HETEROCYCLIC ANALOGS OF PLEIADIENE. XVI.* NITRATION OF PERIMIDINE AND ITS 1- AND 2-METHYL DERIVATIVES

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Perimidine and 2-methylperimidine are nitrated by 1 mole of nitric acid in acetic acid to give a mixture of 4(9)- and 6(7)-mononitro derivatives. Renitration gives a mixture of 6,9- and 6,7-dinitroperimidines. Depending on the conditions, 6,7,9-trinitroperimidines and 4,6,7,9-tetranitroperimidines are formed when a large excess of nitric acid is present. 1-Methylperimidine is nitrated by 1 mole of nitric acid to give a mixture of 4-, 6-, and 7-mononitro derivatives.

Continuing our research on the nitration of aceperimidines [2], we studied the nitration of perimidine and its 1- and 2-methyl-substituted derivatives. In contrast to aceperimidines, which are nitrated exclusively in the 4 and 9 (ortho) positions, in perimidines, judging from the results of acylation [1] and quantum-mechanical calculations, one might expect reaction also in the 6 and 7 (para) positions. Sachs [3] nitrated perimidine with excess nitric acid (sp. gr. = 1.4) in glacial acetic acid and isolated a dinitro derivative, the structure of which he was unable to establish. The nitration of 2-methylperimidine with an eightfold excess of HNO_3 also leads to a dinitro derivative of unestablished structure [4]. We studied the reaction of perimidines I with 1, 2, or more moles of nitric acid in glacial acetic acid (the use of a nitrating mixture, potassium nitrate in sulfuric acid, and

*See [1] for communication XV

TABLE 1. Nitration of Perimidines

Starting compound	HNO_3, mole	Reaction product	Yield, %
Perimidine	1	4 (9)-Nitroperimidine	23
		6 (7)-Nitroperimidine	9
2-Methylperimidine	1	4 (9)-Nitro-2-methylperimidine	18
		6 (7)-Nitro-2-methylperimidine	46
1-Methylperimidine	1	4-Nitro-1-methylperimidine	9
		6-Nitro-1-methylperimidine	46
		7-Nitro-1-methylperimidine	25
4 (9)-Nitro-2-methylperimidine	1	6,9-Dinitro-2-methylperimidine	87
6 (7)-Nitro-2-methylperimidine	1	6,9-Dinitro-2-methylperimidine	46
		6,7-Dinitro-2-methylperimidine	39
6, 7-Dinitroperimidine	1	6,7,9,-Trinitroperimidine	74
Perimidine	2	4 (9)-Nitroperimidine	7
		6,9-Dinitroperimidine	41
		6,7-Dinitroperimidine	19
		7,9-Dinitroperimidine	4
		6,7,9-Trinitroperimidine	3
2-Methylperimidine	2	4 (9)-Nitro-2-methylperimidine	4
		6,9-Dinitro-2-methylperimidine	35
		6,7-Dinitro-2-methylperimidine	22
		7,9-Dinitro-2-methylperimidine	15
Perimidine	16	6,7,9-Trinitroperimidine	70
2-Methylperimidine	8	6,7,9-Trinitro-2-methylperimidine	50

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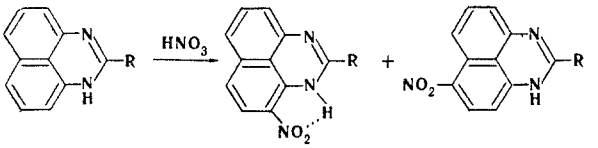
ethyl nitrate in sulfuric or acetic acid did not give positive results). The results obtained are presented in Table 1.

The slightly soluble mononitrates of I precipitated from the reaction mixtures in the reaction of 1 mole of nitric acid with solutions of I in acetic acid. These precipitated salts are not converted to nitro compounds. The latter are formed only when the nitrates dissolve, and this is achieved by heating and the use of a large amount of acetic acid. The mononitration of I can therefore be accomplished only in dilute (1:100 or higher) acetic acid solutions. Nitration is accompanied by the formation of the deep-red color that is peculiar to nitroperimidines. Under these conditions, the density of the nitric acid is not important: identical results were obtained when nitric acid with densities of 1.32 to 1.5 g/cm^3 was used. The resulting isomers are separated by means of column chromatography with aluminum oxide. Two mononitro isomers are formed in the nitration of I. One of them has a considerably higher R_f value, is more soluble in nonpolar and slightly polar solvents, and is less deeply colored. Characteristic properties of the second isomer are its appreciable solubility in water and its low solubility is chloroform, its low R_f value, and its deeper color. On the basis of these data, a 9-nitro structure with an intramolecular hydrogen bond (II) was proposed for the first isomer, and a 6(7)-nitro structure (III) was proposed for the second isomer.*



Ia,b II a,b IIIa,b

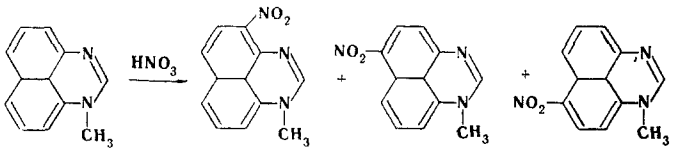
I-III a R = H; b R = CH_3

Confirmation of structure II and III was obtained by PMR spectroscopy. In the spectrum of 2-methyl-9-nitroperimidine (in CF_3COOH) the proton of the NH group tied up in an intramolecular hydrogen bond appears at considerably weaker field (δ 11.59 ppm) than the NH proton in the spectrum of the para isomer (δ 10.55 ppm). A doublet from the H_8 proton, which is in the ortho position relative to the nitro group, is found at weaker field in the region of aromatic-proton absorption. The PMR spectrum of the p-nitro isomer has a simpler form, inasmuch as the proton in the peri position relative to the nitro group is strongly deshielded due to coupling with the oxygen atom of the NO_2 group [6]. This proton appears as a weakly split doublet at 8.01 ppm. The signal from the protons of the CH_3 group in o-nitro isomer IIb is found at weaker field (2.41 ppm) than in the spectrum of p-nitro isomer IIIb (2.24 ppm) because of the closer location of the nitro group.

In the IR spectra of dilute chloroform solutions of perimidines with an o-nitro group the ν_{NH} band appears as a broad peak of medium intensity at 3275-2390 cm^{-1}, i.e., 140-150 cm^{-1} lower than in the spectrum of perimidine itself; this is also due to the formation in o-nitro perimidines of an intramolecular hydrogen bond. We were unable to measure the IR spectra of chloroform solutions of 6(7)-nitroperimidines because of their extremely low solubility.

Of fundamental significance in the study of electrophilic substitution in the perimidine series is the problem of the ratio of ortho and para substitution. The ratio of the para and ortho isomers in the nitration of 2-methylperimidine is 2.6:1 for an overall yield of 64%. In the case of perimidine itself, more of the o-nitro derivative can be isolated, but the overall yield of mononitro compounds here is only 32%. The greater portion of the perimidine is oxidized under the influence of nitric acid to a brown-black substance that is only slightly soluble in the ordinary organic solvents and apparently has a dimeric quinoid structure. Evidence in favor of this is the high yield of products of mononitration of 1-methylperimidine (IV), in which the formation of quinoid structures is impossible:

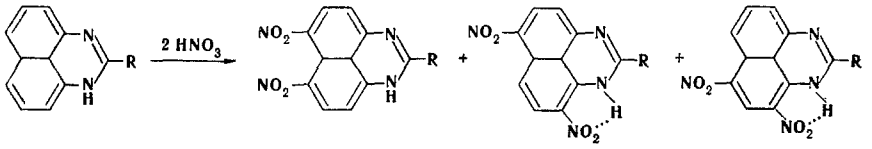
*In view of the presence of an intramolecular hydrogen bond in II, the ortho nitro group is considered to be in the 9 position rather than in the 4 position. Thus we will call IIa 9-nitroperimidine.



IV V VI VII

In the nitration of 1-methylperimidine (IV) with 1 mole of HNO_3 we isolated three mononitro derivatives in 8.8, 45.5, and 24.5% yields. The first of these substances was also formed in the methylation of 4(9)-nitroperimidine in alkaline media and thus is 1-methyl-4-nitroperimidine (V) (the formation of the 9-nitro isomer in the methylation of IIa and the nitration of IV is not observed because of steric and electronic factors). The other two substances are formed in the methylation of the N-anion of 6(7)-nitroperimidine. We assigned the 1-methyl-7-nitroperimidine structure (VII) to the low-melting and, consequently, less symmetrical isomer, and the second isomer then is apparently 1-methyl-6-nitroperimidine (VI). It is important to note that in the nitration of IV the reaction proceeds primarily in the para position.

A mixture of three dinitro compounds is formed along with a small amount of the 4(9)-mononitro derivative in the nitration of perimidine and 2-methylperimidine with 2 moles of nitric acid:



I VIII IX X

I, VIII-X a R = H; b R = CH_3

One of the dinitro compounds isolated differs markedly from the other two with respect to its low chromatographic mobility and low solubility in chloroform. Its PMR spectrum consists of only two doublets, each of which has an integral intensity of two proton units. The latter fact indicates a symmetrical structure for this isomer. We have established that this dinitro compound is also formed in the nitration of 6(7)-nitro-2-methylperimidine but is not formed in the nitration of 4(9)-nitro-2-methylperimidine. This indicates unambiguously that it has the 6,7-dinitroperimidine structure (VIII) rather than the structure of the 4,9-dinitro isomer. The other two dinitro compounds have practically identical R_f values and are moderately soluble in chloroform, and their PMR spectra are more complex; this constitutes evidence for an asymmetrical orientation of the nitro group. Judging from the PMR spectra of a mixture of these dinitro compounds, the predominant isomer in the mixture is the compound with nitro groups in different rings. We obtained it in pure form in the case of nitration of perimidine itself. For perimidine we were also able to isolate a second asymmetrical dinitro isomer, the PMR spectrum of which contains a singlet at weak field (δ 8.75 ppm). This constitutes evidence that it has a 7,9-dinitroperimidine structure (Xa). We were unable to separate asymmetrical isomers IXb and Xb, the products of nitration of 2-methylperimidine, but we were able to easily establish their ratio from the PMR spectrum of a mixture of them. The yields of the 7,9-dinitro derivative is 4% in the nitration of perimidine and 15% in the nitration of 2-methylperimidine. However, the chief products of dinitration of perimidine and 2-methylperimidine are 6,9-dinitro isomers IX (Table 1).

We isolated 6,7,9-trinitroperimidine (XIa) in 70% yield from the nitration of perimidine with a large excess of nitric acid and gentle heating. It structure was proved by its PMR spectrum and its formation during the nitration of 6,7-dinitroperimidine (VIIIa). (See scheme on following page.)

The formation of the dinitro derivative during the nitration of 2-methylperimidine in acetic acid with 8 moles of nitric acid [4] was not confirmed. Under these conditions we isolated only 6,7,9-trinitro-2-methylperimidine in 50% yield.

4,6,7,9-Tetranitroperimidine (XII) is formed in good yield by heating trinitroperimidine

TABLE 2. Properties of Nitroperimidines

	mp, °C (crystallization solvent)	R_f*, Al_2O_3, $CHCl_3$	ν_{NH}+	UV spectrum		Empirical formula	Found, %			Calc., %		
				λ_{max}	lg ε		C	H	N	C	H	N
IIa	235—236 (ethanol)	0,66	3293	460	3,99	$C_{11}H_7N_3O_2$	61,5	3,5	19,4	61,9	3,3	19,7
IIIa	240—241 (water)	0,02		475	3,93	$C_{11}H_7N_3O_2 \cdot {}^1/_2H_2O$	59,5	3,6	18,8	59,5	3,6	18,9
IIb	221 (ethanol)	0,90	3290	462	4,10	$C_{12}H_9N_3O_2$	63,4	4,1	18,5	63,4	4,0	18,5
IIIb	230—350 dec. (methanol)	0,30		475	4,02	$C_{12}H_9N_3O_2$	63,2	4,3	18,7	63,4	4,0	18,5
V	259 (ethanol	0,56		445	3,96	$C_{12}H_9N_3O_2$	63,4	4,0	18,7	63,4	4,0	18,5
VI	263 (ethanol)	0,60		490	4,06	$C_{12}H_9N_3O_2$	63,4	4,0	18,7	63,4	4,0	18,5
VII	218 (ethanol)	0,70		470	4,02	$C_{12}H_9N_3O_2$	63,4	4,3	19,2	63,4	4,0	18,5
VIIIa	238 (ethanol)	0,02				$C_{11}H_6N_4O_4$	51,0	2,1	21,6	51,2	2,4	21,7
VIIIb	230—350 dec. (dioxane)	0,02		425	4,19	$C_{12}H_8N_4O_4$	52,2	3,1	20,0	52,9	3,0	20,5
IXa	262—263 (dioxane)	0,56	3275	440	4,39	$C_{11}H_6N_4O_4$	51,6	2,8	21,5	51,2	2,4	21,7
IXb	242 (nitrobenzene)	0,84	3275	440	4,28	$C_{12}H_8N_4O_4$	53,4	3,3	20,2	52,9	3,0	20,5
Xa	284 (dioxane)	0,52				$C_{11}H_6N_4O_4$	51,3	2,5		51,2	2,4	
XIa	264 (dioxane)	0,01				$C_{11}H_5N_5O_6$	43,9	1,8	23,6	43,6	1,7	23,1
XIb	267 (dioxane)	0,01	3275	425	4,27	$C_{12}H_7N_5O_6$	45,2	2,5	22,3	45,4	2,2	22,1

*Activity V Al_2O_3 in the Brockmann classification.
†We were unable to record the IR spectra of the other compounds because of their low solubility in $CHCl_3$.

XI XII

XIa R=H; b R=CH_3

XIa in excess fuming nitric acid. The latter is also obtained as a small amount of impurity in the nitration of perimidine itself at 100° with excess HNO_3 in acetic acid.

EXPERIMENTAL METHOD

The PMR spectra of trifluoroacetic acid or dimethyl sulfoxide (DMSO) solutions of the compounds (0.3 mole/liter) were measured with a Tesla spectrometer (80 MHz) at 20° with hexamethyldisiloxane as the internal standard. The IR spectra of saturated solutions in chloroform were measured with a UR-20 spectrometer. The UV spectra of methanol solutions were measured with an SF-4A spectrophotometer.

Nitration of Perimidine (Ia). A) With 1 Mole of Nitric Acid. A 0.1-ml (2.5 mmole) sample of nitric acid (sp. gr. 1.5) was added to a solution of 0.42 g (2.5 mmole) of Ia in 50 ml of acetic acid, during which yellow perimidine nitrate precipitated. The mixture was heated at 70-80° to dissolve the nitrate, after which the solution was stirred at this same temperature for another hour. After this, almost all of the acetic acid was removed by vacuum distillation at 40-50°, 30 ml of water was added to the residue, and the resulting brown precipitate was removed by filtration, washed with water, and dried. The nitro compounds were extracted with ethanol in a Soxhlet extractor until the alcohol solution no longer became colored. The extract was chromatographed with a column filled with aluminum oxide with initial elution with chloroform to give 0.12 g (22.7%) of IIa and subsequent elution with chloroform–ethanol (10:1) to give 0.05 g (9.4%) of IIIa. The alcohol-insoluble dark-brown residue (2.27 g) was similar to the product of oxidation of perimidine [7] with respect to the results of elementary analysis.

B) With 2 Moles of Nitric Acid. A 0.42-ml (10 mmole) sample of nitric acid (sp. gr. 1.5) was added to a solution of 0.84 g (5 mmole) of Ia in 50 ml of glacial acetic acid, and the mixture was worked up as described above with extraction with chloroform rather than with alcohol. The chloroform-insoluble residue was crystallized from ethanol to give 0.2 g (15%) of VIIIa. The chroform extract was chromatographed with a column filled with aluminum

oxide with elution by chloroform to give, successively, 0.88 g (7%) of IIa, 0.53 g (41%) of IX, and 0.05 g (4%) of Xa. Subsequent elution with chloroform–alcohol gave 0.05 g (4%) of VIIIa and 0.05 g (3%) of XIa. PMR spectrum of IXa (in DMSO, 100°, δ, ppm): 7.1 (d, H_4), 7.95 (d, H_8), 8.12 (d, H_7), 8.15 (s, H_2), and 8.43 (d, H_5).

C) With Excess Nitric Acid. A 2-ml (44 mmole) sample of nitric acid (sp. gr. 1.4) was added dropwise to a solution of 0.42 g (2.5 mmole) of Ia in 12 ml of glacial acetic acid, and the mixture was stirred at 20° for 2 h and then at 50° for 1 h, after which it was cooled and poured into water. The aqueous mixture was neutralized with ammonia, and the resulting precipitate was removed by filtration, washed with water, dried, and recrystallized from dioxane to give 0.54 g (70%) of light-brown prisms of XIa.

Nitration of 2-Methylperimidine (Ib). A) With 1 Mole of Nitric Acid. The reaction was carried out as in the nitration of perimidine with 1 mole of nitric acid, and the mixture was extracted with chloroform until the chloroform solution no longer took on a deep-orange color. The chloroform-insoluble residue was dissolved in acetone and passed through a layer of aluminum oxide to give IIIb (42% yield). The chloroform extract was passed through a column filled with aluminum oxide with initial elution with chloroform to give IIb (18%) and subsequent elution with chloroform–alcohol (7:1) to give IIIb (4%). PMR spectrum of IIb (in CF_3COOH, δ, ppm): 2.41 (s, CH_3), 6.80 (q, H_4), 7.09 (d, H_7), 7.31 (m, H_5, H_6), 7.65 (d, H_8), and 11.59 (s, NH). PMR spectrum of IIIb (in CF_3COOH, δ, ppm): 2.24 (s, CH_3), 6.47 (d, H_4), 6.71 (d, H_9), 7.28 (m, H_5), 8.01 (d, H_8), 8.09 (d, H_6), and 10.55 (s, NH).

B) With 2 Moles of Nitric Acid. The reaction was carried out as in the nitration of Ia with 2 moles of nitric acid. The reaction mixture was cooled, and the resulting precipitate was removed by filtration, washed on the filter with ether, dried, and crystallized from dioxane to give VIIIb (22%). The filtrate was poured into cold water, and the resulting orange precipitate was removed by filtration, dried, and dissolved in chloroform. The chloroform solution was chromatographed with a column filled with aluminum oxide to give IIb (4.4%) and IXb (50%). PMR spectrum of VIIIb (in DMSO, δ, ppm): 6.87 (d, H_4, H_9) and 8.20 (d, H_5, H_8).

C) With Excess Nitric Acid. A 2-ml (44 mmole) sample of nitric acid (sp. gr. 1.4) was added dropwise to a solution of 1 g (5.5 mmole) of Ib in 12 ml of glacial acetic acid, and the precipitated nitrate gradually dissolved. The solution was then stirred at 80° for 30 min and at 40-50° for 1.5 h. It was then cooled and poured into 20 ml of ethanol. The resulting precipitate was removed by filtration, washed with alcohol, and crystallized from aqueous acetic acid or dioxane to give 0.9 g (50%) of light-brown prisms of XIb. PMR spectrum (in DMSO, δ, ppm): 7.11 (d, H_4), 8.35 (d, H_5), and 8.77 (s, H_8).

Nitration of 1-Methylperimidine (IV). A 0.1-ml (2.5 mmole) sample of nitric acid (sp. gr. 1.5) was added to a solution of 4.5 g (2.5 mmole) of IV in 20 ml of glacial acetic acid. The reaction mixture turned red, and the reaction was accompanied by gradual deepening of the red color. The mixture was stirred at 40-50° for 40 min, after which it was cooled and poured into 200 ml of water. The aqueous mixture was extracted with small portions of chloroform until the chloroform layer no longer became colored. The extract was washed several times with water, a portion of the solvent was evaporated, and the residual concentrated solution was chromatographed with a column filled with aluminum oxide with successive elution of 0.14 g (24.5%) of VII, 0.26 g (45.5%) of VI, and 0.05 g (8.8%) of V.

Nitration of 2-Methyl-9-nitroperimidine (IIb). A 0.1-ml (2.47 mmole) sample of nitric acid (sp. gr. 1.5) was added to a solution of 0.56 g (2.47 mmole) of IIb in 50 ml of glacial acetic acid, after which the mixture was stirred at 60-70° for 3 h. The acid was removed completely by vacuum distillation, water was added to the residue, and the resulting solid was removed by filtration and washed on the filter with water. The dry residue was dissolved in chloroform and passed through a column filled with aluminum oxide to give 0.55 g (87%) of IXb.

Nitration of 2-Methyl-6(7)-nitroperimidine (IIIb). This compound was nitrated by the method used to nitrate IIb. The residue remaining after removal of the acetic acid by distillation was washed with water, dried, and extracted with chloroform. Chloroform-insoluble VIIIb was crystallized from dioxane to give a product in 39% yield. The chloroform extract was partially evaporated, and the residual concentrated solution was passed through a column filled with aluminum oxide with elution by chloroform to give IXb (46% yield).

Nitration of 6,7-Dinitroperimidine (VIIIa). An equimolecular amount of nitric acid (sp. gr. 1.5) was added to a solution of VIIIa in glacial acetic acid, and the mixture was stirred at 60-70° for 2 h. The acid was then removed by vacuum distillation, and the dry residue was crystallized from dioxane to give XIa in 74% yield.

Methylation of 9-Nitroperimidine (IIa). A solution of 0.150 g (1.87 mmole) of potassium hydroxide in 20 ml of alcohol was added to a solution of 0.27 g (1.25 mmole) of IIa in 30 ml of ethanol, after which 0.355 g (2.5 mmole) of methyl iodide was added dropwise. The mixture was then stirred for 3 h with gradual raising of the temperature to 100°. The alcohol was then removed by distillation and the residue was washed several times with water, dried, and dissolved in chloroform. The chloroform solution was chromatographed with a column filled with aluminum oxide to give 0.12 g (43%) of V and 0.09 g (33%) of IIa.

Methylation of 6(7)-Nitroperimidine (IIIa). This reaction was carried out as described for IIa. Column chromatography gave, successively, VII (16%) and VI (29%), and elution with chloroform–ethanol (7:1) gave IIIa (37%).

4,6,7,9-Tetranitroperimidine (XII). This compound was obtained by heating 0.5 g (1.65 mmole) of XIa with 1 ml (24 mmole) of nitric acid (sp. gr. 1.5) at 80° for 1 h. The mixture was cooled and poured into 20 ml of cold water, and the resulting yellow precipitate was removed by filtration, washed with water, and dried to give 0.5 g (86%) of a product with mp 259°.

The ammonium salt of XII, with mp 259° (dec., from ethanol), was obtained as red crystals by trituration of XII with ammonium hydroxide. Found: C 35.8; H 1.7; N 26.3%. $C_{11}H_7N_7O_8$. Calculated: C 36.2; H 1.9; N 26.8%. PMR spectrum (in DMSO, δ, ppm): 8.85 (s, H_5, H_8), 8.67 (s, H_2), and 4.50 (t, NH_4^+, J = 51.2 Hz).

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