HETEROCYCLIC ANALOGS OF PLEIADIENE

III. Reactivity of the Nitrogen Atoms of Perimidine and Aceperimidine*

A. F. Pozharskii and I. S. Kashparov

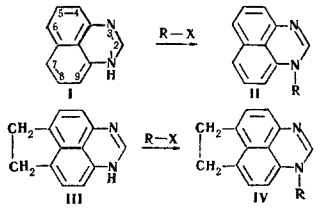
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 1, pp. 111–115, 1970

UDC 547.856.7

Methods of synthesizing various N-substituted perimidines and aceperimidines have been studied. It has been established that because of the autoxidation of the N-anions of perimidine, 2-methylperimidine, and aceperimidine, the alkylation of these compounds in an alkaline medium must be carried out in an inert atmosphere. Previously-unknown N-substituted perimidines and aceperimidines have been synthesized. The ionization constants of the compounds obtained have been measured in 10% aqueous ethanol at 25 ± 1° C.

There has been no substantial progress whatever in the chemistry of perimidine (I) since Sachs' broad investigations [2]. The sporadic investigations of individual authors have been connected mainly with methods closing the hetero ring of I (see the review [3]). Nevertheless, in view of their structural and electronic characteristics [1], the most intriguing point in the perimidines must be their reactivity and not methods of preparing them, in which they differ little from the naphthoimidazoles isomeric with them.

We began our investigations of the chemistry of perimidine with a study of methods for synthesizing its N-substituted derivatives. Only one representative of this series was known previously, 1,2-dimethylperimidine [4]. It was obtained in low yield (30%) by treating 2-methylperimidine with methyl p-toluenesulfonate at 100° C. Under these conditions, as is well known, the reaction takes place through the pyridine N-atom with the formation of a quaternary salt from which treatment with alkali liberates the base. Our methylation of perimidine carried out under similar conditions also led to a low yield (22%) of N-methyl perimidine. In the treatment of the quaternary salt with alkali, pronounced resinification was observed. The same results were given by the methylation of perimidine and its silver salt with methyl iodide in xylene. The alkylation of the imidazole in a neutral medium leads to somewhat higher yields (35–50%) and is not accompanied by resinification [5]. Apparently because of the low acidity of the NH group, the methylation of perimidine with diazomethane is also unsuccessful (Table 1). In view of this, we resolved to carry out methylation under alkaline conditions which, in the imidazole series, takes place via the anion and is, therefore, more effective. The performance of the reaction in liquid ammonia in the presence of sodium amide, usually giving good results [6,7], here proved inapplicable once again because of the pronounced resinification of the reaction mixture. When perimidine was methylated with methyl iodide in



ethanolic alkali, the yield of 1-methylperimidine reached 50%. Simultaneously, the formation of a considerable amount of a black crystalline substance which greatly complicated the purification of the N-methyl derivative was observed. In view of the presence of a high positive charge on the $C_{(2)}$ of the perimidine molecule [1], we first assumed that the formation of the byproduct was the result of a far-reaching reaction between the 1-methylperimidine and OH^- or $C_2H_5O^-$ ions. However, 1-methylperimidine proved to be stable to the action of alkaline agents under these conditions. It remained to be assumed that the side reactions were undergone by the N-anion formed in the presence of alkali. In actual fact, when perimidine was treated with ethanolic or aqueous alkali the solution immediately acquired

*For part II, see [1].

a black color and after brief heating, the above-mentioned black product separated out quantitatively. Its composition was $(C_{11}H_7N_2O)_X$, and the impossibility of its formation in an atmosphere of nitrogen shows that it is obtained by the oxidation of the N-anion of perimidine with atmospheric oxygen. Since 2-methylperimidine gives a product of analogous composition, $(C_{12}H_9N_2O)_X$, in an alkaline medium, it may be considered that it is the naphthalene moiety of the perimidine system that undergoes oxidation. The N-anion of aceperimidine undergoes oxidation with somewhat greater difficulty.* Such instability of N-anions in heteroaromatic compounds is a phenomenon of extreme rarity, observed to some extent, so far as we know, only in the case of phenothiazine [8].

Table 1. Results of the Methylation of Perimidine Under Various Conditions

Methylating agent	Conditions	Yield of 1-methylperimidine, %
$CH_3OSO_2—C_6H_4—CH_3$	Fusion, 100° C	22
CH_2N_2	Dioxane, 20° C	5
CH_3I	Xylene, 140° C	27
" "	Silver salt of perimidine, xylene, 140° C	5
" "	Liquid ammonia, $NaNH_2$	12
" "	Boiling in ethanolic alkali	47—50

The alkylation of perimidine and aceperimidine in an ethanolic solution of alkali in an atmosphere of nitrogen enabled us to obtain the previously unknown N-alkyl derivatives II and IV with higher yields than in the presence of atmospheric oxygen (Table 2). Similarly, in the methylation with methyl iodide (1 mole) of 2-methylperimidine in ethanolic alkali the yields of 1,2-dimethylperimidine were 68 and 47% in an atmosphere of nitrogen and under the usual conditions, respectively. The benzylation of perimidine takes place with greater difficulty than usual [5]. Thus, in the reaction of I in an alkaline medium with benzyl(dimethyl)phenylammonium chloride and with benzyl chloride, the yields of 1-benzylperimidine were, respectively, 4 and 47%.

We were unable to effect the direct N-arylation of perimidine by the methods proposed for five-membered nitrogen heterocycles [5] and phenoxazine [9] because of the complete resinification of the reaction mixture.

It has recently been shown [10] that perimidine adds fluoroolefins at the NH group. We have established that it also readily adds a molecule of formaldehyde with the formation of the N-hydroxymethyl derivative (II; R = CH_2OH). We obtained N-methoxymethylperimidine (II, R = CH_2OCH_3) by the reaction of I (2 moles) with methoxymethyl chloride (1 mole) in dry benzene.

Table 2. N-Substituted Perimidines and Aceperimidines

Alkylating agent	Compound	R	Solvent for recrystallization	Mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %	
						C	H	N	C	H	N	in an atmosphere of N_2	under the usual conditions
CH_3I	II	CH_3	Heptane	120—121	$C_{12}H_{10}N_2$	79.11	5.34	14.99	79.09	5.53	15.36	67	47
C_2H_5Br(I)	II	C_2H_5	Heptane	115—116	$C_{13}H_{12}N_2$	79.39	6.15	14.42	79.56	6.16	14.27	57—63	20
n-C_3H_7I	II	n-C_3H_7	Aqueous ethanol	72—73	$C_{14}H_{14}N_2$	79.68	6.54	13.59	79.96	6.71	13.32	64	34
i-C_3H_7I	II	i-C_3H_7	Aqueous ethanol	67—68	$C_{14}H_{14}N_2$	79.72	6.61	13.11	79.96	6.71	13.32	35	—
$C_6H_5CH_2Cl$	II	$C_6H_5CH_2$	Octane	135—136	$C_{18}H_{14}N_2$	83.99	5.70	10.68	83.69	5.47	10.84	47	17
CH_2O	II	CH_2OH	Water	202—203	$C_{12}H_{10}N_2O$	72.43	4.86	14.20	72.71	5.09	14.13	—	98
CH_3OCH_2Cl	II	CH_3OCH_2	Benzene	65—66	$C_{13}H_{12}N_2O$	73.32	5.39	13.01	73.56	5.69	13.19	—	62
CH_3I	IV	CH_3	Aqueous ethanol	201—202	$C_{14}H_{12}N_2$	81.02	6.09	13.24	80.74	5.81	13.45	66	46
C_2H_5Br	IV	C_2H_5	Aqueous ethanol	120—121	$C_{15}H_{14}N_2$	81.03	6.47	12.68	81.08	6.35	12.60	60	—
n-C_3H_7Br	IV	n-C_3H_7	Hexane	60—62	$C_{16}H_{16}N_2$	81.09	6.50	12.00	81.32	6.82	11.85	57	—

*The elucidation of the actual structure of the oxidation products is difficult because of their complete insolubility in all known solvents and requires special investigations.

Table 3. Ionization Constants, pK_a, of the Cations of Perimidine and a Number of Model Compounds in 10% Aqueous Ethanol and 25 ± 1° C

Compound	pK_a
Perimidine	5.91
1-Methylperimidine	5.86
1-Ethylperimidine	5.93
1-Propylperimidine	5.87
1-Isopropylperimidine	5.99
1-Methoxymethylperimidine	4.96
Aceperimidine	6.12
1-Methylaceperimidine	6.16
1-Ethylaceperimidine	6.14
Naphthalene-1,8-diamine	4.44
Naphthalene-1,2-diamine	4.76
Naphtho[1,2]imidazole	5.31
Naphtho[2,3]imidazole	5.24*
Benzimidazole	5.41

*In water [11].

The N-substituted perimidines are colored substances with greenish and yellow-greenish shades. The N-alkylaceperimidines are golden-yellow compounds. They all readily protonate and alkylate at the pyridine nitrogen atom, which is favored by their extremely high basicities (Table 3). According to quantum-mechanical calculations [1], in the perimidine molecule there is a considerable shift of the π-electronic density from the μ-carbon atom to the naphthalene-1,8-diamine residue. This permits an explanation of the low acidity and high basicity of the perimidines, considerably exceeding the basicity of the isomeric naphthoimidazoles and also those of the benzimidazoles and naphthalene diamines. The perimidine molecule is probably the only example in the nitrogen heterocycles in which such a highly basic center is adjacent to a carbon atom bearing a considerable effective positive charge.

The aceperimidines are stronger bases than the perimidines because of the electron-donating effect of the CH_2—CH_2 bridge.

EXPERIMENTAL

Perimidine (I) was obtained from naphthalene-1,8-diamine and formic acid [2]. Yellow-green crystals with mp 225° C (from ethanol). **Hydrochloride.** Pale yellow needles (from ethanol with ether), mp 304–305° C. Found, %: Cl 17.40. Calculated for $C_{11}H_9ClN_2$, %: Cl 17.33.

Aceperimidine (III) was obtained by the reaction of 4,5-diaminoacenaphthene with formic acid [12]. Light brown crystals with mp 285° C (from ethanol).

1-Methylperimidine (II, R = CH_3). A) A solution of 1.7 g (0.01 mole) of I and 4.3 g (0.03 mole) of methyl iodide in 40 ml of xylene was boiled with stirring for 3 h. The yellow crystalline precipitate that deposited (3.1 g) was filtered off and washed with benzene and was then treated with 10% NaOH solution (20 ml). The resinous mass formed was extracted with chloroform (30 ml). The extract was filtered from the dark chloroform-insoluble oxidation product (0.7 g), and dried with potassium carbonate, after which it was passed through a column of alumina (100 g). The 1-methylperimidine was diluted with chloroform the first fraction being collected. Yield 0.48 g (27%), mp 118° C.

B) Perimidine (0.8 g; 5 mM) and methyl p-toluenesulfonate (0.9 g; 5 mM) were heated in the boiling water bath for 1 h. The melt obtained was dissolved in 100 ml of hot water and treated with ammonia. The precipitate was extracted with 20 ml of chloroform. The chloroform was evaporated off and the residue was recrystallized from aqueous ethanol. Yield 0.2 g (22%), mp 120° C.

C) The silver salt of perimidine (dark green powder, insoluble in water and organic solvents) was obtained by the method proposed for the silver salt of benzimidazole [5]. A suspension of 4.1 g (15 mM) of the silver salt of I in 30 ml of anhydrous xylene was treated with 1 ml (15 mM) of methyl iodide and boiled with stirring for 3 hr. The 1-methylperimidine was precipitated from the solution in the usual way. Yield 0.13 g (5%), mp 120° C.

D) To a solution of 0.8 g (5 mM) of I in 70 ml of dioxane was gradually added 60 ml (5 mM) of a freshly-prepared ethereal solution of diazomethane (titer 0.0039 g/ml). After a day, the solvent was distilled off from the reddening

solution and the residue was treated with 20 ml of chloroform. The 1-methylperimidine was isolated from the chloroform extract by chromatography, as in method A. Yield 0.05 g (5%), mp 118° C.

E) Perimidine (1.7 g; 0.01 mole) and methyl iodide (1.4 g; 0.01 mole) were added to a freshly-prepared solution of sodium amide (0.39 g; 0.01 mole) in 40 ml of liquid ammonia. The mixture was stirred and the ammonia was allowed to evaporate off slowly. The resinous residue was extracted with chloroform (30 ml). The oxidation product (0.8 g) was filtered off. The chloroform was evaporated, the residue was dissolved in 5% HCl and boiled with carbon, and the 1-methylperimidine was precipitated with ammonia. Yield 0.23 g (12%), mp 118° C.

F) Compound I (3.36 g; 0.02 mole) and methyl iodide (2.84 g; 0.02 mole) were added to a solution of 1.4 g (0.02 mole) of KOH in 35 ml of ethanol. The mixture was boiled for 3 hr. After cooling, the black precipitate and the KI were filtered off and washed with a small amount of ethanol, and the solvent was distilled off from the filtrate. The residue was treated with chloroform (50 ml). The 1-methylperimidine was isolated as in method (a). Yield 1.7 g (47%), mp 120–121° C (from heptane; bp 210° C (3 mm)). **Hydrochloride.** Yellow needles from ethanol with ether, mp 261–262° C. Found, %: Cl 16.32. Calculated for $C_{12}H_{11}ClN_2$, %: Cl 16.21. **Methiodide.** A solution of 0.360 g (2 mM) of II, R = CH_3, and 0.6 g (4 mM) of methyl iodide in 5 ml of ethanol was boiled for 2 hr and cooled, and the yellow precipitate was filtered off. Yield 0.650 g (100%), mp 269–270° C (from ethanol). Found, %: I 39.03. Calculated for $C_{13}H_{13}IN_2$, %: I 39.14.

General method for preparing N-alkyl derivatives of perimidine and aceperimidine. With the continuous passage of nitrogen, a solution of 0.01 mole of KOH in 10 ml of ethanol and an alkyl halide (0.01 mole) were added to a solution of 0.01 mole of I or III in 30 ml of ethanol. The mixture was boiled in an atmosphere of nitrogen for 3 hr and filtered, and the N-alkyl derivative was isolated from the filtrate as described in method (A).

The alkylation of 2-methylperimidine was carried out similarly. Compounds II and IV are soluble in the majority of organic solvents and practically insoluble in water and petroleum ether.

1-Benzylperimidine (II, R = $C_6H_5CH_2$). To a solution of 0.4 g (0.01 mole) of NaOH in 10 ml of water were added 1.7 g (0.01 mole) of perimidine and a saturated aqueous solution of 2.5 g (0.01 mole) of benzyl(dimethyl)phenylammonium chloride. The mixture was heated in the boiling water bath for 30 min after which the dimethylaniline was distilled off with steam. The resinous mass formed was treated with 30 ml of chloroform and the extracts were dried with potassium carbonate. After the chloroform had been driven off, the residue was distilled in vacuum. A fraction boiling at 230-240° C (5 mm) was collected. Yield 0.095 g (~4%). Yellowish crystals with mp 135-136° C (from octane).

Reaction of perimidine with potassium methoxide. A solution of 0.5 g of perimidine in 25 ml of ethanol containing 0.2 g of KOH was boiled for 3 hr. The black precipitate that deposited was filtered off and washed with water. Yield 0.49 g. The product obtained was insoluble in water and organic solvents but dissolved in concentrated acids, from which it was precipitated with ammonia. It did not melt at 350° C. A similar product was formed by heating perimidine with 20% aqueous KOH. Found, %: C 72.88; H 3.79; N 15.57. Calculated for $C_{11}H_7N_2O$, %: C 72.51; H 3.32; N 15.37.

For the product of the oxidation of the anion of 2-methylperimidine, found, %: C 66.61; H 4.36; N 12.87. Calculated for $C_{12}H_9N_2O \cdot 2H_2O$, %: C 67.28; H 4.70; N 13.07.

1-Hydroxymethylperimidine (II, R = CH_2OH). To a solution of 2 g of perimidine in 30 ml of methanol was added 3 ml of 40% formalin and the mixture was left for 1 hr. On the following day the methanol was distilled off and the residue (2.35 g, 98%) was recrystallized from water, mp 202–203° C.

1-Methoxymethylperimidine (II, R = CH_3OCH_2). To a suspension of 3.36 g (0.02 mole) of perimidine in 50 ml of anhydrous benzene was added 0.8 g (0.01 mole) of methoxymethyl chloride and the mixture was boiled for 1 hr and then filtered hot. The filtrate was evaporated to half bulk. On cooling, pale yellow needles of the N-substituted derivative precipitated. Yield 1.33 g (62%), mp 65–66° C (from benzene).

The ionization constants were measured by the potentiometric titration of a 0.01 N solution of the substance in 10% aqueous ethanol with 0.01 N HCl solution on an LPU-01 instrument.

REFERENCES

1. A. F. Pozharskii and E. N. Malysheva, KhGS [Chemistry of Heterocyclic Compounds], 6, 103, 1970.
2. F. Sachs, Ann., 365, 66, 1909.
3. J. H. Richmond, Six-Membered Heterocyclic Nitrogen Compounds with Three Condensed Rings, N.Y. 518, 1958.
4. R. A. Jeffreys, J. Chem. Soc., 2394, 1955.
5. A. F. Pozharskii, collection: Outlines of the Chemistry of the Azoles [in Russian], Izd-vo Rost. un-ta, 24, 1965.
6. A. M. Roe, J. Chem. Soc., 2195, 1963.
7. H. Gilman, R. Nelson and J. Champaigne, J. Am. Chem. Soc. 74, 4205, 1952.
8. D. F. Honston, E. B. Kester, and F. Deeds, J. Am. Chem. Soc., 71, 3816, 1949.
9. H. Gilman and L. O. Moore, J. Am. Chem. Soc., 79, 3485, 1957.
10. W. Ried and H. Lohwasser, Angew. Chem., 78, 904, 1966.
11. D. J. Brown, J. Chem. Soc., 1974, 1958.
12. F. Sachs and G. Moseback, Ber., 44, 2870, 1911.

20 February 1968

Rostov-on-Don State University