HETEROCYCLIC ANALOGS OF PLEIADIENE

IV*. REACTIVITY OF THE C_2 ATOM IN THE PERIMIDINE AND ACEPERIMIDINE SERIES

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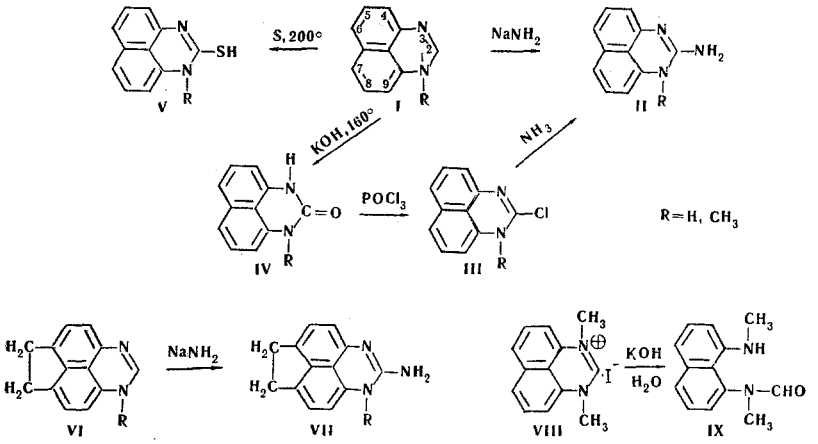
N-substituted derivatives of perimidine and aceperimidine are readily aminated by sodium amide in position 2 with the formation of previously unknown 2-amino derivatives. Some other reactions taking place at the μ-carbon atom of perimidine have also been studied: direct hydroxylation with caustic potash, the ammonolysis of the 2-chloro derivatives, the action of alkalis on the quarternary salts, and the direct thiolation of the perimidines with sulfur, leading to 2-mercaptoperimidines.

According to quantum-mechanical calculations [2], nucleophilic substitution reactions of the C_2 atom should be highly characteristic for the molecule of perimidine I. In the present paper we give experimental results confirming this conclusion.

As was found, 1-substituted perimidines, and also aceperimidines, readily participate in the Chichibabin reaction with sodium amide in xylene or dimethylaniline, which leads to the formation in high yields of the previously unknown 2-aminoperimidines II and 2-aminoaceperimidines VII (Table 1).

In the case of the 1-alkylperimidines, the best results were obtained in dimethylaniline, while the aceperimidines are aminated preferentially in xylene. The high solubility of 2-amino-1-benzylperimidine in dimethylaniline and in xylene greatly complicates the isolation and purification of the amine.

In contrast to 1-methoxymethylbenzimidazole [3], 1-methoxymethylperimidine could be subjected to amination, although under more severe conditions (160°C, dimethylaniline). This confirms the conclusion drawn previously [4] that for a successful Chichibabin reaction, in addition to an effective positive charge



*For Communication III, see [1].

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TABLE 1. Characteristics of the Compounds Synthesized

Compound	R	Solvent for Crystallization	mp, °C	Empirical formula	Found, %			Calculated, %			Yield*, %
					C	H	N	C	H	N	
II	CH_3	Benzene	236—237	$C_{12}H_{11}N_3$	72,85	5,58	21,29	73,07	5,62	21,30	90 (75)
II	C_2H_5	Ditto	227—228	$C_{13}H_{13}N_3$	73,77	5,89	19,74	73,90	6,20	19,90	90
II	C_3H_7	Water	167—168	$C_{14}H_{15}N_3$	74,67	6,81	18,87	74,63	6,71	18,65	70
II	$CH_2C_6H_5$	Aqueous ethanol	221—222	$C_{18}H_{15}N_3$	78,95	5,40	15,12	79,02	5,53	15,38	70
II	CH_2OCH_3	Ditto	170—171	$C_{13}H_{13}N_3$	68,55	5,70	18,37	68,70	5,81	18,49	30 (75)
VII	CH_3	„ „	269—270	$C_{14}H_{13}N_3$	75,12	5,95	18,61	75,31	5,87	18,82	30 (75)
VII	C_2H_5	„ „	205—206	$C_{15}H_{15}N_3$	75,77	6,12	17,95	75,92	6,37	17,77	25 (68)
IV	CH_3	Acetic acid	229—230	$C_{12}H_{10}N_2O$	72,54	4,96	14,30	72,71	5,08	14,13	95
III	CH_3	Absolute xylene	98—99	$C_{12}H_9ClN_2$	66,37	4,20	12,97	66,52	4,20	12,93	90
IX	CH_3	Ethanol	209—210	$C_{13}H_{14}N_2O$	73,07	6,42	12,79	72,87	6,57	13,07	100
V	H	Aqueous ethanol	—	$C_{11}H_8N_2S$	65,82	3,96	13,77	65,97	4,02	13,98	100
V	CH_3	Ditto	230—231	$C_{12}H_{10}N_2S$	67,20	4,60	13,04	67,26	4,70	13,07	95

*The yields of aminoperimidines and aminoaceperimidines when the reactions were carried out in xylene are given in parentheses.

on the carbon atom, the pyridine nitrogen atom must also have adequate basicity. The pK_a values of the 1-methoxymethyl derivatives of benzimidazole and perimidine are, respectively, 4.17 and 4.91. The amination of the methoxymethyl derivatives is best performed in xylene, and it is easy to isolate the amine formed from the reaction mixture.

For a direct proof of the entry of the amino group into position 2 we also performed an independent synthesis of 2-aminoperimidines from the 2-hydroxyperimidines IV. The chlorine atom in a 2-chloroperimidine III, on treatment with an alcoholic solution of ammonia or with water, is readily replaced by an amino or a hydroxy group, which once again confirms the presence of a high effective positive charge on the C_2 atom of the perimidine system. Probably because of the high mobility of the chlorine atom, the alkylation of a 2-chloroperimidine in alcoholic or aqueous alkali even in an atmosphere of nitrogen leads to the formation of resinous products. Attempts to perform the methylation of 2-chloroperimidine with diazomethane did not lead to the desired results, either: it was possible to isolate the starting material (93%) and only 3% of the 1-methyl derivative from the reaction mixture.

We did not succeed in performing the amination of perimidines with sodium amide in liquid ammonia (-33°C) or the reaction with hydroxylamine under the conditions characteristic for the benzothiazoles [5].

We have found that the 1-alkylperimidines readily undergo Chichibabin direct hydroxylation with caustic potash [6]. Hydroxylation takes place rapidly, is accompanied by the evolution of the theoretical amount of hydrogen, and leads to the formation of the 2-hydroxyperimidines IV in high yield.

Perimidines, like imidazoles [8], are readily thiolated on being heated with sulfur with the formation of 2-mercapto derivatives V, which can also be obtained by fusing 1,8-naphthylenediamines with thiourea.

The perimidinium salts VIII, like imidazolium salts [7], readily form the pseudo bases IX on brief heating with aqueous alkalis.

EXPERIMENTAL

The 1-substituted perimidines I and aceperimidines VI were obtained as described previously [1].

Their amination takes place rapidly with the evolution of a large amount of hydrogen and is usually complete after 10-15 min in dimethylaniline and after 1 hr in xylene. The only difficulty is the ready oxidizability of the sodium derivative of the amine formed during the reaction. Because of this, amination and, particularly, the decomposition of the sodium salt of the amine with water must be carried out in an atmosphere of nitrogen.

2-Amino-1-methylperimidine (II, R = CH_3). a. A solution of 1.8 g (0.01 mole) of I (R = CH_3) in 10 ml of dry dimethylaniline was added with stirring to a suspension of 0.78 g (0.02 mole) of $NaNH_2$ in 5 ml of

dimethylaniline heated to 70-80°C. After the addition of the whole of the solution, the temperature was slowly raised to 110-115°C and was kept at this level until the evolution of hydrogen had ceased. The reaction took place vigorously, and was practically complete after 10-15 min. Cooling and the treatment of the sodium derivative of the amine with water (15 ml) were carried out in an atmosphere of nitrogen. The amine formed was filtered and was washed successively with water, benzene, and petroleum ether. Yield 1.7 g (90%). Colorless needles with mp 236-237°C (from benzene).

b. A solution of 1.8 g (0.01 mole) of I (R = CH_3) in 25 ml of dry xylene was added to a suspension of 0.78 g (0.02 mole) of $NaNH_2$ in 10 ml of xylene. The mixture was boiled with stirring until the evolution of hydrogen ceased, which generally required not more than 1 hr. The amine was isolated as described above.

The amination of the other 1-substituted perimidines and aceperimidines was carried out similarly (see Table 1).

c. 2-Chloro-1-methylperimidine (0.7 g, 3 mmoles) was heated in a sealed tube with an ethanolic solution of ammonia (0.3 g, 15 mmoles, in 20 ml of ethanol) at 100°C for 3 hr. The tube was opened and the amine was precipitated with water. Yield 0.58 g (90%). Colorless needles with mp 237°C (from benzene). A mixture with the amination product gave no depression of the melting point.

2-Aminoperimidine (II, R = H) was obtained by the ammonolysis of 2-chloroperimidine in the same way as 2-amino-1-methylperimidine. Yield 90%. Mp 239-240°C (from water), which corresponds to literature data [9]. When 2-aminoperimidine was obtained from 1,8-naphthylenediamine and cyanogen bromide under the conditions for the synthesis of 2-aminobenzimidazole [10], the amino derivative was produced with yield of 30% in a form very difficult to purify.

Perimidone (IV, R = H). A mixture of 2.3 g (0.01 mole) of 1,8-naphthylenediamine hydrochloride and 1.2 g (0.02 mole) of urea was heated at 200°C for 30 min. The melt was triturated and treated with water. Yield 1.8 g (100%). Colorless plates with mp 305°C (from acetic acid), which corresponds to literature data [9].

2-Chloroperimidine (III, R = H). Perimidone (5.5 g, 0.03 mole) was boiled with phosphorus oxychloride (30 ml) for 3 hr. Then the excess of phosphorus oxychloride (20 ml) was distilled off and the residue was poured onto ice. The green crystals of the 2-chloroperimidine hydrochloride were filtered off and washed with a large volume of cold water. The 2-chloroperimidine was carefully precipitated from the filtrate with ammonia. Yield 5.4 g (91%). Pale green plates with mp 194°C (from absolute acetone), which corresponds to literature data [9].

1-Methyl-2-oxoperimidine (IV, R = CH_3). A mixture of 1.8 g (0.01 mole) of I (R = CH_3) and 1.2 g (0.02 mole) of dry KOH was heated to 160°C and kept at this temperature until the evolution of hydrogen had ceased (3-5 min). Then the melt was treated with 20 ml of 5% HCl, the mixture was filtered, and the residue was washed with water. Yield 1.85 g (95%), mp 230°C (from acetic acid).

2-Chloro-1-methylperimidine (VI, R = CH_3) was obtained similarly to 2-chloroperimidine. Yield 90%. Mp 98-99°C (from absolute xylene).

N-Formyl-N,N'-dimethyl-1,8-naphthylenediamine (IX). A solution of 0.33 g (1 mmole) of 1,3-dimethylperidinium iodide (VIII) in 5 ml of water was treated with 10 ml of 10% KOH solution. The mixture was heated in the water bath for 30 min. The grey precipitate that deposited was filtered off and washed with water. Yield quantitative. Colorless needles with mp 209°C (from ethanol).

2-Mercaptoperimidine (V, R = H). Perimidine (1.6 g, 0.01 mole) was fused with sulfur (0.96 g, 0.03 mole) at 200°C for 10-15 min. The melt was treated with 10% NaOH solution, boiled with carbon, and neutralized with acetic acid. Yellow high-melting powder soluble in ethanol, acetone, chloroform, and alkalis, and practically insoluble in ether, benzene, water and acids. Yield quantitative. 2-Mercapto-1-methylperimidine was obtained similarly.

2-Mercaptoperimidine was also formed in quantitative yield by fusing 1,8-naphthylenediamine hydrochloride with thiourea.

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