HETEROCYCLIC ANALOGS OF PLEIADIENE

XIX.* REACTION OF PERIMIDINE DERIVATIVES WITH ORGANOMETALLIC COMPOUNDS

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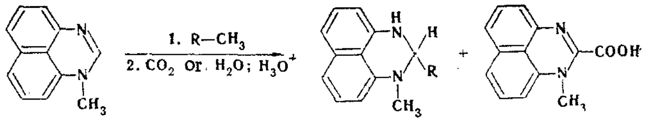
UDC 547.419.6.559.732.856.7

1-Substituted and 1,2-disubstituted perimidines and their quaternary salts react with organometallic compounds to give almost exclusively products of addition to the C=N bond. The latter are readily oxidized by chloranil or manganese dioxide to the corresponding 2-substituted perimidines. Metallation (8%) in the 2 position occurs only in the reaction of n-butyllithium with 1-methylperimidine. 1-Methyl-2-chloroperimidine reacts with organolithium compounds to give mainly 2-substituted perimidines.

Up until now, the reactions of perimidines with organometallic compounds have not been studied, although this problem is an extremely interesting one. On the one hand, the increased aromaticity of perimidines and the unusually high polarization of the C=N bond [2, 3] favor the addition of organometallic compounds to give 2,3-dihydroperimidines; on the other hand, the high positive charge on the μ-carbon atom may promote an increase in the acidity of the C_2–H bond and lead to its metallation. We have studied the effect of organolithium and organomagnesium compounds of the aliphatic, aromatic, and heteroaromatic series with 1-substituted perimidines and their quaternary salts.

It was found that, regardless of the temperature and solvent, mainly products of addition to the C=N bond (II) (Table 1) are formed in the reaction of 1-methylperimidine (I) with these organometallic compounds. Their structures were proved by the appearance in their IR spectra of a band of stretching vibrations of the NH group at 3400 cm^{-1} in chloroform solution. Attempts to establish the formation of an organometallic compound by carbonation of the reaction mixture or by reaction with benzaldehyde was successful in only one case: the previously unknown 1-methylperimidine-2-carboxylic acid (III) is formed in 5-8% yield along with 1-methyl-2-(n-butyl)-2,3-dihydroperimidine (85% yield) in the reaction of I with n-butyllithium in ether–toluene after carbonation. Acid III is readily decarboxylated at 74°C to give 1-methylperimidine.

Organolithium compounds also readily add to the C=N bond of 1,2-disubstituted perimidines (IV) to give 2,2-disubstituted 2,3-dihydroperimidines (V).



I II III

I a R=p-$CH_3C_4H_9Li$; b C_6H_5Li; c α-C_4H_3SLi; d C_6H_5MgBr; II a R=p-C_4H_9; b R=C_6H_5; c R=α- thienyl

The addition of organomagnesium compounds proceeds in low yields in this case.

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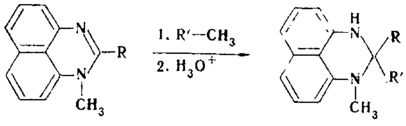
*See [1] for communication XVIII.

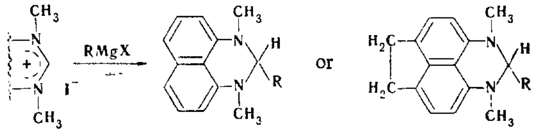
Rostov State University, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1682-1687, December, 1975. Original article submitted February 7, 1975.



IV V

IV a $R=n\text{-}C_4H_9$; b $R=C_6H_5$; V a $R=R'=n\text{-}C_4H_9$; b $R=R'=C_6H_5$

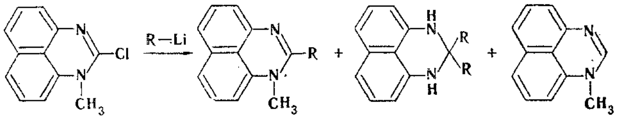
1,3-Dialkylperimidinium (VI) and 1,3-dialkylaceperimidinium (VII) salts add organometallic compounds to the C=N bond quantitatively:



VI, VII VIII a-c IX a-c

VIII, IX a $R=CH_3$; b $R=C_6H_5$; c R=α-thienyl

In order to increase the yield of 1-methyl-2-lithioperimidine we subjected 1-methyl-2-chloroperimidine (X) to reaction with n-butyllithium and phenyllithium. However, a mixture of substances consisting of the corresponding 2-substituted perimidine (XI), 2,2-disubstituted 2,3-dihydroperimidine (V), and 1-methylperimidine (28-47, 3-12, and 5-21%, respectively) was isolated when the reaction mixture was carbonated or treated with benzophenone:



X XI V I

XI a $R=n\text{-}C_4H_9$; b $R=C_6H_5$

Compounds XI are formed as a result of the Wurtz reaction, whereas dihydro derivatives V are formed by addition of excess organometallic reagents to XI. The mechanism of the formation of 1-methylperimidine (I) is not at all clear. It cannot include a step involving the formation of 1-methyl-2-lithioperimidine, inasmuch as carbonation of the reaction mixture does not lead to the isolation of the acid, and the addition of benzophenone does not give the corresponding carbinol. It might be assumed that I is formed as a result of one-electron transfer from the organolithio compound to X with subsequent reaction of the anion radical with the solvent and elimination of a chloride ion [4]. 1-Methyl-2-chloroperimidine does not react with lithium metal in refluxing toluene or ether.

The 2,3-dihydroperimidines (II) obtained are light-orange oils that darken in air as a consequence of slow oxidation to the corresponding 1-methyl-2-substituted perimidines. We used this fact to develop a new and extremely convenient method for the preparation of 2-substituted perimidines. Manganese dioxide and, particularly, chloranil proved to be the most suitable oxidizing agents for the conversion of dihydro derivatives II to perimidines (Table 2). Oxidation with pure oxygen gives poor results.

Thus our investigation showed that perimidines react with organometallic compounds to give almost exclusively products of addition to the C=N bond. In this respect, perimidines are closer to azines and acyclic compounds containing a C=N bond [5] than to highly aromatic 1-substituted benzimidazoles, which also have an amidine system of bonds and are primarily metallated by the action of organometallic compounds [6, 7].

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectrometer. The properties of the compounds are presented in Table 3.

Reaction of 1-Methylperimidine with n-Butyllithium. A solution of 5.48 g (0.04 mole) of freshly distilled butyl bromide in 10 ml of absolute ether was added with stirring to a cooled (to 0°) suspension of 0.56 g (0.08 g-atom) of finely ground lithium in 30 ml of absolute ether in a nitrogen atmosphere at such a rate that the lithium remained shiny; 30 min after the addition of all of the butyl bromide, a solution of 1.8 g (0.01 mole) of

TABLE 1. Reaction of Perimidine Derivatives with Organometallic Compounds

Starting compound	Reagent	Reaction conditions				Reaction products	Yield, %
		solvent	temp., °C	time, h	method of isolation		
I	n-Butyllithium	Ether–toluene	0	2	CO_2	III	5
						IIa	84
I	n-Butyllithium	Ether–toluene	−78	1	CO_2	III	8
						IIa	87
I	n-Butyllithium	THF	−78	2	CO_2	IIa	98
I	Phenyllithium	Ether–toluene	Refluxing	1	C_6H_5CHO	IIb	96
I	Phenyllithium	Ether–toluene	−78	2	CO_2	IIb	94
I	Phenylmagnesium bromide	Ether–toluene	Refluxing	1	H_2O	IIb	91
I	α-Thienyllithium	Ether–toluene	Refluxing	1	CO_2	IIc	94
IVa	n-Butyllithium	Ether–toluene	0	1.5	CO_2	Va	60
IVb	Phenyllithium	Ether–toluene	−15	1	CO_2	Vb	77
IVb	Phenylmagnesium bromide	Ether–toluene	Refluxing	9	H_2O	Vb	5
VI	Methylmagnesium iodide	Ether	Refluxing	0.2	H_2O	VIIIa	90
VI	Phenylmagnesium bromide	Ether	Refluxing	0.3	H_2O	VIIIb	75
VI	α-Thienylmagnesium iodide	Ether	Refluxing	0.5	H_2O	VIIIc	90
VII	Methylmagnesium iodide	Ether	Refluxing	0.2	H_2O	IXa	90
VII	Phenylmagnesium bromide	Ether	Refluxing	0.3	H_2O	IXb	91
VII	α-Thienylmagnesium iodide	Ether	Refluxing	0.5	H_2O	IXc	91
X	n-Butyllithium	Ether–toluene	0	1.5–2	CO_2	I	17
						XIa	28
						Va	2
X	n-Butyllithium	Ether–toluene	0	1.5–2	$(C_6H_5)_2CO$	I	21
						XIa	30
						Va	2.5
X	Phenyllithium	Ether–toluene	−78	2	CO_2	XIb	45
						Vb	12
X	Phenyllithium	Ether–toluene	−78	2	$(C_6H_5)_2CO$	I	5
						XIb	47
						Vb	9

TABLE 2. Oxidation of 1-Methyl-2,3-dihydroperimidines IIa-c to 1-Methyl-2-substituted Perimidines

Starting compound	Oxidizing agent	Time, h	Yield, %
IIa	Oxygen	24	29
IIb	Oxygen	24	20
IIa	Chloranil	1	62
IIb	Chloranil	1	65
IIc	Chloranil	1.5	76
IIa	Manganese dioxide	5	76

TABLE 3. Properties of the Compounds

Compound	mp (bp), °C	Empirical formula	Found, %			Calc., %		
			C	H	N	C	H	N
IIa	186—188 (3 mm)	$C_{16}H_{20}N_2$	80,2	8,4	11,7	79,9	8,4	11,6
IIb	218—219 (3 mm)	$C_{18}H_{16}N_2$	82,6	6,1	10,6	83,0	6,2	10,8
IIc	214—217 (3 mm)	$C_{16}H_{14}N_2S$	72,3	5,5	10,9	72,1	5,3	10,5
III	74 (dec.)	$C_{13}H_{10}N_2O_2$*	—	—	—	—	—	—
IVa	85 (from heptane	$C_{16}H_{18}N_2$	79,9	7,4	11,5	80,6	7,6	11,7
Va	—	$C_{20}H_{28}N_2$	81,5	10,4	8,8	81,1	9,5	9,5
Vb	148 (from octane)	$C_{24}H_{20}N_2$	85,6	6,3	7,7	85,6	6,0	8,3
VIIIc	181—182 (from alcohol)	$C_{17}H_{16}N_2S$	72,9	5,6	10,1	72,8	5,8	10,0
IXb	179—180 (from alcohol	$C_{21}H_{20}N_2$	83,6	6,5	9,5	83,7	6,7	9,3
IXc	209—210 (from alcohol)	$C_{19}H_{18}N_2S$	74,2	5,7	9,3	74,5	5,9	9,1

*In view of the facile decarboxylation of the compound we were unable to obtain satisfactory results of elementary analysis.

1-methylperimidine in 30 ml of absolute toluene was added all at once at 0° to the n-butyllithium solution. After 2 h, the mixture was carbonated with dry ice. The excess CO_2 was evaporated, and 30 ml of water was added to the brown-red solution containing a small amount of a fine yellow precipitate. The layers were separated, and the solvent was removed from the organic layer by distillation to give 2 g (84%) of 1-methyl-2-(n-butyl)-2,3-dihydroperimidine IIa, which was purified by vacuum distillation to give a light-red oil. IR spectrum (chloroform), cm^{-1}: ν_{N-H} 3420.

The aqueous layer was heated with charcoal and filtered, and the filtrate was cooled and acidified with 10% acetic acid. The precipitated 1-methylperimidine-2-carboxylic acid (II) was removed by filtration and dried in a vacuum desiccator to give light-yellow crystals. IR spectrum (mineral oil), cm^{-1}: $\nu_{C=O}$ 1690 and ν_{O-H} 3450.

1-Methyl-2-phenyl-2,3-dihydroperimidine (IIb). A) Several drops of a solution of 6.28 g (0.04 mole) of bromobenzene in 10 ml of absolute ether were added at 20-25° in a nitrogen atmosphere to a stirred suspension of 0.56 g (0.08 g-atom) of finely cut lithium; warming up of the reaction mixture and cleaning of the lithium surface were observed. The remainder of the bromobenzene was added at such a rate that the mixture boiled gently. After all of the bromobenzene had been added, the mixture was stirred for 15-20 min. A solution of 1.8 g (0.01 mole) of 1-methylperimidine in 30 ml of absolute toluene was then added all at once, and the mixture was stirred at room temperature for 2 h or refluxed for 1 h, after which it was carbonated. The product [2.4 g (96%)] was isolated by the method used to isolate IIa and was purified by vacuum distillation to give a yellow oil that gradually darkened. IR spectrum (chloroform), cm^{-1}: ν_{N-H} 3400.

B) Absolute ether (10 ml) was added to 0.72 g (0.03 g-atom) of powdered magnesium that had been allowed to stand over calcium chloride and activated with a crystal of iodine, after which several drops of a solution of 4.7 g (0.03 mole) of dry bromobenzene in 8 ml of absolute ether were added with stirring. After the reaction had begun, the mixture was allowed to reflux gently; when spontaneous refluxing ceased, the mixture was refluxed until all of the magnesium had dissolved (~30 min). A solution of 1.8 g (0.01 mole) of 1-methylperimidine in 30 ml of absolute toluene was then added all at once, and the mixture was refluxed for 40 min. It was then cooled, and 15 ml of water was added carefully (spattering is possible when the water is added rapidly). The layers were separated, and the solvent was removed from the organic layer by distillation to give 2.2 g (91%) of chromatographically pure IIb.

1-Methyl-2-(α-thienyl)-2,3-dihydroperimidine (IIc). A solution of 4.2 g (0.05 mole) of freshly distilled thiophene was added with stirring in the course of 20 min to a cooled (to 0°) ether solution of n-butyllithium obtained (as in the synthesis of IIa) from 0.56 g (0.08 g-atom) of lithium and 5.48 g (0.04 mole) of butyl bromide. The mixture was stirred for another hour at 20-25°, after which a solution of 1.8 g (0.01 mole) of 1-methylperimidine in 30 ml of absolute toluene was added to the resulting solution of α-thienyllithium. The mixture was refluxed for 1 h, after which it was carbonated, and IIc was isolated and purified as in the preparation of IIa. IR spectrum (chloroform), cm^{-1}: ν_{N-H} 3400.

1-Methyl-2,2-dibutyl-2,3-dihydroperimidine (Va). A solution of 0.36 g (0.0015 mole) of 1-methyl-2-butylperimidine in 15 ml of absolute toluene was added to 0° to 10 ml of a cooled (to 0°) ether solution of n-butyllithium obtained (as in the synthesis of IIa) from 0.14 g (0.02 g-atom) of lithium and 1.4 g (0.01 mole) of butyl bromide. The mixture was stirred at 0° for 1.5 h, after which it was carbonated. The excess CO_2 was evaporated, and 25 ml of water was added to the remaining yellow-green solution. The aqueous mixture was shaken and separated, and the organic layer was washed to neutrality with water, dried, and evaporated. The mixture of the starting perimidine (~25%) and the reaction product was dissolved in alcohol, and a saturated solution of picric acid was added. The alcohol was evaporated, and the residue was dissolved in 15 ml of benzene. The benzene solution was passed through a column filled with 70 g of aluminum oxide with elution by benzene to give 0.25 g (60%) of light-yellow chromatographically pure oil Va, which darkened with time. The product did not form a hydrochloride or picrate. IR spectrum (chloroform), cm^{-1}: ν_{N-H} 3410.

1-Methyl-2,2-diphenyl-2,3-dihydroperimidine (Vb). A solution of 0.25 g (0.001 mole) of 1-methyl-2-phenylperimidine in 6-8 ml of absolute toluene was added all at once to 10 ml of a cooled (to −15°) ether solution of phenyllithium obtained, as in the synthesis of IIb, from 0.1 g (0.015 g-atom) of lithium and 1.5 g (0.01 mole) of bromobenzene. The mixture was stirred at −15° for 1 h, after which it was carbonated with dry ice. The excess CO_2 and solvent were evaporated, and the residue was suspended in 20 ml of benzene. The undissolved inorganic salts were removed by filtration, and the filtrate was passed through a column filled with 120 g of aluminum oxide with elution by benzene. The first fraction was collected, and the solvent was evaporated to give 0.25 g (77%) of light-brown crystals, which were crystallized to give a gray powder. IR spectrum (chloroform), cm^{-1}: ν_{N-H} 3400.

1,2,3-Trimethyl-2,3-dihydroperimidine (VIIIa). A 1.1-g (0.003 mole) sample of 1-methylperimidine methiodide was added to a solution of methylmagnesium iodide obtained from 0.24 g (0.01 g-atom) of magnesium shavings and 2.1 g (0.015 mole) of methyl iodide in 50 ml of absolute ether. The suspension was stirred and refluxed for 5-10 min until a colorless solution had formed. The mixture was cooled and transferred to a separatory funnel and washed with 40 ml of water to remove the magnesium iodide. The ether was removed by distillation, and the residue crystals were dried at 100° to give 0.63 g (90%) of colorless needles of VIIIa with mp 126° (from alcohol) (mp 126° [7]).

1,3-Dimethyl-2-phenyl-2,3-dihydroperimidine (VIIIb). As in the preceding experiment, colorless plates of VIIIb, with mp 176-177° (from alcohol) (mp 176-177° [7]), were obtained in 75% yield from 1-methylperimidine methiodide.

1,3-Dimethyl-2-(α-thienyl)-2,3-dihydroperimidine (VIIIc). Magnesium shavings [0.24 g (0.1 g-atom)] were heated with a crystal of iodine in a reaction flask in order to coat their surface with iodine vapors, after which a solution of 2.1 g (0.01 mole) of 2-iodothiophene in 50 ml of absolute ether was added. The mixture was stirred and refluxed until the magnesium had dissolved completely, after which 1.3 g (0.004 mole) of 1-methylperimidine methiodide was added to the gray solution, and the suspension was refluxed for 30-40 min until a gray mass formed. The product (VIIIc) was isolated as in the preparation of VIIIa to give 1 g (90%) of colorless needles.

1,2,3-Trimethyl-2,3-dihydroaceperimidine (IXa). This compound, with mp 146-147° (from alcohol) (in agreement with the melting point in [7]), was obtained as sand-colored prisms in 90% yield by reaction of methylmagnesium iodide with 1-methylaceperimidine methiodide as in the preparation of VIIIa.

1,3-Dimethyl-2-phenyl-2,3-dihydroaceperimidine (IXb). This compound was obtained in 91% yield by the method used to prepare VIIIb.

1,3-Dimethyl-2-(α-thienyl)-2,3-dihydroaceperimidine (IXc). Sand-colored prisms of this compound were obtained in 91% yield by the method used to prepare VIIIc.

Reaction of 1-Methyl-2-chloroperimidine with Phenyllithium. A solution of 2.1 g (0.01 mole) of 1-methyl-2-chloroperimidine in 30 ml of absolute toluene was added all at once to a cooled (to −78°) ether solution of phenyllithium obtained as described for IIb from 0.56 g (0.08 g-atom) of lithium and 6.28 g (0.04 mole) of bromobenzene. After 2 h, the mixture was carbonated. The excess CO_2 was evaporated, and the residue was treated with 30 ml of water. The layers were separated, and the organic layer was dried, concentrated to 20 ml, and passed through a column filled with 120 g of aluminum oxide with elution by benzene. The first fraction [0.4 g (12%)] contained 1-methyl-2,2-diphenyl-2,3-dihydroperimidine (Vb). The gray crystals had mp 148° (from octane). No melting-point depression was observed for a mixture of the product with an authenic sample. The IR spectra were also identical. The second fraction [1.3 g (48%)] contained 1-methyl-2-phenylperimidine. The third fraction [0.1 g (5%)] contained 1-methylperimidine.

Reaction of 1-Methyl-2-chloroperimidine with Butyllithium. 1-Methyl-2,2-dibutyl-2,3-dihydroperimidine (Va) [0.08 g (2.5%)] (identified by comparison of its IR spectrum with the spectrum of a genuine sample), 1-methyl-2-butylperimidine [0.75 g (31%)], and 1-methylperimidine [0.5 g (21%)] were isolated from the reaction of 2.1 g (0.01 mole) of 1-methyl-2-chloroperimidine with an ether solution of n-butyllithium obtained as in the preparation of IIa from 0.56 g (0.08 g-atom) of lithium and 5.5 g (0.04 mole) of butyl bromide under conditions similar to those in the preceding experiment.

Oxidation of IIa-c with Chloranil. A solution of 0.01 mole of II and 0.01 mole of chloranil in 30 ml of absolute toluene was refluxed for 1 h, after which the solvent was removed by distillation, and the residue was dissolved by heating in 40-50 ml of 15% hydrochloric acid. The acid solution was boiled with charcoal twice and filtered. The filtrate was cooled and filtered to remove the unchanged chloranil. The filtrate was neutralized with ammonia, and the reaction product was extracted with chloroform. The extract was washed with water and dried, and the solvent was removed by distillation to give chromatographically pure crystals of 2-substituted perimidine.

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HETEROCYCLIC ANALOGS OF PLEIADIENE

XX.* ACYLATION OF PERIMIDONES, THIOPERIMIDONES, AND 2,3-DIHYDROPERIMIDINES

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UDC 547.856.7.07:542.951.9

Perimidones, thioperimidones, and 2,3-dihydroperimidines are acylated by carboxylic acids in polyphosphoric acid somewhat more readily than perimidines and give 6-acetyl derivatives when there are substituents attached to the nitrogen atom or a mixture of 4- and 6-acetyl derivatives with predominance of the latter in the case of N-unsubstituted compounds.

In our previous paper [2] we showed that perimidines (I), like π-donor aromatic systems (for example, phenols and their alkyl ethers [3]), are readily acylated by carboxylic acids in polyphosphoric acid (PPA) to give 6(7)-acylperimidines at 70-80°C and 4(9)-acylperimidines at 120-150°. Inasmuch as this is hardly the first case of Friedel-Crafts acylation in heterocycles containing a pyridine nitrogen atom, it was important to ascertain whether it is the result of the specific π-donor character of the perimidine system as a whole [4] or is a phenomenon peculiar to the π-donor 1,8-naphthalenediamine fragment. In the latter case, one might have expected that compounds such as 2,3-dihydroperimidines (II), perimidones (III), and thioperimidones (IV) would also underto acylation by carboxylic acids in PPA. The present research was devoted to verification of this possibility. [See structure on top of next page.]

We have found that 1,3-dimethyl-2,3-dihydroperimidine (II) is acetylated by the CH_3COOH-PPA system at 45-50° to give V in 55% yield. The structure of acylation product V and of 6(7)-acylperimidines [2] are readily proved by PMR spectroscopy owing to deshielding of the aromatic peri proton of the unshared pair of electrons of the oxygen atom of the CH_3CO group.

The acylation of perimidones has already been reported. It has been shown [5] that perimidone is acylated by benzoyl chloride in the presence of $AlCl_3$ to give a monobenzoylperimidone of unestablished structure.

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*See [1] for communication XIX.

Rostov State University, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1688-1691, December, 1975. Original article submitted February 7, 1975.