HETEROCYCLIC ANALOGS OF PLEIADIENE.
XXVI.[*] REACTION OF 1-METHYLPERIMIDINE AND 1-METHYL-2-CHLOROPERIMIDINE WITH ALKALI METALS AND THEIR NAPHTHALENIDES

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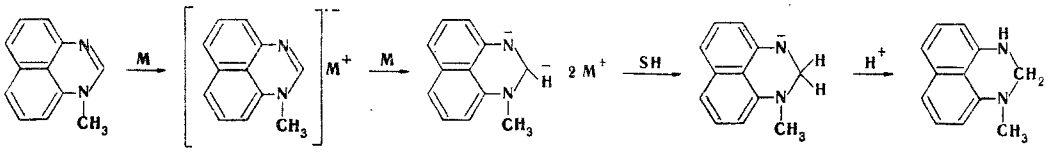
1-Methylperimidine reacts with alkali metals or their naphthalenides to give, depending on the nature of the metal and the experimental conditions, an anion radical or a dianion. The latter are converted to a mixture of 1-methyl- and 1-methyl-2,3-dihydroperimidines. In the case of naphthyllithium, 1-methyl-2-α-naphthylperimidine was also isolated in 30% yield. 1-Methyl-2-chloroperimidine reacts with the same reagents to give primarily 1-methylperimidine. 1-Methyl-2,3-dihydroperimidine and 1,1'-dimethyl-2,2'-diperimidinyl are also formed in small amounts.

It has been previously shown [2] that 1-methylperimidine (I) reacts with organometallic compounds to give almost exclusively products of addition to the C=N bond. The formation of 1-methyl-2-lithioperimidine in 8% yield was recorded in only one case (in the reaction of I with n-butyllithium in ether–toluene at –78°C). In the present research we continued our search for methods for the preparation of 2-metalloperimidines. We studied the reaction of I and 1-methyl-2-chloroperimidine with alkali metals and their adducts with naphthalene. It has recently been shown that the use of naphthalenides gives good results in the metallation of azole rings [3].

A dark-green solution of the anion radical of 1-methylperimidine is formed in the reaction of I with sodium metal in tetrahydrofuran (THF) at –60°. Its ESR spectrum consists of 42 components of the hfs, the assignment of which was made on the basis of a calculation of the theoretical spectrum by the McLachlan method [4]. The maximum spin density[†] is found in the 2 and 6 positions ($a_{H_{2,6}} = 5.15$ Oe; $\rho_e = 0.22$); it is characteristic that the experimental spin densities are approximately identical on both nitrogen atoms ($a_N \approx a_{N_2} = 1.1$ Oe) (Fig. 1). A solution of anion radical II becomes diamagnetic and its color changes to red-brown when it is allowed to stand for a long time or is heated. Replacement of sodium by potassium under the same conditions leads immediately to the formation of a red-brown diamagnetic solution. Subsequent treatment of this solution with benzophenone or dry ice, as well as aeration, leads in all cases to the formation of the starting 1-methylperimidine (78-80%) and 1-methyl-2,3-dihydroperimidine V (10-13%). These data exclude the formation of an organometallic compound and the existence of dianion III in free form, since otherwise the products of their reaction with the indicated reagents would have been isolated. It is most likely that the dianion (III) formed from the anion radical undergoes immediate protonation by the solvent to give anion IV, which is subsequently converted to V.



I II III IV V

M = Na, K
SH = solvent

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[*] See [1] for communication XXV.

[†] According to McConnel [5], Q = –23.7 Oe.

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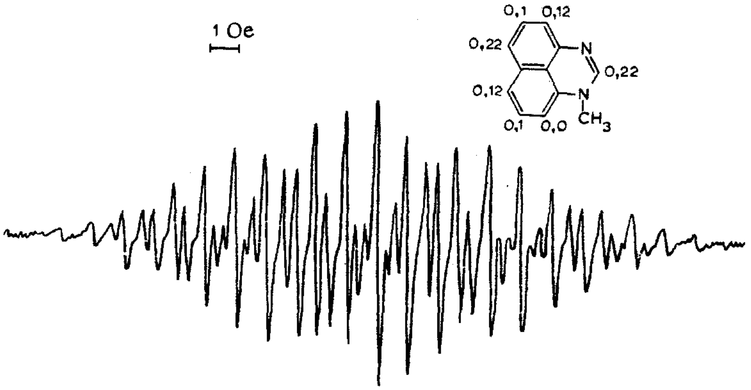
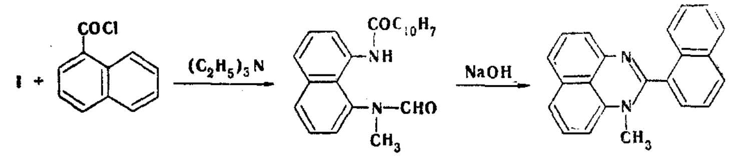


Fig. 1. ESR spectrum of the anion radical of 1-methylperimidine in THF at −60° (the ρ_e values of the carbon atoms are indicated in the formula).

The high percentage of regenerated I is evidently explained by passivation of the metal surface as the reaction takes place and the low rate of the process itself because of the heterogeneity of the reaction mixture. In fact, when THF was replaced by liquid ammonia, in which both alkali metals are soluble, the ammonium chloride (a protonating agent) was subsequently added, the yield of V was 38% in the case of potassium and 61% in the case of sodium, and the residue was starting I.

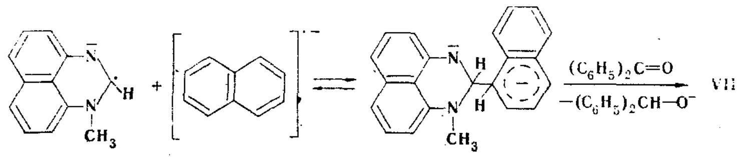
Thus, with respect to its behavior toward alkali metals, 1-methylperimidine differs sharply from 1-alkylbenzimidazoles, which form 1,1'-dialkyl-2,2'-dibenzimidazolyls [6]. This difference is explained by the fact that the formation of the indicated dibenzimidazolyls proceeds through a step involving the formation of 1-aklyl-2-metallobenzimidazoles, which subsequently add to a molecule of the starting 1-alkylbenzimidazole. It follows from our experiments that 1-methylperimidine is not metallated under these conditions.

The reaction of I with naphthyllithium in THF and subsequent treatment of the mixture with benzophenone or carbon dioxide give an extremely difficult-to-separate mixture of substances, from which we were able to extract 40-55% of starting I, 30% of V, and 10-14% of the previously undescribed 1-methyl-2-α-naphthylperimidine (VII). The structure of the latter was proved by alternative synthesis by means of recyclization [7]:



VI VII

The addition of a naphthalene residue to the 2 position of the perimidine molecule is extremely unexpected, since naphthyllithium is not a carbanion. The reaction probably proceeds via the following ion-radical scheme:

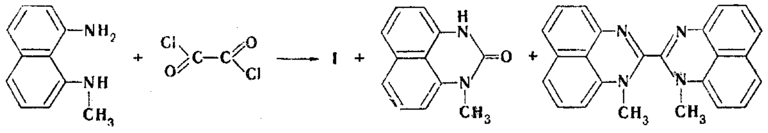


II VIII

A large part of the spin density in anion radical II is concentrated in the μ position. This circumstance promotes recombination of the naphthalene and II anion radicals to give dianion VIII. The latter is oxidized by benzophenone to give VII. We also isolated a small amount (0.04-0.06 g from 1.8 g of I) of a crystalline substance that is readily soluble in organic solvents and contains an NH group (ν_{NH} 3470 cm^{-1}) from the products of this reaction. We were unable to establish the structure of this compound, but it is not 1-methyl-2-α-naphthyl-2,3-dihydroperimidine (the formation of which might have been assumed), which we synthesized by reduction of VII. The same substance is formed in trace amounts in the reaction of I with potassium metal.

The reaction of I with naphthylsodium proceeds with difficulty. The only reaction product is V in trace amounts. This difference in the reactivity of I with respect to naphthyllithium and naphthylsodium is possibly a consequence of their different reactivities. It has been shown that naphthyllithium exists in THF at 20° in the form of the more reactive separated ion pair, while naphthylsodium exists in the form of the less reactive contact ion pair [8].

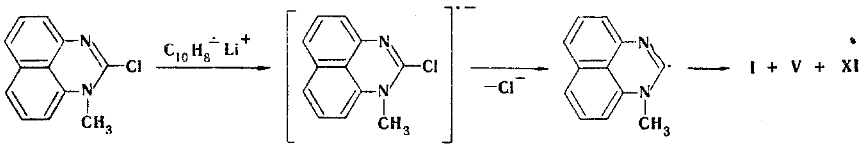
We subsequently subjected 1-methyl-2-chloroperimidine (XII) to reaction with naphthyllithium. The products of this reaction were 1-methylperimidine (66%), its dihydro derivative V (16%), and a yellow high-melting substance, similar with respect to its IR spectrum and the results of analysis to 1-methylperimidine. Since a signal at δ 7.6 ppm related to the H proton in the spectrum of 1-methylperimidine (Fig. 2) is absent in the PMR spectrum of this compound in trifluoroacetic acid, we assigned a 1,1'-dimethyl-2,2'-diperimidinyl structure to it. The structure of XI was definitively confirmed by alternative synthesis from N-methyl-1,8-naphthalenediamine and oxalyl chloride:



IX X XI

In contrast to the reaction of oxalyl chloride with 1,8-naphthalenediamine, which leads to 2,2'-diperimidinyl in 90-95% yield [9], the formation of a dimer in the case of the N-methyl-substituted compound proceeds with considerably greater difficulty, and it is obtained in only 3% yield. The principal reaction products in this case are I (35%) and 1-methylperimidone (20%). 1-Methylperimidine-2-carboxylic acid chloride is evidently formed initially and is hydrolyzed to the acid itself, which, because of its instability [2], undergoes decarboxylation. The formation of 1-methylperimidone is most likely the result of the reaction of IX with phosgene formed because of decomposition of the oxalyl chloride.

Thus, the reaction of XII with naphthyllithium can be represented as follows. The first step consists in electron transfer from naphthyllithium to the π-antibonding orbital of XII to give anion radical XIII. The latter is stabilized with splitting out of a chloride ion, which leads to σ radical XIV. This radical splits out hydrogen from the solvent to give I but, as a result of recombination, gives XI. The formation of I is a secondary reduction process via the previously discussed scheme.



XII XIII XIV

The reaction of XII with sodium metal in THF proceeds with difficulty: I and V were obtained in 13% and 8% yields, respectively, after 4 h at −20°, and dimer XI was formed in

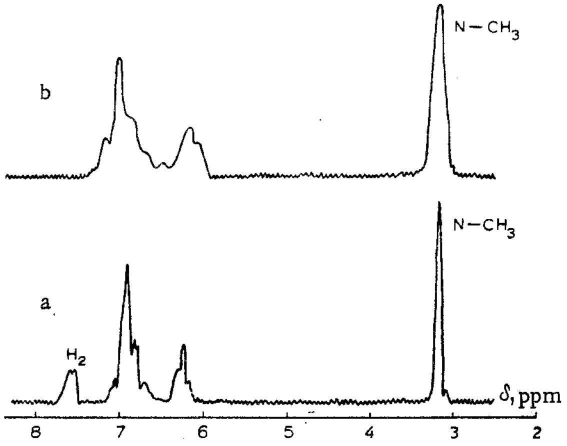


Fig. 2. PMR spectra (in CF_3COOH): a) 1-methylperimidine; b) 1,1'-dimethyl-2,2'-diperimidinyl.

trace amounts. Approximately 62% of the starting compound was regenerated. An increase in the temperature does not lead to an improvement in the results because of more rapid passivation of the metal surface.

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of trifluoroacetic acid solutions of the compounds were recorded with a Tesla spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The ESR spectrum was recorded with a Varian E-12 spectrometer. Chromatography was carried out on activity V (Brockmann scale) aluminum oxide; the R_f values for an Al_2O_3–benzene system are presented.

Reaction of I with Naphthyllithium. A 0.21-g (0.03 g-atom) sample of finely cut lithium was added with stirring in a nitrogen atmosphere to a solution of 3.2 g (0.025 mole) of naphthalene in 20 ml of absolute THF. After 3 h, a solution of 1.8 g (0.01 mole) of I in 15 ml of THF was added in the course of 10-15 min to the dark-green solution of naphthyllithium, and the mixture was stirred at room temperature for 4 h. A solution of 4.5 g (0.025 mole) of benzophenone in 15 ml of THF was added to the mixture, during which the color changed from dark-red to green. After 2 h, 15 ml of water was added, and the layers were separated. The aqueous layer was washed with ether, the ether extract was combined with the THF layer, and the solvent was removed by distillation. The residue was treated four times with a mixture of concentrated HCl (15-20-ml portions) and ether. The ether layer, which contained naphthalene and benzophenone, was discarded, and the hydrochloric acid layer was neutralized with ammonium hydroxide and extracted with chloroform. The extract was dried with anhydrous Na_2SO_4, and the solvent was removed by distillation. The reaction products were separated with a column (300 g of Al_2O_3) or (better) by thin-layer chromatography (TLC). In the first case the substances were collected in 3-5 ml fractions. Removal of the solvent gave 25-32% V (R_f 0.7), 40-55% starting I (R_f 0.3), and 10-14% VII in the form of yellow crystals with mp 184° (from octane) (R_f 0.5). Found: C 85.26; H 5.15; N 8.91%. $C_{22}H_{16}N_2$. Calculated: C 85.71; H 5.20; N 9.09%. No melting point depression was observed for a mixture of this product with an authentic sample. A similar result was obtained when benzophenone was replaced by dry ice.

Reaction of I with Naphthylsodium. A 0.7-g (0.03 g-atom) sample of finely granulated sodium was added with stirring in a nitrogen atmosphere to a solution of 3.8 g (0.03 mole) of naphthalene in 20 ml of absolute THF. After 2 h, a solution of 1.8 g (0.01 mole) of I in 15 ml of THF was added to the dark-green solution of naphthylsodium, and the mixture was stirred at room temperature for 5 h. A solution of 5.4 g (0.03 mole) of benzophenone in 15 ml of THF was then added, and the mixture was stirred for 1.5 h. Ethanol (3-4 ml) and 15 ml of water were then added to destroy the unchanged sodium, and the layers were separated. The solvent was removed from the organic layer by distillation, and the residue was treated with three to four 10-15-ml portions of concentrated HCl. The hydrochloric acid extract was neutralized with ammonium hydroxide to precipitate yellow crystals of starting I in up to 90% yield. Replacement of benzophenone by methanol in the last step led to the same result.

Reaction of XII with Naphthyllithium. A solution of 2.16 g (0.01 mole) of XII [10] in 10 ml of THF was added with stirring in a nitrogen atmosphere to a THF solution of naphthyllithium, obtained from 3.8 g (0.03 mole) of naphthalene and 0.24 g (0.035 g-atom) of lithium, during which the mixture warmed up slightly and turned red. The mixture was stirred at room temperature for 2 h, after which a solution of 5.4 g (0.03 mole) of benzophenone in 10 ml of THF was added. After 2 h, 15 ml of water was added. After separation into layers, fine crystals of 1,1'-dimethyl-2,2'-diperimidinyl (XI) formed at the interface of the two layers. They were removed by filtration and dried to give 0.15 g (4%) of shiny yellow crystals with mp >360° (from DMF) that were only slightly soluble in organic solvents. Found: C 78.93; H 5.05; N 15.53%. $C_{12}H_9N_2$. Calculated: C 79.56; H 4.97; N 15.47%. The layers were separated, and the aqueous layer was washed with ether. The extract was combined with the THF layer, the solvents were removed by distillation, and the residue was treated three times with 20-ml portions of a mixture of concentrated HCl and ether. The hydrochloric acid solution was neutralized with ammonia and extracted with chloroform. The chloroform was evaporated, and the residue was chromatographed through a column filled with 150 g of Al_2O_3 (elution with benzene) to give 0.3 g (16%) of V (first zone) and 1.2 g (66%) of I (second zone).

Reaction of I with Sodium Metal. A solution of 1.8 g (0.01 mole) of I in 30 ml of THF was added with stirring in a nitrogen atmosphere to a suspension of 0.28 g (0.012 g-atom) of finely granulated sodium in 5 ml of THF, and the mixture was stirred at room temperature for 5 h, during which the sodium gradually became passivated. The solution was decanted, the solvent was evaporated, and the residue was dissolved in benzene. The benzene solution was chromatographed through a column filled with Al_2O_3 (elution with benzene). Removal of the solvent from the eluate gave 0.24 g (13%) of V and 1.4 g (80%) of starting I. No substantial effect on the results was observed when the reaction was carried out at −78° and the THF was replaced by benzene.

Reaction of I with Potassium Metal. The reaction was carried out at 20 and 80° in toluene as in the reaction with sodium. Workup gave I in 78% yield and V in 10% yield.

Reaction of I with Potassium (Sodium) in Liquid Ammonia. A 0.52-g (0.013 g-atom) sample of potassium metal was added in portions to a light-yellow suspension of 0.9 g (0.005 mole) of I in 50-60 ml of liquid ammonia. A persistent blue coloration was formed at the end of the addition. Ammonium chloride [0.31 g (0.013 mole)] was added, during which clarification of the reaction mixture was observed. The ammonia was evaporated, the residue was dissolved in benzene, and the inorganic salts were removed by filtration. The filtrate, which contained I and V, was chromatographed through a column filled with Al_2O_3 (elution with benzene), and the solvent was removed to give 0.46 g (51%) of I and 0.34 g (38%) of V. A persistent blue coloration was not observed when potassium was replaced by sodium [0.34 g (0.015 g-atom)]. The products were similarly isolated to give 0.24 g (27%) of starting I and 0.54 g (61%) of V.

Reaction of XII with Sodium Metal. A suspension of 0.23 g (0.01 g-atom) of finely granulated sodium in 10 ml of THF in an inert atmosphere was activated with drops of isoamyl alcohol, after which it was cooled to −20°, and a solution of 2.16 g (0.01 mole) of XII in 30 ml of THF was added with stirring. The mixture was then stirred until the sodium became passive and was no longer shiny (3-4 h). The metal became passivated more rapidly when the temperature was raised. The solution was decanted from the sodium residues, and the solvent was evaporated. The residue was dissolved in benzene, and the solution was chromatographed through a column filled with Al_2O_3 (elution with benzene) with collection of small fractions (5-7 nm). Removal of the solvent gave up to 62% starting XII, 8% V, and 13% I.

Reaction of IX with Oxalyl Chloride. A 1.7-g (0.01 mole) sample of IX was dissolved in 25 ml of absolute benzene, and a solution of 1.4 g (0.011 mole) of oxalyl chloride in 10 ml of benzene was added with stirring, during which a bulky light-colored precipitate, which gradually darkened, formed. The mixture was refluxed with stirring for 2-2.5 h, after which the precipitate was removed by filtration, triturated with concentrated ammonium hydroxide, removed by filtration, and washed with water to remove ammonium hydroxide. The products were separated by column chromatography (elution with chloroform) to give 3% XI (first zone), 35% I (second zone), and 20% X (third zone).

N-Methyl-N-formyl-N'-(α-naphthoyl)-1,8-naphthalenediamine (VI). A 0.6-g (0.006 mole) sample of triethylamine was added to a solution of 0.9 g (0.005 mole) of I in a mixture of 20 ml of ether and 5 ml of benzene, after which a solution of 1 g (0.0055 mole) of α-naphthoyl chloride in 5 ml of ether was added, and the mixture was stirred at room temperature for 30 min and refluxed for 30 min. The precipitate was removed by filtration and washed with water and ether. The oily brown lump was crystallized by trituration with petroleum ether to give 0.82 g of yellowish crystals. Another 0.5 g of reaction product was isolated from the ether layer of the filtrate by evaporation for an overall yield of 1.32 g (74%) of cream-colored crystals with mp 136° (from benzene-petroleum ether). IR spectrum (chloroform): ν_{CO} 1690 and ν_{NH} 3440 cm^{-1}. Found: C 77.63; H 5.06; N 7.45%. $C_{23}H_{17}N_2O_2$. Calculated: C 78.17; H 4.84; N 7.92%.

1-Methyl-2-(α-naphthyl)perimidine (VII). A 1-g (0.003 mole) sample of VI was suspended in 20 ml of 20% NaOH solution, and the suspension was refluxed for 1 h with periodic stirring. The solid material melted, and a thin film floated on the surface of the refluxing alkali. The mixture was cooled, and the resulting lump was separated, washed with water, and triturated with petroleum ether. The product was purified by chromatography through a column filled with 100 g of Al_2O_3 (elution with benzene). The first fraction was collected and worked up to give 0.55 g (62%) of light-yellow crystals with mp 184° (from octane). Found: C 84.92; H 5.25; N 8.99%. $C_{22}H_{16}N_2$. Calculated: C 85.69; H 5.20; N 9.08%.

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REACTION OF AMIDINES OF ALIPHATIC CARBOXYLIC ACIDS WITH DIMETHYL ACETYLENEDICARBOXYLATE

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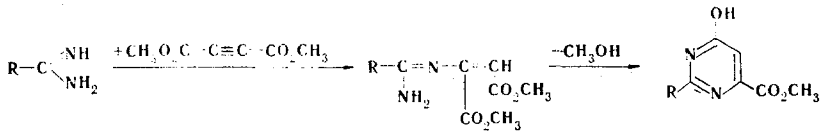
It was established that dimethyl acetylenedicarboxylate reacts with acetamidine to give methyl 4-hydroxy-2-methylpyrimidine-6-carboxylate, with formamide to give a linear addition product, and with trichloroacetamide to give cyclic and linear reaction products. The structures of the products were proved by alternative synthesis and the IR and mass spectra.

The literature does not contain data on the addition of carboxylic acid amidines to dimethyl acetylenedicarboxylate (DMAD).

In the present research we studied the addition of acetamidine, trichloroacetamidine, and formamidine to DMAD. One might have expected that esters (II) of 2-substituted 4-hydroxypyrimidine-6-carboxylic acids would be obtained via this reaction as a result of cyclization of the linear addition products (I).

Only a cyclization product — methyl 4-hydroxy-2-methylpyrimidine-6-carboxylate (IIa) — was isolated in the reaction of acetamidine with DMAD in methanol in the presence of sodium methoxide.



I–II a R–CH$_3$; b R CCl$_3$; c R H   Ia-c   IIa-c

The structure of IIa was confirmed by elementary analysis and identification with a sample of the ester obtained from 4-hydroxy-2-methylpyrimidine-6-carboxylic acid [1]. The reaction of acetamidine with DMAD at various temperatures (–15, 0, 20, and 65°C) was always accompanied by a great deal of resinification, and IIa was obtained in up to 15% yield. This is probably explained by the low stability of the acetamidine base and its Ia derivative.

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