SYNTHESIS AND ALKYLATION OF AMIDINES OF THE PHENANTHRIDINE SERIES

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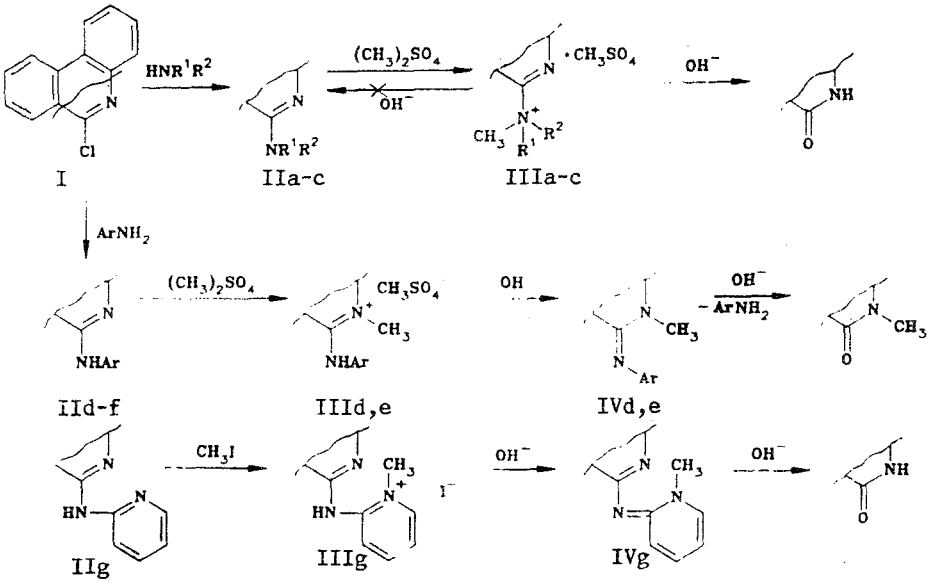
UDC 547.836.3

A number of 6-aminophenanthridines have been synthesized; upon alkylation, these compounds form amidinium salts. Depending on the structure of the original amidine, the alkylation may proceed at the exocyclic (n-alkyl), phenanthridine (N-aryl), or pyridine [N-(2-pyridyl)] nitrogen atom.

A classical reaction of 6-chlorophenanthridine is the replacement of the chlorine by an amino group [1]. The amidines that are obtained are of interest as synthones and biologically active compounds [2-4]. However, the presently known methods of synthesis of these compounds, particularly the aromatic amidines [5], give low yields; and only very limited information is available on their reactivities. Here we are proposing a new method for the synthesis of amidines of the phenanthridine series, and we are also reporting on the methylation of these compounds.

Our studies have shown that a good yield in the reaction of chlorine replacement by an amino group can be obtained by refluxing the iminochloride I directly in a solution of the corresponding amine. With aliphatic amines, the reaction is completed in 4 h (amidines IIa-c); the reaction with aniline or 2-aminopyridine (compounds IId-g) requires 7-h refluxing. In all cases, the reaction proceeds smoothly as a result of the presence of traces of $POCl_3$ in the reaction mixture. It was found that the substitution would proceed only after adding 3-4 drops of $POCl_3$, or as a result of using the iminohalide I without previous recrystallization from alcohol [6]. If compound I was first recrystallized, formation of the amidines IIa, d-g was not observed at all, and in other cases, only the start of the reaction was observed (as monitored by TLC).



IIa and IIIa, R^1 = H, R^2 = $CH_2C_6H_5$; IIb and IIIb, $R^1 = R^2 = (CH_2)_5$; IIc and IIIc, $R^1 = R^2 = (CH_2)_2O(CH_2)_2$; IId-IVd, Ar = C_6H_5; IIe-IVe, Ar = m-$CH_3C_6H_4$; IIf, Ar = o-$CH_3C_6H_4$

Institute of Organic Chemistry, Urals Branch, Russian Academy of Sciences, Perm. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1361-1364, October, 1991. Original article submitted February 12, 1990.

0009-3122/91/2710-1091$12.50

TABLE 1. Characteristics of Compounds II-IV

Compound	Empirical formula	mp, °C	R_f	UV spectrum of bases, λ_{max}, nm (and log ε)	PMR spectrum, ppm	Yield, %
IIa	$C_{20}H_{16}N_2$	97...99	0,70	210 (4,15); 239 (4,30); 270 sh (3,95); 294 sh (3,46); 324 (3,60); 335 sh (3,58)	4,87 (2H, d, CH_2); 5,45 (s, NH); 7,18...8,71 (13H, m, Ar)	70
IIf	$C_{20}H_{16}N_2$	123...125	0,73	210 (4,38); 240 (4,30); 265 (4,05); 295 sh (3,80); 330 sh (4,03); 342 (4,13)	2,27 (3H, s, CH_3); 6,68...8,71 (12H, m, Ar)	62
IIg	$C_{18}H_{13}N_3$	159...160	0,85	210 (4,10); 241 (4,23); 267 sh (4,04); 277 sh (3,85); 339 (3,83); 365 sh (3,66); 392 (3,41)	6,61...7,53 (12H, m, Ar)	65
IIIa	$C_{22}H_{22}N_2O_4S$	222...223	0,79	210 (4,22); 242 (4,37); 265 (3,87); 303 sh (3,52); 337 (3,46)	3,70 (3H, s, CH_3N); 4,85 (2H, d, CH_2); 6,88...8,63 (m, 13H, Ar)	81
IIIb	$C_{20}H_{24}N_2O_4S$	175...176	—	—	1,70 (br-s, 6H, $3CH_2$); 3,40 (m, 4H, $2CH_2$—N); 3,77 (br-s, 6H, CH_3N and CH_3O); 7,33...8,95 (m, 8H, Ar)	69
IIIc	$C_{19}H_{22}N_2O_5S$	196...197	—	—	3,40 (br-s, 4H, $2CH_2$—O); 3,93 (br-s, 10H, CH_3N, $2CH_2$—N and CH_3O); 7,20...9,00 (m, 8H, Ar)	78
IVd	$C_{20}H_{16}N_2$	123...125	0,84	210 (4,08); 240 (4,25); 257 sh (4,15); 282 sh (3,81); 340 (3,67)	3,46 (s, 3H, CH_3N); 6,15...8,60 (m, 13H, Ar)	83
IVe	$C_{21}H_{18}N_2$	—	0,90	210 (4,10); 240 (4,38); 256 sh (4,32); 285 sh (3,42); 315 sh (3,88); 340 (3,78)	2,20 (s, 3H, CH_3—Ar); 3,47 (s, 3H, CH_3N); 6,35...8,23 (m, 12H, Ar)	92
IVg	$C_{19}H_{15}N_3$	—	0,87	210 (4,15); 243 (4,28); 265 sh (4,18); 275 sh (3,90); 372 (3,86)	3,72 (s, 3H, CH_3N); 6,58...8,99 (m, 12H, Ar)	87

Alkylation of the amidines is complicated by the presence of two reaction centers. Iodomethylates of 6-aminophenanthridines were obtained for the first time by Reese [7], who was not able to prove the structure of all of the amidine salts that were formed. Hence it has been of interest to study the structure of the quaternary amidinium salts that we have obtained, as influenced by alkyl (IIa-c), aromatic (IId-f), or 2-pyridine (IIg) substituents. When subjected to the action of methyl iodide in boiling ethanol, the only amidine that was quaternized was IIg. None of the other amines was methylated under these conditions; only for the N-benzylamidine Ia did we find traces of an iodomethylate, the base of which, according to TLC data, is identical to the base obtained from the salt IIIa. However, the alkylation proceeds quite smoothly under the action of dimethyl sulfate. Upon refluxing with dimethyl sulfate in absolute benzene, the amidines IIa-c form colorless precipitates of the salts IIIa-c, and the N-arylamidines form the yellow substances IIId, e. The amidine IIf is not quaternized, probably because of steric hindrance from the o-methyl group [8].

The regiospecificity of alkylation is directly related to the nature of the substituent on the nitrogen atom in position 6. In the case of alkyl substituents (IIa-c), the reaction takes place at the exocyclic nitrogen atom; in the aromatic amidines IId, e it takes place at the nitrogen atom of the heterocycle, and in compound IIg at the pyridine nitrogen atom. When treated with 10% NH_4OH, the methylsulfates of IIIb, c give hygroscopic quaternary bases; compounds IVd, e, g and the base from the salt IIIa are stable. Using TLC data and PMR spectra taken in $CDCl_3$ in the interval from —40° to +25°C, we were unable to distinguish the Z and E isomers of the bases IVd, e, g; this may be related to the low energy barrier of the process of Z $\rightleftarrows$ E isomerization.

With the aim of proving the structure of the amidine methylsulfates, we investigated the splitting of these compounds in an alkaline medium. After boiling the N-alkylamidine salts IIIa-c in 20% NaOH in ethylene glycol with 10% added water, we were unable to detect methanol (GLC) or the original amidines IIb, c (TLC), i.e., the products of the usual Hoffmann degradation. The substances recovered from the reaction mixture were identified as 6-phenanthridone (mixed melting point, PMR and IR spectra) and the corresponding N-methylamines (TLC data). Analogously, the products of degradation of the amidines IVd, e under the same conditions were identified as N-methyl-6-phenanthridone [9] and aniline and m-toluidine, respectively. Upon hydrolysis of compound IIIg, out of the complex mixture of degradation products we were able to identify only 6-phenanthridone. The unexpected path of degradation (splitting) of compounds IIIb, c can be explained by thermodynamic control, i.e., the energy advantage of the 6-phenanthridone molecule.

We obtained spectra of those compounds that had not been described previously (Table 1). In the spectra of the bases of the amidines IIa, d, e, g, we observe an absorption band of the NH group in the 3400-3480 cm^{-1} region, which disappears after methylation (bases IVa, d, e, g). In the spectra of compounds IVd-g, we find a distinct band of the C=N group (1625-1635 cm^{-1}).

In the PMR spectra, the proton of the NH group is observed in the form of a singlet for the amidine IIa (5.45 ppm); in the aromatic amidines IId-g, this signal is masked by the multiplet of the aromatic protons, as confirmed by the total integral intensity. Differences in the structure of the alkylation products are confirmed by the difference in chemical shifts of the singlets corresponding to protons of N-methyl groups: for the base IIIa, 3.70 ppm; for the bases IIId, e, which are identically alkylated at the ring nitrogen, the respective values are 3.46 and 3.47 ppm; and for the N-methylpyridine compound IVg, the value is 3.72 ppm.

Analysis of the UV spectra of the azomethines IVd, e, g shows that the spectra of compounds IVd, e are similar to each other, whereas the spectrum of the base IVg differs from that of the original substance IIg and also from those of the azomethines IVd, e; this also reflects a difference in structure of the compounds that are methylated at the nitrogen atom of the phenanthridine ring (IVd, e) or that of the pyridine ring (IVg).

EXPERIMENTAL

The PMR spectra were taken in an RYa-2310 spectrometer (60 MHz), with salts IIIb, c in DMSO-D_6 and all others in the form of the bases in $CDCl_3$; internal standard HMDS. The IR spectra were recorded in a UR-20 instrument (solutions in CCl_4, 0.01 M), the UV spectra in an SF-26 spectrophotometer in ethanol. The TLC was performed on Silufol UV-254 plates in an acetone/ethanol/chloroform system (1/3/6), with development by iodide vapor. The GLC was performed in an LKhM-8MD instrument (katharometer detector, 2000 × 3 mm column, Polysorb 1, carrier gas helium, 300 ml/min, 100°C). The 6-phenanthridone and the N-methyl-6-phenanthridone were isolated from the reaction mixture by dilution with water.

Characteristics and yields are listed in Table 1 for the phenanthridines that were obtained for the first time in the present work.

The elemental analyses for C, H, N, and S are in agreement with the calculated data.

6-Aminophenanthridines IIa-f (General Procedure). To 2.15 g (10 mmoles) of 6-chlorophenanthridine [6], 3-4 drops of $POCl_3$ were added, and the mixture was refluxed in 10-12 ml of the appropriate amine for a period of 4 h (IIa-c) or 7 h (IId-g). The resinous mass that was obtained in this reaction was dissolved in 20 ml of hot DMFA, and the solution was cooled and then poured into 100 ml of water. The precipitate was filtered off and washed thoroughly with water (IIa-g), then with pentane (IId-g), until no more of the original amine was found in the filtrate (monitored by TLC). The washed precipitate was dried and recyrstallized: IIa, f, g from 2-propanol; IIb, c [10], IId [11], and IIe [5] from methanol.

A reaction was carried out in the same manner with the chlorimine I obtained immediately after the reaction of 6-phenanthridone with $POCl_3$, but the yield in this case was 10-20% lower.

N-methyl-N-(6-phenanthridinyl)ammoniumMethylsulfates(IIIa-c),6-Arylamino-5-methylphenanthridinium Methylsulfates (IIId, e), and 6-Arylimino-5,6-dihydro-5-methylphenanthridines (IVd, e). Solutions of 10 mmoles of the bases IIa-e in 30 ml of absolute benzene were refluxed with 2.23 ml (15 mmoles) of freshly distilled dimethyl sulfate for 1 h (IIa-c) or 2 h (IId, e). The precipitate of the salts IIIa-c, d, e was filtered off, dried, and recrystallized from 2-propanol; mp 205-207°C (salt IIId) and 170-172°C (methylsulfate IIIe). The salts IIId, e were dissolved in water, and 10% NH_4OH was added, giving the azomethines IVd, e, which were filtered off, dried, and recrystallized from methanol.

2-(6-Phenanthridinyl)amino-N-methylpyridinium Iodide (IIIg) and 6-(1,2-Dihydro-1-methyl-2-pyridiyl)iminophenanthridine (IVg). A solution of 2.71 g (10 mmoles) of the base IIg was refluxed in 30 ml of ethanol with 1.24 ml (20 mmoles) of CH_3I for 2 h; upon cooling to room temperature, a crystalline precipitate of the iodomethylate IIIg was formed; this was filtered off, dried (mp 193-195°C) and then dissolved in water with the addition of 10% NH_4OH to obtain the base IVg.

LITERATURE CITED

1. L. Walls, in: *Heterocyclic Compounds*, Vol. 4, R. C. Elderfield (ed.), Wiley, New York (1951).
2. R. J. Grout, in: *The Chemistry of Amidines and Imidates*, S. Patai (ed.), Interscience, London (1975), p. 255.
3. V. G. Granik, *Usp. Khim.*, **52**, 669 (1983).
4. A. G. Mikhailovskii, in: Summaries of Papers from 10th Conference of Young Scientists, Syntheses and Investigation of Biologically Active Compounds, Riga (1989), p. 56.
5. M. E. Omar A.-Mohsen, N. S. Habib, and M. Adoulwafa Omaima, *Pharmazie*, **32**, 758 (1977).
6. G. M. Badger, J. H. Seidler, and B. J. Thomson, *J. Chem. Soc.*, No. 12, 3207 (1951).
7. C. B. Reese, *J. Chem. Soc.*, No. 5, 895 (1958).
8. V. M. Potapov, *Stereochemistry* [in Russian], Khimiya, Moscow (1988), p. 309.
9. V. Petrov and W. Wragg, *J. Chem. Soc.*, No. 10, 1410 (1947).
10. B. R. T. Keene and G. L. Turner, *Tetrahedron*, **27**, 3405 (1971).
11. H. Seidl, R. Huisgen, and R. Grashey, *Chem. Ber.*, **102**, 926 (1969).