HETEROCYCLIC ANALOGS OF PLEIADIENE. XV.* DIRECT ACYLATION OF PERIMIDINES IN THE NAPHTHALENE RING. SYNTHESIS OF 4(9)- and 6(7)-ACYLPERIMIDINES

A. F. Pozharskii, I. V. Borovlev, and I. S. Kashparov

UDC 547.856.7: 542.951.9

It is shown that perimidines and aceperimidines are acylated by carboxylic acid or their anhydrides in polyphosphoric acid to give 6(7)-acylperimidines at 70-80° (kinetic control) and 4(9)-acylperimidines at 120-150° (thermodynamic control). Acetylation of the perimidines with acetic anhydride also takes place in the presence of perchloric acid.

It has been shown that perimidine is a typical π-surplus system that readily forms charge-transfer complexes even with weak π acids [2] and that its N-anion is extremely easily oxidized [3]. One therefore might have expected that not only nucleophilic substitution reactions [4] but also electrophilic substitution reactions such as, for example, Friedel—Crafts acylation would be characteristic for perimidines. The present paper is devoted to a study of this reaction.

The literature does not contain data relating to the reactivities of perimidines with respect to electrophiles. According to the results of quantum-chemical calculations by the Hückel MO method the maximum negative charge in the neutral perimidine molecule is concentrated in the 4 and 9 positions (the ortho position with respect to the heteroring) with somewhat less negative charge in the 6 and 7 positions (the para positions) [5, 6]. The meta positions (5 and 8) have practically zero charge, and electrophilic substitution reactions involving them seem unlikely. A similar charge distribution is also retained in the perimidinium cation (Fig. 1). On the other hand, the cation-localization energies that we calculated for the ground state of perimidine and the perimidinium cation indicate greater preferableness of attack by electrophiles at the para positions as compared with the 4 and 9 positions (Fig. 1).

Perimidine is not acylated under the conditions of acylation of perimidine [7]. However, we found that perimidines are smoothly acylated by acid anhydrides in the presence of perchloric and polyphosphoric acids (PPA). When PPA is used, the acylation can be carried out directly with carboxylic acids of the aliphatic, aromatic, or heterocyclic series. The use of perchloric acid is less satisfactory, inasmuch as pronounced resinification of the reaction mixture is observed when it is present. It was found that perchloric acid is suitable only for acetylation of perimidines with acetic anhydride.

Aceperimidine (I) is readily acylated by low-molecular-weight carboxylic acids at 75-80°C in PPA. The yields of monoacyl-substituted compounds are somewhat higher (78-80%) in the case of aliphatic acids than in the case of aromatic acids (53-61%). In the acylation of aceperimidine with stearic acid the reaction proceeds very slowly and the maximum yield of stearoylaceperimidine obtained was only 10% (Table 1). (See scheme on following page.)

*See [1] for communication XIV.

Rostov State University, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 543-549, April, 1975. Original article submitted February 11, 1974; revision submitted June 24, 1974.

TABLE 1. Acylation of Perimidines

Starting compound	Acylating agent	Temp., °C	Time, h	Yield of isomers, % 4(9)	6(7)
Aceperimidine	CH_3COOH– PPA	70—75	2	78	—
The same	$(CH_3CO)_2O$—$HClO_4$	115	*	72	—
" "	CH_3CH_2COOH–PPA	75—85	2	80	—
" "	$C_{17}H_{35}COOH$– PPA	80—85	8		
		120—125	4	10	—
" "	C_6H_5COOH– PPA or $(C_6H_5CO)_2O$– PPA	75—80	4	61	—
" "	p-$CH_3OC_6H_4COOH$–	100—110	5	53	—
1-Methylaceperimidine	CH_3COOH– PPA	70—75	2,5	60	—
The same	$(CH_3CO)_2O$—$HClO_4$	115	*	37	—
Perimidine	CH_3COOH– PPA or $(CH_3CO)_2O$– PPA	70—75	4	12	82
The same	$(CH_3CO)_2O$—$HClO_4$	70—75	3,5	12	52
" "	$(CH_3CO)_2O$—$HClO_4$	115	*	60	—
" "	CH_3COOH– PPA	125—135	2,5	70	—
" "	C_6H_5COOH–PPA	80—85	3	6	57
" "	C_6H_5COOH–PPA	135—145	3	31	—
2-Methylperimidine	CH_3COOH– PPA	75—80	3	15	80
The same	$(CH_3CO)_2O$—$HClO_4$	115	*	23	—
" "	CH_3COOH—PPA	130—140	3	57	—
2-Phenylperimidine	CH_3COOH—PPA	75—80	2	14	65

*The acylation time at the indicated temperature was 30-40 sec (see the experimental section).

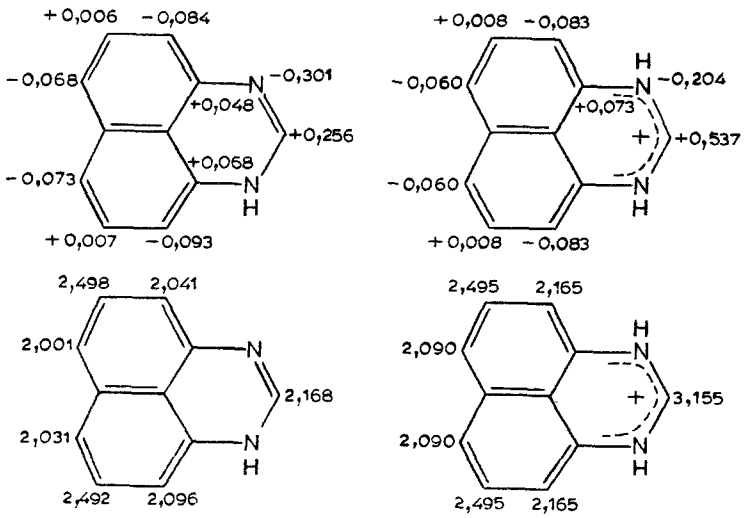
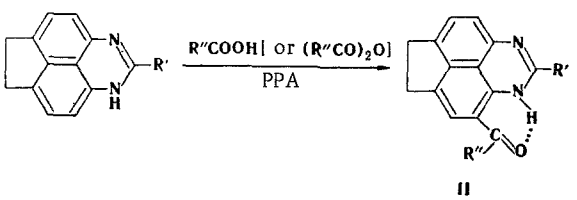


Fig. 1. Effective atomic charges (top) and cation-localization energies (bottom) for the neutral perimidine molecule and the perimidinium cation calculated by the Hückel MO method.



II

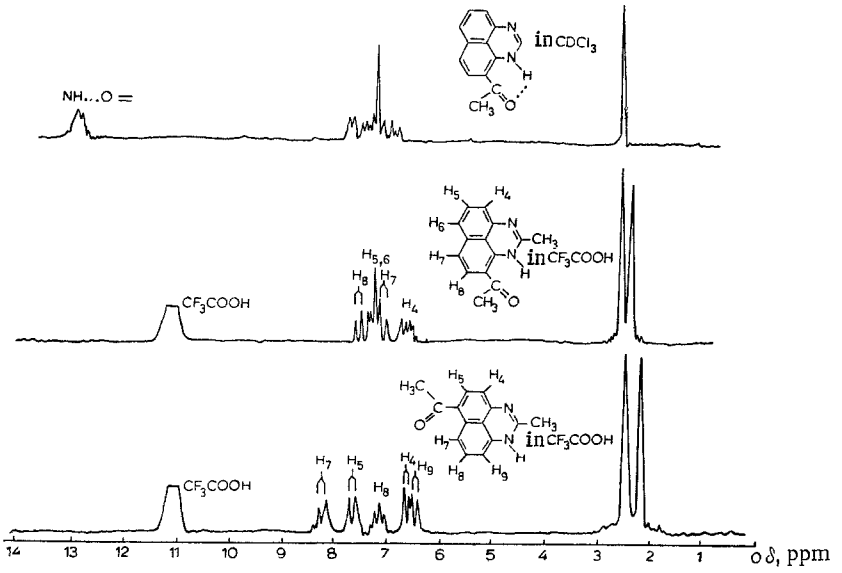


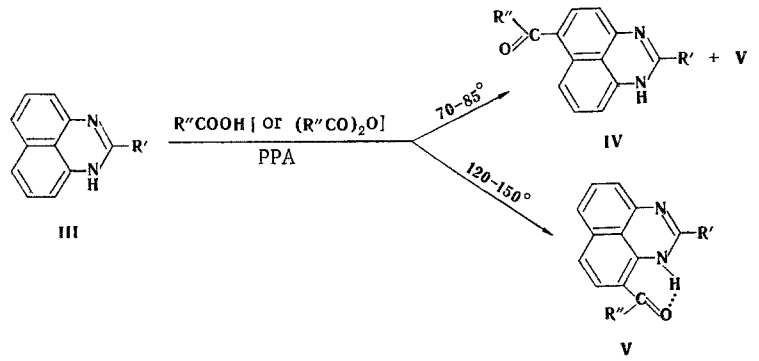
Fig. 2. PMR spectra of some acetylperimidines.

The properties of the monoacyl derivatives of aceperimidine leave no doubt that they belong to the 4(9) rather than to the 5(8) series. The PMR spectrum of a solution of acetylaceperimidine (II, R' = H, R' = CH_3) in deuterochloroform contains a broad signal of the proton of an NH group (δ 11.64 ppm) tied up in an intramolecular hydrogen bond with the acetyl group; this is possible only in 9-acetylaceperimidine. The ν_{NH} band in the IR spectra of dilute solutions of all of the acylaceperimidines is markedly broadened and reduced in frequency (3250 cm^{-1}) as compared with the analogous band observed for aceperimidine (3430 cm^{-1}); this also indicates the presence of an intramolecular hydrogen bond.

As expected from the quantum-chemical calculations, the acylation of perimidines gives two different monoacyl derivatives. Judging from the PMR data (δ 12.45 ppm in $CDCl_3$) and the IR spectra (ν_{NH} 3250 cm^{-1}), one of them is the 4(9) isomer, and the other is the 6(7) isomer (ν_{NH} 3430 cm^{-1}). The PMR spectrum of p-acylperimidines in the region of aromatic proton absorption has the form of a first-order spectrum and is the well-resolved sum of the peaks of two spin systems of the AX and A'KX' type (Fig. 2). This is explained by the fact that the peri proton in the nonacylated ring is shifted strongly to weak field due to the deshielding effect of the unshared pair of electrons of the oxygen atom in the $COCH_3$ (compare the data obtained for 1-acetylnaphthalene [8]). The signal of this proton in the spectrum of 2-methyl-6(7)-acetylperimidine in trifluoroacetic acid appears at 8.28 ppm as a doublet with J_{ortho} = 9 Hz (the meta coupling constant is small). The doublet (δ 7.72 ppm, J_{ortho} = 8 Hz) is affiliated with the H_5 proton in the ortho position relative to the acetyl group. The triplet at δ 7.18 ppm corresponds to the meta H_8 proton of the nonacylated ring. The assignment of doublets at 6.63 and 6.48 ppm to the H_4 and H_9 protons is obvious (J_{8-9} = 7.8 Hz).

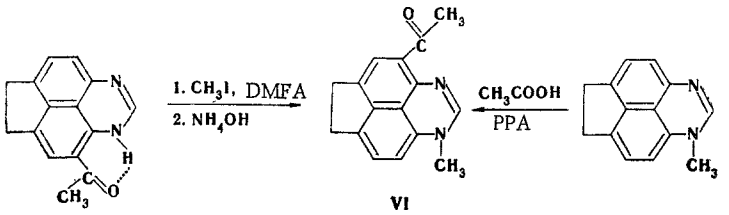
It was found that, depending on the temperature conditions, the reaction may proceed to give primarily the 4(9)- or 6(7)-monoacylperimidines. Under mild conditions (70-85°) acylation in both the R"COOH—PPA and $(CH_3CO)_2O$—$HClO_4$ systems is mainly the p-acyl derivative (55-85%) along with a small amount of the ortho isomer (6-17%); at 120-150°, 4(9)-acylperimidines, the yield of which reaches 70% (Table 1), become the only products. (See scheme on following page.)

The formation of the ortho isomer at higher temperature is apparently the result of rearrangement of the para isomer. p-Acylperimidines are rearranged to o-acylperimidines at higher temperatures (120-150°) in PPA. The rearrangement also occurs at 70-80° but very slowly. It was found that the yield of 4(9)-acetylperimidine was 10% when 6(7)-acetylperimidine was heated in PPA under the conditions of acetylation of perimidine, i.e., 6-17% of the ortho isomer formed during low-temperature acylation of perimidines is the result of rearrangement rather than the result of direct o-acylation. The formation of benzoic acid is observed in the rearrangement of 6(7)-benzoylperimidine in PPA, and this leads to a



decrease in the yield of 4(9)-benzoylperimidine (25%). This fact shows that the first step in the rearrangement is deacylation of p-acylperimidine under the influence of PPA. We did not observe rearrangement of the para isomer to the ortho isomer in acetic anhydride in the presence of perchloric acid or in an inert solvent (xylene); in the first case, the rearrangement was carried out under the conditions of the o-acetylation of perimidines (an increase in the reaction time led to resinification). Consequently, the formation of the ortho isomers in the acetylation with acetic anhydride in the presence of perchloric acid is the result of direct ortho substitution.

The higher thermodynamic stability of o-acylperimidines is apparently due to the strong intramolecular hydrogen bond, which is so strong in II and V that they cannot be converted to anions and subjected to methylation with methyl iodide even in alcoholic alcohol (compare with 4-acylperimidones [7]). The methylation of 9-acetylaceperimidine with methyl iodide was carried out in a neutral medium (DMFA) with subsequent treatment of the resulting salt with alkali. Inasmuch as the reaction under these conditions may proceed only at the pyridine nitrogen atom, the methylation product (94% yield) is 1-methyl-4-acetylaceperimidine (VI). Compound VI was also obtained in 60 and 37% yields, respectively, in the acetylation of 1-methylaceperimidine in CH_3COOH—PPA and $(CH_3CO)_2O$—$HClO_4$ systems:



No other reaction products were detected in the acetylation of 1-methylaceperimidine.

Thus the N-methyl group completely hinders acylation at the 9 position.

The use of PPA sometimes makes it possible to combine the two reactions. Thus the reaction of 1,8-diaminonaphthalene with 2 moles of acetic acid in PPA at 120-125° led immediately to 2-methyl-4(9)-acetylperimidine in 45% yield. The reaction with 5,6-diaminoacenaphthene (in the form of the dihydrochloride) proceeds similarly.

Thus electrophilic substitution in the perimidine series proceeds primarily in the para position in the case of kinetic control, i.e., it is determined by the localization energies rather than the effective atomic charges. This constitutes evidence that the structure of the transition state in the acylation is similar to that of a σ complex, and p-quinoid structure VII is more advantagous than o-quinoid structure VIII:

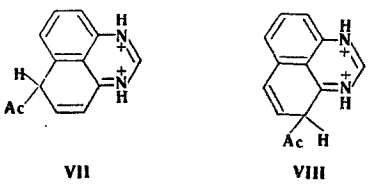


TABLE 2. Properties of the Compounds Obtained

Compound type	R′	R″	mp, °C (crystallization solvent)	ν_{NH}, cm^{-1}	R_f[a]	Color of the compound	Empirical formula	Found, %			Calc., %		
								C	H	N	C	H	N
II	H	CH_3	235—236 (ethanol)	3255	0,22	Yellow	$C_{15}H_{12}N_2O$	76,2	5,0	12,0	76,2	5,1	11,8
II	H	$CH_3C_6H_2$	171—172 (ethanol)	3260	0,35	Yellow	$C_{16}H_{14}N_2O$	76,6	5,9	11,2	76,8	5,6	11,2
II	H	$C_{17}H_{35}$	91—92 (heptane)	3255	0,53	Yellow	$C_{31}H_{44}N_2O$	81,2	9,6	5,8	80,8	9,6	6,1
II	H	C_6H_5	246—247 (ethanol)	3258	0,25	Bright-red	$C_{20}H_{14}N_2O$	80,8	5,0	9,1	80,5	4,8	9,4
II	H	p-$CH_3OC_6H_4$	208—209 (ethanol)	3260	0,20	Orange	$C_{21}H_{16}N_2O_2$	76,5	5,0	8,2	76,8	4,9	8,5
II	CH_3	CH_3	181—182 (heptane)	3246	0,66	Yellow	$C_{16}H_{14}N_2O$	77,0	5,9	11,5	76,8	5,6	11,2
VI	—	—	195—196 (toluene)	—	0,24	Yellow	$C_{16}H_{14}N_2O$	76,9	5,8	11,1	76,8	5,6	11,2
IV	H	CH_3	221—222 (aqueous ethanol)	3429	0,68[b]	Yellow	$C_{13}H_{10}N_2O$	74,6	4,9	13,1	74,3	4,8	12,8
V	H	CH_3	201—202 (aqueous ethanol)	3200	0,26	Yellow-green	$C_{13}H_{10}N_2O$	74,5	4,8	13,0	74,3	4,8	12,8
IV	CH_3	CH_3	201—202 (toluene)	3426	0,76[b]	Yellow-green	$C_{14}H_{12}N_2O$	75,0	5,6	12,3	74,9	5,3	12,5
V	CH_3	CH_3	195—196 (aqueous ethanol)	3200	0,58	Yellow-green	$C_{14}H_{12}N_2O$	75,0	5,3	12,5	74,9	5,3	12,5
IV	C_6H_5	CH_3	198—200 (benzene)	3430	0,86[b]	Orange-red	$C_{19}H_{14}N_2O$	80,0	5,2	9,4	79,7	4,9	9,8
V	C_6H_5	CH_3	164—165 (ethanol)	3320	0,97	Yellow-green	$C_{19}H_{14}N_2O$	79,6	5,2	9,4	79,7	4,9	9,8
IV	H	C_6H_5	227—229 (benzene)	3426	0,73[b]	Yellow	$C_{18}H_{12}N_2O$	79,4	4,5	10,4	79,4	4,4	10,3
V	H	C_6H_5	208—209 (benzene-petroleum ether)	3250	0,38	Yellow	$C_{18}H_{12}N_2O$	79,8	4,7	10,6	79,4	4,4	10,3

[a] In chloroform.

[b] In chloroform–ethanol (10:1).

With respect to their ease in undergoing acylation, perimidines are similar to phenols, for which acylation reactions in the presence of perchloric acid [9] and PPA [10, 11], as well as rearrangement of p-acyl derivatives to ortho isomers [12], are well known.

EXPERIMENTAL METHOD

The quantum-chemical calculations were made by the simple Hückel MO method in accordance with the procedure in [6]. The PMR spectra were recorded with a Tesla BS 487C spectrometer with hexamethyldisiloxane as the internal standard. The IR spectra of chloroform solutions were recorded with a UR-20 spectrometer.

The course of the reactions was followed by means of thin-layer chromatography (TLC). The compounds were purified and the isomers were separated by means of chromatography with a column filled with activity IV (Brockmann classification) aluminum oxide. The 4(9)-acylperimidines (first fraction) were eluted with chloroform, and the 6(7)-acylperimidines (second fraction) were eluted with chloroform–alcohol (10:1).

Acylation of Perimidines in PPA. A mixture (protected from air moisture) of 10 mmole of the appropriate perimidine or aceperimidine, 15 mmole of a carboxylic acid (or 7.5 mmole of its anhydride) and a tenfold (by weight, based on the perimidine) amount of PPA was stirred at a definite temperature for several hours (see Table 1). The hot reaction mixture was poured in the form of a fine stream into 200 ml of vigorously stirred cold water, after which the mixture was made alkaline to pH-8.5 with ammonia, and the resulting precipitate (sometimes resinous) was separated, washed with water, dried and subjected to column chromatography.

Acetylation in the Presence of Perchloric Acid. A) A total of 3 ml of 57% perchloric acid was added dropwise to a vigorously stirred suspension of 5 mmole of the appropriate perimidines or aceperimidine in 10 ml of acetic anhydride at such a rate that the temperature of the mixture rose to 115° toward the end of the addition, after which the mixture was maintained at this temperature for 30-40 sec. The reaction mass was then allowed to cool with stirring at room temperature for another 30 min. It was then treated with 10% ammonium hydroxide to pH 8-8.5, and the resulting precipitate was separated by filtration, washed with water, dried, and subjected to column chromatography to give the corresponding 4(9)-acetylperimidine or 4(9)-acetylaceperimidine (Table 1).

B) A total of 3 ml of 57% perchloric acid

was added dropwise with stirring and cooling to 10 ml of acetic anhydride, after which 1 g (6 mmole) of perimidine was added. The mixture was stirred at 70-75° for 3.5 h, after which it was cooled, and the resulting precipitate was removed by filtration, suspended in 50 ml of water, and treated with ammonia. The resulting crystals were separated by filtration, washed with water, dried, and subjected to column chromatography to give 0.15 g (12%) of 4(9)-acetylperimidine and 0.65 g (52%) of 6(7)-acetylperimidine.

Rearrangement of 6(7)-Acetylperimidine. A) The reaction of 1.05 g (5 mmole) of 6(7)-acetylperimidine with stirring in PPA (10 g) for 2.5 h at 130-145° gave 0.77 g (73%) of 4(9)-acetylperimidine (the product was isolated and purified as described for acylation in PPA).

B) A mixture of 1.05 g (5 mmole) of 6(7)-acetylperimidine, 0.15 ml (2.5 mmole) of acetic acid, and 10 g of PPA was stirred at 70-75° for 4 h, after which the product was isolated and purified by the general method to give 0.11 g (10%) of 4(9)-acetylperimidine and 0.87 g (83%) of starting 6(7)-acetylperimidine.

Rearrangement of 6(7)-Benzoylperimidine. A total of 0.17 g (25%) of 4(9)-benzoylperimidine was isolated from a stirred reaction mixture containing 0.68 g (2.5 mmole) of 6(7)-benzoylperimidine in PPA (7 g) at 130-140° after 4 h. Crystals of benzoic acid, which sublimed from the reaction mixture, formed on the walls of the flask during the reaction.

Preparation of 2-Substituted 4(9)-Acylperimidines Directly from peri-Diamines. 2-Methyl-4(9)-acetylperimidine. A total of 1.0 g (45%) of V ($R'=R''=CH_3$) (the product was isolated and purified by the general method for acylation in PPA) was obtained from the reaction of 1.58 g (10 mmole) of 1,8-naphthalenediamine with 1.45 ml (25 mmole) of acetic acid in 20 g of PPA at 120-125° for 3.5 h.

2-Methyl-4(9)-acetylaceperimidine. A total of 1.0 g (40%) of II ($R'=R''=CH_3$) (HCl was evolved in the first 30 min of the reaction) was formed as a result of the reaction of 2.57 g (10 mmole) of 5,6-diaminoacenaphthene dihydrochloride with 1.7 ml (30 mmole) of acetic acid in 20 g of PPA, initially at 95° for 3 h and then at 120-130° for 30 min.

Methylation of 4(9)-Acetylaceperimidine. A 0.63-ml (10 mmole) sample of methyl iodide was added to a suspension of 1.18 g (5 mmole) of 4(9)-acetylaceperimidine in 15 ml of DMFA, and the mixture was stirred on a boiling water bath for 1 h. It was then cooled, and the resulting precipitate was removed by filtration, suspended in 50 ml of water, and treated with ammonia. The resulting yellow crystals were separated, washed with water and 5 ml of alcohol, and dried to give 1.18 g (94%) of VI. No melting-point depression was observed for a mixture of this product with the product of acetylation of 1-methylaceperimidine in CH_3COOH—PPA and $(CH_3CO)_2O$—$HClO_4$ systems.

Only the starting compound was isolated in 80% yield in an attempt to methylate 4(9)-acetylaceperimidine in alcohol alkali by the method in [3].

LITERATURE CITED

1. V. A. Anisimova and A. F. Pozharskii, Khim. Geterotsikl. Soedin., 137 (1974).
2. A. F. Pozharskii, I. S. Kashparov, P. J. Holls, and V. Zaletov, Khim. Geterotsikl. Soedin., 543 (1971).
3. A. F. Pozharskii and I. S. Kashparov, Khim. Geterotsikl. Soedin., 111 (1970).
4. A. F. Pozharskii and I. S. Kashparov, Khim. Geterotsikl. Soedin., 1129 (1970).
5. V. I. Minkin, Yu. A. Zhdanov, I. D. Sadekov, O. A. Raevskii, and A. D. Garnovskii, Khim. Geterotsikl. Soedin., 1100 (1967).
6. A. F. Pozharskii and E. N. Malysheva, Khim. Geterotsikl. Soedin., 103 (1970).
7. O. Christman, Chem. Ber., 98, 1282 (1965).
8. V. Balasubramaniyan, Chem. Rev., 66, 578 (1966).
9. G. N. Dorofeenko, Yu. A. Zhdanov, V. I. Dulenko, and S. V. Krivun, Perchloric Acid and Its Compounds in Organic Synthesis [in Russian], Izd. Rostov. Univ. (1965), p. 53.
10. P. D. Gardner, J. Amer. Chem. Soc., 76, 4550 (1954).
11. H. R. Snyder and C. T. Elston, J. Amer. Chem. Soc., 77, 364 (1955).
12. A. H. Blatt, in: Organic Reactions, Vol. 1, New York (1942), p. 342.