SYNTHESIS AND PROPERTIES OF 6-ALKOXYMETHYLPHENANTHRIDINES

V. N. Antonova and É. R. Zakhs

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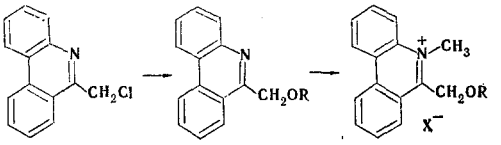
6-Alkoxy(aroxy)methylphenanthridines were obtained from 6-chloromethylphenanthridine. The basicities of the former are considerably lower than the basicity of 6-methylphenanthridine and 0.5 pK_a unit higher than the basicity of 6-chloromethylphenanthridine. The ease of quaternization of the compounds obtained is determined by the magnitude of the basicity.

It is known that the protons of the methyl group of 6-methylphenanthridine are quite labile [1]. This compound undergoes reaction with aldehydes in the presence of zinc chloride to give styryl derivatives [2]. At the same time, we observed that 6-ethyl- and 6-benzylphenanthridines and their quaternary salts do not react with aldehydes. The inertness of these compounds and of the analogous α-alkylpyridines [3] is apparently due to steric factors. In this connection, it seemed of interest to investigate the reactivity of 6-alkoxymethylphenanthridine derivatives, since the electronegative OR groups might considerably increase the lability of the hydrogen atoms of the adjacent methylene group. Of these compounds, only the phenoxy derivative, obtained by the action of phenoxyacetyl chloride on 2-aminodiphenyl and subsequent cyclization of the resulting amide [4], is described in the literature. However, this method is unsuitable for the preparation of a series of 6-alkoxymethylphenanthridines. To synthesize such compounds, we selected 6-chloromethylphenanthridine (I) [5, 6] as the starting material. Chlorine is smoothly replaced by OAlk (OAr) groups during the action of sodium alkoxides on I.



I II-IV V, VI

II, V R = CH_3; III, VI R = C_2H_5; IV R = C_6H_5

The ether group of II-IV is detected in the IR spectra from the absorption at ~1080-1100 cm^{-1} (ν_{COR}). The UV spectra of 6-alkoxymethylphenanthridines (II-IV) are almost independent of the nature of R in the ether group and are very similar to the spectra of 6-chloromethyl- (I) and 6-methylphenanthridine. The presence of absorption maxima at 250, 273 (shoulder), 292-295, 330-335, and 347-351 nm (log ε 4.8, 4.1-4.2, 3.85-3.95, 3.3, and 3.2-3.3, respectively) is characteristic for alcohol solutions of them.

Compounds II-IV are bases and can be isolated as the perchlorates, iodides, and picrates. Because of the electronegativity of the OR group, one might have expected a decrease in the basicity of II-IV relative to 6-methylphenanthridine and difficulty in the preparation of quaternary salts. In fact, the pK_a values of II and III (2.8 and 2.5, respectively, in 95% alcohol) proved to be considerably lower than for 6-methylphenanthridine (4.48 in 50% alcohol [7]) and somewhat higher than for I (2.0 in 95% alcohol). In accordance with this, the quaternization of I-III proceeds with greater difficulty than that of 6-methylphenanthridine. Of course, both dimethyl sulfate in various solvents and methyl p-toluenesulfonic acid can be used to obtain the quaternary salts of the 6-alkoxymethyl derivatives (V, VI). However, we were able to quaternize I only by means of a stronger methylating agent – methyl o-nitrobenzenesulfonate [8]. The quaternary salts of

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phenanthridine derivatives I-III were isolated as the perchlorates (V-VII). The PMR spectral data confirm their structure. Singlets of the protons of the $N-CH_3$ group at 4.5-4.9 ppm are observed in solutions of V-VII in trifluoroacetic acid.

It is known that 1-ethyl-2-alkoxymethylbenzothiazolium salts react with aldehydes in alcohol solution in the presence of piperidine to give styryls [9]. However, quaternary salts V-VII did not react under these conditions.

EXPERIMENTAL

2-Chloroacetamidodiphenyl [R_f 0.43 in a CCl_4–ether (1:1) system*] and 6-chloromethylphenanthridine (I, R_f 0.63 in the same system) were obtained via the method in [5].

6-Methoxymethylphenanthridine (II). A solution of 0.97 g (4.3 mmole) of I in 50 ml of methanol was added with stirring to a solution of sodium methoxide, obtained from 0.92 g (40 mg-atom) of sodium in 50 ml of methanol, after which the mixture was refluxed for 5 h. The methanol was removed by distillation, and 20-25 ml of water was added. Trituration gave crystals of II, which were washed with water and air dried to give 0.75 g (77%) of II with mp 75-76° (from petroleum ether). The product was soluble in ether, acetone, and CCl_4, insoluble in water, and had R_f 0.6 (chloroform). PMR spectrum in CCl_4, δ, ppm: 3.5 (CH_3), 5.0 (CH_2); in CF_3COOH: 3.95 (CH_3), 5.53 (CH_2). Found: C 80.6; H 5.9; N 5.9%. $C_{15}H_{13}NO$. Calculated: C 80.6; H 5.9; N 6.2%. Addition of an aqueous solution of $NaClO_4$ to a hydrochloric acid solution of II gave the perchlorate with mp 198-207° [dec., from water (1:10)]. Found: N 4.4%. $C_{15}H_{13}NO \cdot HClO_4$. Calculated: N 4.4%. The hydriodide with mp 197-198° (dec.) was similarly obtained. Found: N 4.5%. $C_{15}H_{13}NO \cdot HI$. Calculated: N 4.1%. Reaction of II with picric acid in benzene gave the picrate with mp 134-135° (from water). Found: N 12.4%. $C_{15}H_{13}NO \cdot C_6H_3N_3O_7$. Calculated: N 12.4%.

6-Ethoxymethylphenanthridine (III). A solution of 1.56 g (6.9 mmole) of I in 20 ml of absolute ethanol was added to a solution of sodium ethoxide, obtained from 0.73 g (32 mg-atom) of sodium and 50 ml of absolute ethanol, and the mixture was refluxed for 5 h and cooled. The precipitated NaCl was removed by filtration, and III was isolated as in the case of II to give 1.12 g (69%) of III with mp 47° (from petroleum ether). The product was readily soluble in ether, acetone, and CCl_4, insoluble in water, and had R_f 0.6 (chloroform), 0.89 [CCl_4–ether (1:1)]. PMR spectrum in CCl_4, δ, ppm: 1.1 (triplet, J = 7 Hz, CH_3), 3.5 (quartet, J = 7 Hz, CH_2), 5.0 ($ArCH_2O$). Found: C 81.1; H 6.4; N 5.9%. $C_{16}H_{15}NO$. Calculated: C 81.0; H 6.3; N 5.9%. Salts III were obtained by a method similar to that used for salts II. The perchlorate had mp 169-170° [from water (1:20)]. Found: N 4.1%. $C_{16}H_{15}NO \cdot HClO_4$. Calculated: N 4.1%. The hydriodide had mp 145-146° [from water (1:10)]. Found: N 3.5%. $C_{16}H_{15}NO \cdot HI$. Calculated: N 3.3%.

6-Phenoxymethylphenanthridine (IV). A solution of 1.65 g (7.5 mmole) of I in 45 ml of ethanol was added to a refluxing solution of 1.61 g (17 mmole) of phenol and 0.94 g (23.6 mmole) of sodium hydroxide in 30 ml of ethanol, and the mixture was refluxed for 5 h. It was then cooled, the precipitated NaCl was removed by filtration, and 0.43 g (21%) of IV with mp 142° (from alcohol) [4] and R_f 0.86 [CCl_4–ether (1:1)] was isolated as in the preparation of II. PMR spectrum in CF_3COOH, δ, ppm: 6.1 (CH_2), 7.2 (C_6H_5). The hydrochloride had mp 200-201° [from water (1:20)]. The perchlorate had mp 178° (from water).

Methyl o-Nitrobenzenesulfonate. A solution of 22.1 g (0.1 mole) of o-nitrobenzensulfonyl chloride [10] in 250 ml of absolute ether was added to a solution of sodium methoxide, obtained from 2.3 g (0.1 g-atom) of sodium and 50 ml of methanol, and the mixture was stirred at 0.5° for 1 h. The solvent was removed by distillation, and the residue was filtered to give 17.4 g (80%) of methyl o-nitrobenzenesulfonate with mp 60°. To purify this product, it was dissolved in ether (1:10) and precipitated with petroleum ether (mp 60-90°) [11].

5-Methyl-6-chloromethylphenanthridine Perchlorate (VII). A mixture of 0.12 g (0.5 mmole) of I and 0.32 g (1.5 mmole) of methyl o-nitrobenzenesulfonate was heated at 90-100° for 5 h. The melt was washed with benzene (five 10-ml portions) and ether (five 10-ml portions), and the residue was dissolved in 30 ml of hot water and treated with charcoal. The filtrate was treated with 5 ml of saturated aqueous $NaClO_4$ solution, and the precipitated VII was removed by filtration, washed with 20 ml of water and ether, and dried at 80-100° to give 0.12 g (66%) of VII with mp 236° [dec., from alcohol (1:40)]. UV spectrum in alcohol λ_{max}, nm (log ε): 248, 352 (4.56, 3.60). PMR spectrum in CF_3COOH, δ, ppm: 4.8 (CH_3), 5.7 (CH_2). Found: Cl 20.8; N 4.1%. $C_{15}H_{13}Cl_2NO_4$. Calculated: Cl 20.8; N 4.1%.

*The R_f values obtained during chromatography in a thin layer of activity II Al_2O_3 are presented here and elsewhere.

5-Methyl-6-methoxymethylphenanthridine Perchlorate (V). A. A mixture of 0.35 g (1.5 mmole) of II and 3.7 g (20 mmole) of methyl p-toluenesulfonate was heated at 105-110° for 4 h and at 130° for 5 h. The melt was washed with ether (five 20-ml portions), dissolved in 50 ml of hot water, and treated with charcoal. Compound V was precipitated by the addition of $NaClO_4$ solution to give 0.39 g (74%) of V with mp 165-167° [from water (1:50)]. UV spectrum in alcohol, λ_{max}, nm (log ε): 245, 340 (4.48, 3.76). PMR spectrum in CF_3COOH, δ, ppm: 3.8 ($O-CH_3$), 4.8 ($N-CH_3$), 5.5 (CH_2). Found: C 57.2; H 4.9; Cl 10.5; N 4.2%. $C_{16}H_{16}ClNO_5$. Calculated: C 57.0; H 4.8; Cl 10.6; N 4.2%.

B. A 0.16-ml (1.7 mmole) sample of dimethyl sulfate was added to a solution of 0.28 g (1.3 mmole) of II in 10 ml of dimethylformamide, and the mixture was heated at 110-120° for 4 h. The solvent was removed by vacuum distillation, and the residue was washed with ether and dissolved in 50 ml of hot water. The solution was treated with charcoal, and V was precipitated by the addition of $NaClO_4$ solution to give 0.12 g (31%) of V with mp 165°. The sample was identical to a sample obtained via method A.

5-Methyl-6-ethoxymethylphenanthridine Perchlorate (VI). A mixture of 0.12 g (0.5 mmole) of III and 1.2 g (6 mmole) of methyl p-toluenesulfonate was stirred thoroughly and heated at 100-110° for 6 h. It was then cooled, and the melt was worked up as in the preceding experiment to give 0.07 g (35%) of VI with mp 130° [from water (1:50)]. UV spectrum, λ_{max}, nm (log ε): 240, 350 (4.70, 3.90). PMR spectrum in CF_3COOH, δ, ppm: 1.1 (triplet, CH_3, J = 7 Hz), 3.7 (quartet, CH_2, J = 7Hz), 4.5 ($N-CH_3$), 5.3 ($Ar-CH_2-O$). Found: C 58.2; H 5.1; Cl 10.2 ; N 3.9%. $C_{17}H_{18}ClNO_5$. Calculated: C 58.0; H 5.0; Cl 10.1; N 4.0%.

The UV spectra of alcohol solutions of I-VII [$(1-3)\cdot 10^{-5}$ M] were recorded with an SF-4A spectrophotometer. The pK_a values of I-III were determined by potentiometric titration of 0.01 N alcohol solutions of I-III with aqueous 0.1 N HCl with an LPU-01 apparatus (with glass and silver chloride electrodes). The PMR spectra were recorded at 40 and 60 MHz relative to tetramethylsilane (in CCl_4) or hexamethyldisiloxane and cyclohexane (in CF_3COOH) as the internal standards.

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