of compound II under similar conditions, and 3,4,4-trichloro-1,2,3,4-tetrahydroacridine (VI) is obtained.

IIIa and IIIb form 3,3,9-trichloro-β-quinindane (VIIa) and 4,4,9-trichloro-1,2,3,4-tetrahydroacridine (VIIb), respectively, by reaction with excess PCl_5. The reaction proceeds through a step involving formation of 9-chloro derivatives (VIII), which can be isolated if the reaction is interrupted at the initial stage.

The acid chlorides of the starting acids are initially formed during the chlorination of IVa and IVb with excess PCl_5, followed by the formation of their dichloro derivatives, IXa and IXb. In the case of IVa, 3,3-dichloro-β-quinindane-9-carboxylic acid (Xa) was isolated by treatment of the reaction mass with water, while, in the case of IVb, the major product (53% yield) is the acid chloride of 4,4-dichloro-1,2,3,4-tetrahydroacridine-9-carboxylic acid (IXb), and 4,4-dichloro-1,2,3,4-tetrahydroacridine-9-carboxylic acid (Xb) itself is formed in 12% yield. While acid chloride IXa, which is obtained from IVa after removal of excess reagent and solvent, very readily reacts with alcohol to form ethyl 3,3-dichloro-β-quinindane-9-carboxylate (XIa), the acid chloride of Xb is converted to the corresponding ethyl ester of XIb only after a 5-day reaction with alcohol.

*See [10] for communication IV.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 91-95, January, 1971. Original article submitted June 2, 1969.



The structures of the products isolated were confirmed by spectral data. In comparison with the UV spectra of the starting compounds, in the UV spectra of the chlorination products one observes a small bathochromic shift (5-8 nm), the fine structure of the spectrum decreases to a significant degree, and the ratio of the intensities of the individual bands also changes. The absorption of the chloro derivatives of the β-quinindane series was ~20-30% more intense and was shifted 3-5 nm to the shorter-wave region as compared with the analogous compounds of the tetrahydroacridine series.

Two broad bands at 1920 and 2540 cm^{-1} and two very intense bands at 1730 and 1230 cm^{-1} are observed in the IR spectrum of 3,3-dichloro-β-quinindane-9-carboxylic acid (Xa); these bands are characteristic for quinoline- and pyridinecarboxylic acids, and their presence is explained [2] by a strong intermolecular hydrogen bond of the $-COOH\cdots N\lessgtr$ type of even by a zwitterion structure. The absorption of the ester carbonyl in the IR spectra of esters XIa and XIb is observed at 1728 cm^{-1} (XIa) and 1732 cm^{-1} (XIb).

The presence of a very intense band at 1818 cm^{-1}, which should be ascribed to the absorption of the carbonyl in the COCl group, in the IR spectrum of XIb turned out to be important to establish its structure.

The PMR spectra of the reaction products were decisive for determining the site at which chlorine substitution occurred. The PMR spectra of trichlorides VIIa and VIIb are similar in the region of aromatic proton absorption: the signals of the $C_{(5)}$ and $C_{(8)}$ protons, which are deshielded by the nitrogen and chlorine atoms, respectively, have close δ values and give, as a result of superimposition of two doublets, a split triplet centered at 8.20 ppm for VIIa (in $CDCl_3$) and 8.39 ppm for VIIb (in CCl_4). The signals from the $C_{(6)}$ and $C_{(7)}$ protons are observed as a symmetrical multiplet, centered at 7.70 ppm for VIIa and 7.86 ppm for VIIb. A narrow, symmetrical multiplet (four protons), formed by the $C_{(1)}$ and $C_{(2)}$ methylene protons (a system of the AA'BB' type) is observed in the spectrum of VIIa at 3.18 ppm. The spectrum of VIIb is more complex; it consists of a regular triplet at 3.11 ppm, a distorted triplet at 2.97 ppm, and a complex multiplet centered at 2.29 ppm; all three signals have the same relative intensity of two proton units. The signals were assigned on the basis of the fact that the $C_{(1)}$ protons are more firmly attached because of the proximity of the aromatic ring, and the signals of these protons should therefore be subject to more complex splitting than the signals from the $C_{(3)}$ protons, which are averaged out as a result of the comparatively facile inversion of the ring. The following assignment is then possible: the regular triplet is due to the $C_{(3)}$ protons, the distorted triplet is due to the $C_{(1)}$ protons, while the multiplet can be ascribed to the $C_{(2)}$ protons, the signals of which are split by both the $C_{(1)}$ and $C_{(3)}$ protons.

The aliphatic portion of the PMR spectrum of acid chloride IXb (in CCl_4) is similar to the spectrum of trichloride VIIb: a triplet from the $C_{(3)}$ protons (3.08 ppm), with a (partially superimposed on it) multiplet from the $C_{(1)}$ proton, centered at 2.97 ppm, and, at stronger field, a multiplet from the $C_{(2)}$ protons centered at 2.21 ppm. However, differences are observed in the aromatic portion of the spectrum: the COCl group in IXb deshields the proton in the 8 position to a lesser extent than the chlorine atom attached to $C_{(9)}$ in VIIb, so that this proton has a chemical shift close to the chemical shifts of $C_{(6)}$ and $C_{(7)}$ protons; as a result, all three protons give a broad, weakly split multiplet at 7.69 ppm.

The PMR spectrum of pentachloride V contains a doublet at 8.21 ppm [$C_{(5)}$ proton], a singlet at 8.48 ppm [$C_{(9)}$proton], a multiplet (three protons) from 7.52-6.98 ppm [$C_{(6)}$, $C_{(7)}$, and $C_{(8)}$ protons], and a singlet (one proton) at 4.51 ppm. This sort of spectrum is unambiguous evidence that all five chlorines in V are located in the five-membered ring. The position of the remaining unsubstituted proton cannot be unambiguously resolved on the basis of the spectrum. However, the strong deshielding of the $C_{(9)}$ proton, the signal of which in the spectrum of β-quinindane is superimposed on the multiplet signal of the aromatic protons but, in V, stands out from the latter by more than 0.5 ppm, may be evidence in favor of the fact that two chlorine atoms are situated at the neighboring position [at $C_{(1)}$]. Considering that chlorination primarily proceeds at the 3 position, it may be supposed that the unsubstituted proton is attached to the $C_{(2)}$ atom. The position of the signal of the single proton (4.55 ppm) agrees with this assumption. A chemical shift of 2.82 ppm is observed for the protons in the 1 position in β-quinindane, compared with 1.98 ppm in the 2 position; if one considers only the deshielding effect of chlorine on the same atom as the proton of interest to us, the chemical shift of this proton when it is attached to $C_{(1)}$ should be of the order of 5.3 ppm (the shielding constant for chlorine is 2.5 ppm), as compared with 4.5 ppm when it is attached to $C_{(2)}$; the latter value is close to the experimental value.

Signals of all five aromatic protons (δ_5 8.13 ppm, doublet; δ_9 7.83 ppm, singlet; the $C_{(6)}$, $C_{(7)}$, and $C_{(8)}$ protons form a multiplet from 7.2-7.7 ppm) are also observed in the PMR spectrum of trichloride VI. It is obvious that, as in all of the other compounds, the protons in the α position [attached to $C_{(4)}$] for trichloride VI were replaced by chlorine atoms. Judging from the spectrum, the third chlorine atom is in the 1 or 3 positions but not in the 2 position, since the signal of the methine proton (δ 4.85 ppm) is split by only two protons (the X part of ABX, J=7 Hz, J'=3 Hz). However, since first the α-methylene group and then the neighboring β-methylene group are subjected to chlorination [3] and bromination [4] during the halogenation of tetralin, it can be assumed that 3,4,4-trichloro derivative VI is formed in the chlorination of 1,2,3,4-tetrahydroacridine (II). The signals of the four methylene protons in VI give little information, since they are manifested in the spectra as a very strongly split multiplet from 2.1-3.6 ppm.

The purity of all of the compounds obtained (except acids Xa and Xb and acid chloride IXb) was confirmed by thin-layer chromatography on aluminum oxide.

EXPERIMENTAL

3,3,9-Trichloro-β-quinindane (VIIa). A mixture of 0.50 g (2.7 mmole) of quinindan-9-one (IIIa) [5], obtained by the condensation of aniline with ethyl α-cyclopentanone carboxylate, 6 g (28 mmole) of phosphorus pentachloride, and 2.5 ml of phosphorus oxychloride was heated at 120-130° for 45 min until all solids dissolved. It was then cooled, poured over ice, and neutralized with 22% ammonium hydroxide. The resulting precipitate was filtered and washed repeatedly with water to give 0.71 g (94%) of a product with mp 130-131° [from benzene-hexane (1:3)] and R_S 2.37.* UV spectrum (alcohol), λ_{max}, nm (log ε): 238 (4.59), 263 (4.05), 300 (3.77), 310 (3.75, shoulder), 325 (3.58). Found %: C 52.5; H 2.7; Cl 38.8. $C_{12}H_8Cl_3N$. Calc. %: C 52.9; H 2.9; Cl 39.0.

4,4,9-Trichloro-1,2,3,4-tetrahydroacridine (VIIb). A mixture of 1 g (5 mmole) of 1,2,3,4-tetrahydroacrid-9-one (IIIb) [6] (obtained by condensation of anthranilic acid with cyclohexanone), 5 ml of phosphorus oxychloride, and 12 g (57 mmole) of PCl_5 was heated and worked up in the same way as the reaction used to obtain VIIa to give 1.32 g (92%) of a product with mp 119° (from alcohol) and R_S 2.41. UV spectrum (alcohol): 237 (4.69), 255 (3.45), 294 (3.64), 302 (3.65), 315 (3.59), 329 (3.47). Found %: C 54.7; H 3.6; Cl 36.8. $C_{13}H_{10}Cl_3N$. Calc. %: C 54.5, H 3.5; Cl 37.1.

9-Chloro-β-quinindane (VIIIa). A mixture of 0.5 g (2.7 mmole) of quinindan-9-one (IIIa), 5 ml of phosphorus oxychloride, and 6.0 g (28 mmole) of PCl_5 was heated at 120-130° for 15 min and worked up as in the case of VIIa. The yield of VIIIa after crystallization from hexane was 0.45 g (80.5%) of a product with mp 69-70° (70° [7]). It was identical to an authentic sample of 9-chloro-β-quinindane.

3,3-Dichloro-β-quinindane-9-carboxylic Acid (Xa). A mixture of 1 g (4.9 mmole) of β-quinindane-9-carboxylic acid (IVa) [8], 5 ml of phosphorus oxychloride, and 12 g (57 mmole) of PCl_5 was heated at 120-130° for 1.5 h, after which the reaction mixture was cooled and poured over ice. The precipitated Xa was filtered rapidly and washed with a small amount of water to give 0.71 g (50%) of Xa, which decomposed at ~180° without melting (from ethyl acetate). UV spectrum (alcohol): 240 (4.63); 303 (3.72); 315 (3.74); 324 (3.73, shoulder). Found %: C 55.5; H 3.2; Cl 25.3. $C_{13}H_9Cl_2NO_2$. Calc. %: C 55.3; H 3.2; Cl 25.1.

*Here and elsewhere chromatography was carried out in a thin layer of activity II aluminum oxide with benzene as the solvent and development by iodine vapors. The comparison substance was β-quinindane (I) with R_f ~ 0.30.

Ethyl 3,3-Dichloro-β-quinindane-9-carboxylate (XIa). A mixture of 5.0 g (24.5 mmole) of IVa, 30 ml of phosphorus oxychloride, and 38 g (181 mmole) of PCl_5 was heated at 120-130° for 1.5 h. It was then cooled, the calculated amount of water for conversion of excess phosphorus pentachloride to phosphorus oxychloride was added, the oxychloride was removed by vacuum distillation to dryness, and 25 ml of absolute ethanol and (after 30 min) 100 ml of water were added. The resulting oil was separated, dissolved in ether, and dried with $MgSO_4$. After distillation of the solvent, the residue was triturated with hexane to give 3.5 g (40%) of a product with mp 81-81° (from hexane) and R_S 1.96. UV spectrum (alcohol): 245 (4.50); 323 (3.82); 328 (3.83). Found %: C 57.8; H 4.1; Cl 22.9. $C_{15}H_{13}Cl_2NO_2$. Calc. %: C 58.1; H 4.2; Cl 22.9.

1,1,2,3,3-Pentachloro-β-quinindane (V). This compound, in analogy with Xa, was obtained from 1.0 g (5.9 mmole) of β-quinindane [9], 5 ml of phosphorus oxychloride, and 12 g (57 mmole) of PCl_5. The reaction time was 3 h. The yield of a product with mp 148-149° (from hexane) and R_S 2.51 was 0.35 g. UV spectrum (alcohol): 246 (4.34), 264 (4.22), 298 (4.75), 328 (3.34). Found %: C 42.6; H 1.9; Cl 51.6. $C_{12}H_6Cl_5N$. Calc. %: C 42.4; H 1.8; Cl 52.0.

3,4,4-Trichloro-1,2,3,4-tetrahydroacridine (VI). A mixture of 1.0 g (5.4 mmole) of tetrahydroacridine (II) [9], 5 ml of phosphorus oxychloride, and 12 g (57 mmole) of PCl_5 was heated at 120-130° for 3 h. It was then cooled, poured over ice, extracted with ether, and dried with $MgSO_4$. The solvent was removed by vacuum distillation to give 0.82 g (50%) of a product with mp 108-110° (from alcohol). This product depressed the melting point of trichloride (VIIb) and had R_S 2.06. Found %: C 54.6; H 3.8; Cl 36.8. $C_{13}H_{10}Cl_3N$. Calc. %: C 54.5; H 3.5; Cl 37.1.

Reaction of 1,2,3,4-Tetrahydroacridine-9-carboxylic Acid (IVa) with Phosphorus Pentachloride. A mixture of 5 g (24 mmole) of 1,2,3,4-tetrahydroacridine-9-carboxylic acid [9], 25 ml of phosphorus oxychloride, and 50 g (236 mmole) of PCl_5 was heated at 120-130° for 1.5 h, cooled, and poured over ice. The resulting precipitate was filtered, washed with water, and recrystallized from a small amount of acetonitrile to give 4.1 g (53%) of the acid chloride of 4,4-dichloro-1,2,3,4-tetrahydroacridine-9-carboxylic acid (IXb) with mp 106-107° (dec., from hexane). Found %: C 53.4; H 3.2; Cl 33.9. $C_{14}H_{10}Cl_3NO$. Calc. %: C 53.4; H 3.2; Cl 33.8. UV spectrum (hexane): 241 (4.50), 308 (3.62), 319 (3.67), 331 (3.63).

The insoluble material during the crystallization in acetonitrile was 4,4-dichloro-1,2,3,4-tetrahydroacridine-9-carboxylic acid (Xb) and was obtained in a yield of 0.9 g (12%) and had mp 245-246° (dec., from acetone). Found %: C 56.7; H 4.0; Cl 23.8. $C_{14}H_{11}Cl_2NO_2$. Calc. %: C 56.8; H 3.7; Cl 24.0.

Ethyl 4,4-Dichloro-1,2,3,4-tetrahydroacridinecarboxylate (XIb). A suspension of 0.5 g of the acid chloride of 4,4-dichloro-1,2,3,4-tetrahydroacridinecarboxylic acid (IXb) in 5 ml of absolute ethanol was allowed to stand for 5 days in the dark (until everything had completely dissolved), and the alcohol was removed by vacuum distillation to give 0.36 g (71%) of XIb with mp 92-93° (from hexane) and R_S 1.97. Found %: C 59.3; H 4.9; Cl 21.9. $C_{16}H_{15}Cl_2NO_2$. Calc. %: C 59.3; H 4.7; Cl 21.9.

The IR spectra of mineral oil suspensions of the compounds were obtained with a UR-10 spectrometer. the UV spectra were obtained with a Hitachi (Japan) recording spectrophotometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer (JEOL, Japan) with an operating frequency of 100 MHz; solutions in carbon tetrachloride or deuterochloroform were used with hexamethyldisiloxane as the internal standard; the chemical shifts were converted relative to tetramethylsilane.

LITERATURE CITED

1. L. E. Kholodov and V. G. Yashunskii, Khim. Geterotsikl. Soedin., 1530 (1970).
2. K. Nakanishi, Infrared Spectra and Structure of Organic Compounds [Russian translation], Moscow (1965), p. 196.
3. I. Braun and G. Kirschbaum, Ber., 54, 602, 617 (1921).
4. B. K. Blount, J. Chem. Soc., 553 (1933).
5. B. K. Blount, W. H. Perkin, and S. G. Plant, J. Chem. Soc., 1975 (1929).
6. H. Tiedke, Ber., 42, 624 (1909).
7. B. K. Blount and S. G. Plant, J. Chem. Soc., 376 (1937).
8. L. E. Kholodov, G. P. Syrova, V. G. Yashunskii, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., 78 (1970).
9. W. Borsche, Ann., 377, 120 (1910).
10. I. F. Tishchenkova, L. E. Kholodov, and V. G. Yashunskii, Khim. Geterotsikl. Soedin., 87 (1971).