HETEROCYCLIC ANALOGS OF PLEIADIENE

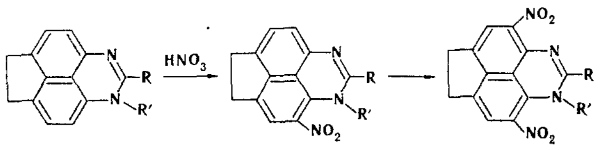
XIII.* NITRATION OF ACEPERIMIDINE AND ITS DERIVATIVES

V. N. Koroleva and A. F. Pozharskii

UDC 547.856.7:542.958.1

Aceperimidine and its 1- and 2-substituted derivatives are nitrated in the 4 and 9 positions to give mono- or dinitro derivatives, depending on the amount of nitric acid.

Very little study has been devoted to electrophilic substitution in the perimidine series [2, 3]. The results of quantum-mechanical calculations show that the reactivities of the 6 and 7 and 4 and 9 positions in perimidine with respect to electrophilic particles should be close [4, 5]. In order to simplify the analysis of the structures of the substances formed and to select a method, we therefore began an investigation of electrophilic substitution reactions with aceperimidine (Ia), in which the 6 and 7 positions are blocked. In the present study we have examined the nitration of aceperimidine and its 1- and 2-alkyl-substituted derivatives.



I a-d II a-d III a-c

I-III a R=R′=H; b R=CH$_3$, b R′=H; c R=H, R′=CH$_3$; I, II d R=R′=CH$_3$

The action of nitric acid at room temperature on an acetic acid solution of Ia precipitated aceperimidine nitrate, which was converted to nitro compound IIa when it was introduced into concentrated sulfuric acid at −8°C. The yield of IIa, however, does not exceed 40% under these conditions. In addition, experiments in sulfuric acid are difficult to reproduce, apparently because of the fact that concentrated sulfuric acid, as we will point out in one of our following communications, protonates perimidine in the 4 (9) and 6 (7) positions, and in the presence of an oxidizing agent (HNO$_3$) a considerable portion of the starting compound undergoes profound transformations with the disrupted (as a result of protonation) aromatic structure. This probably explains the fact that nitro compound IIa could not be obtained by direct nitration of aceperimidine with nitric acid or potassium nitrate.

It is considerably more convenient to use glacial acetic acid instead of sulfuric acid in the nitration of aceperimidines. Up to 50% of mononitro compound II and a small amount (7-17%) of dinitro derivative III are obtained for an equimolar reagent ratio. Mononitration proceeds only in very dilute solutions (less than 0.5-1%) because of the low solubility of the nitrate of the starting aceperimidine. Thus if Ia is present as 7% of the total amount of acetic acid used, practically no nitration occurs even at 100° for 6 h.

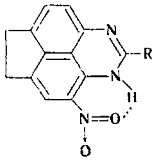
Resinification of the perimidines during nitration is undoubtedly a consequence of their high sensitivity to oxidizing agents [2]. Inasmuch as the nitro group increases the resistance of the compounds to the action of oxidizing agents, the introduction of a second nitro group into the aceperimidines occurs without resinification and in considerably higher yield. For example, the yield of 1-methyl-4,9-dinitroaceperimidine in the nitration of 1-methyl-4-nitroaceperimidine is 80%.

---

*See [1] for communication XII.

Rostov State University, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 702-705, May, 1974. Original article submitted June 21, 1973.

The selection of the structure of the mononitroaceperimidines as 4(9) isomers rather than 5(8) isomers was made on the basis of the following data: 1) all of the quantum-mechanical indexes of the reactivity are considerably more favorable with respect to electrophilic substitution for the ortho rather than for the meta positions of the naphthalene ring; 2) nitroperimidines are deeply colored or crimson colored, which indicates the presence of direct conjugation between the donor π system of the heteroring and the nitro group [the latter is possible in the 4(9) isomer but not in the 5(8) isomer]; 3) the band of the NH group in the IR spectra of dilute chloroform solutions of nitroperimidines IIa,b and IIIa,b is broadened and is observed at 3325-3335 cm^{-1}, which is more than 100 cm^{-1} lower than the ν_{NH} band in the spectra of I. This is most likely associated with the formation of a weak intramolecular hydrogen bond, which is possible only in the 4(9) isomer.



IIa,b

Both of the ring protons in the PMR spectrum of dinitroaceperimidine IIIa give one signal; this attests to their equivalence and, consequently, to the identical character of the two nitro groups, which are thus situated in the 4 and 9 positions.

In the nitration of 1-methylaceperimidine (Ic) with an equimolar amount of nitric acid the nitro group enters exclusively the sterically less hindered 4 position. This is evidenced both by the very fact of the formation of only one isomer, despite the close values of the π-electron density in the 4 and 9 positions of 1-methylperimidines [4, 5], and by the formation of exclusively the same isomer during methylation of nitro compound IIa in alkaline media. In the latter case, the nitro group should interfere with methylation at the nearest nitrogen atom not only due to steric hindrance but also due to its own strong inductive effect. We obtained a small amount of 1-methyl-9-nitroaceperimidine (8%) and nitro compound IIIc, together with traces of 1-methyl-4,9-dinitroaceperimidine, in the nitration of aceperimidine Ic under the conditions used for the preparation of dinitro derivative IIIa from aceperimidine Ia. However, when the amount of acetic acid and the nitration time were increased, we were able to obtain 1-methyl-4,9-dinitroaceperimidine in 66% yield.

The compounds synthesized in this research are the first representatives of the previously unknown nitroperimidines. We will report the properties of the latter in a future paper.

EXPERIMENTAL

The UV spectra of methanol solutions were obtained with an SF-4A spectrophotometer. The PMR spectra of trifluoroacetic acid solutions were recorded with a Tesla spectrometer (80 MHz) with hexamethyldisiloxane (HMDS) as the internal standard.

Aceperimidine Nitrate. A solution of 0.22 ml (5 mmole) of nitric acid (sp. gr. 1.4) in 3 ml of glacial acetic acid was added to a suspension of 0.97 g (5 mmole) of aceperimidine in 10 ml of glacial acetic acid. After 30 min, the aceperimidine nitrate was removed by filtration and washed successively with glacial acetic acid and ether to give yellow plates with mp 282-283° (from ethanol). The yield was 0.92 g (72%). Found %: C 61.0, H 4.3, N 16.3. $C_{13}H_{10}N_2 \cdot HNO_3$. Calculated %: C 60.7; H 4.3; N 16.3.

4-Nitroaceperimidine (IIa). A) A 0.55-g sample of aceperimidine nitrate was added in small portions in the course of 45 min to cooled (to −8°) concentrated sulfuric acid (5 ml), after which the mixture was stirred at this temperature for 15 min. It was then poured over ice, and the mixture was neutralized with ammonia. The precipitate was removed by filtration, washed with water, dried, and chromatographed with a column (Al_2O_3 and $CHCl_3$) to give 0.2 g (40%) of 4-nitroaceperimidine as crimson needles with mp > 350° (from DMF). ν_{N-H} 3335 cm^{-1}. λ_{max} 486 nm, log ε 4.04. PMR spectrum, δ, ppm: 3.00 (s, CH_2CH_2), 6.76 (d, 4-H), 7.14 (d, 5-H), 7.40 (s, 8-H), 8.04 (d, 2-H), 11.5 (broad s, NH).* Found %: C 65.4; H 4.0; N 17.0. $C_{13}H_9N_3O_2$. Calculated %: C 65.3; H 3.8; N 17.5.

B) A 0.105-ml (2.5 mmole) sample of nitric acid (sp. gr. 1.5) was added dropwise to a solution of 0.48 g (2.5 mmole) of aceperimidine in 100 ml of glacial acetic acid, and the resulting yellow precipitate

---

*The abbreviations used here and subsequently are s for singlet and d for doublet.

of aceperimidine nitrate dissolved when the mixture was heated to 80° to give a dark-red solution. The mixture was stirred at 40–50° for 2 h, after which it was cooled and poured into cold water. The precipitate was removed by filtration, washed with water, dried, and chromatographed (with a column filled with Al_2O_3 and elution with $CHCl_3$) to give, initially, 0.28 g (47%) of mononitroaceperimidine and then 0.12 g (17%) of dinitroaceperimidine.

4,9-Dinitroaceperimidine (IIIa). A solution of 0.21 ml (5 mmole) of nitric acid (sp. gr. 1.5) in 3 ml of acetic acid was added dropwise to a solution of 0.48 g (2.5 mmole) of aceperimidine in 25 ml of glacial acetic acid, and the mixture was stirred at 60–70° for 3 h. It was then cooled, and the precipitate was removed by filtration, washed with water, and dried to give 0.5 g (70%) of a red substance that darkened and charred without melting at 280–305° (from dioxane). ν_{N-H} 3330 cm^{-1}. λ_{max} 475 nm, log ε 4.23. PMR spectrum, δ, ppm: 3.16 (s, CH_2CH_2), 3.61 (s, NH), 7.85 (s, 5- and 8-H), 8.48 (s, 2-H). Found %: C 55.2; H 3.2; N 19.5. $C_{13}H_8N_4O_4$. Calculated %: C 54.9; H 2.8; N 19.7.

1-Methylaceperimidine Nitrate. This compound was obtained by the method used to prepare aceperimidine nitrate. The yellow plates had mp 257-258° (from ethanol). The yield was 70%. Found %: C 61.8; H 4.9; N 15.6. $C_{14}H_{12}N_2 \cdot HNO_3$. Calculated %: C 62.0; H 4.8; N 15.5.

1-Methyl-4-nitroaceperimidine (IIc). A) The experiment was carried out under conditions similar to those in the synthesis of IIa in sulfuric acid. The red needles had mp 268-269° (from DMF). The yield was 54%. λ_{max} 470 nm, log ε 3.99. PMR spectrum, δ, ppm: 3.0 (s, CH_2CH_2), 3.42 (s, N–CH_3), 6.75 (d, 9-H), 7.2 (d, 8-H), 7.4 (s, 5-H), 8.1 (d, 2-H), 10.05 (broad s, NH). Found %: C 66.3; H 4.4; N 16.5. $C_{14}H_{11}N_3O_3$. Calculated %: C 66.4; H 4.3; N 16.6.

B) The method used to prepare IIa in glacial acetic acid was used to obtain IIc in 58% yield.

C) A solution of 0.148 g (1.87 mmole) of KOH in 20 ml of alcohol was added to a suspension of 0.3 g (1.25 mmole) of nitroaceperimidine in 30 ml of ethanol, after which 0.355 g (2.5 mmole) of methyl iodide was added, and the mixture was stirred for 3 h while the temperature was gradually raised to 100°. The alcohol was then removed by distillation, and the residue was treated with water, and the starting nitroaceperimidine was then washed out with alkali (with monitoring by chromatography). The residue was washed with water and dried to give 0.15 g (47%) of product.

1-Methyl-4,9-dinitroaceperimidine (IIIc). A) A 0.21-ml (5 mmole) sample of HNO_3 (sp. gr. 1.5) was added dropwise to a solution of 0.52 g (2.5 mmole) of aceperimidine Ic in 60 ml of glacial acetic acid, and the mixture was stirred at 70–80° for 4 h. It was then cooled and poured into cold water. The precipitate was removed by filtration, washed with water, dried, and chromatographed (with a column filled with Al_2O_3 and elution with $CHCl_3$) to give 0.49 g (66%) of dinitro derivative IIIc as an orange powder with 261-262° (dec., from dioxane). λ_{max} 450 nm, log ε 4.17. Found %: C 56.4; H 3.4; N 19.1. $C_{14}H_{10}N_4O_4$. Calculated %: C 56.4; H 3.4; N 18.8.

B) A 0.05-ml (1.2 mmole) sample of HNO_3 (sp. gr. 1.5) was added dropwise to a solution of 0.3 g (1.2 mmole) of nitroaceperimidine IIc in 50 ml of glacial acetic acid, and the mixture was stirred at 60–70° for 2 h, after which was cooled and poured into cold water. The precipitate was removed by filtration, washed with water, dried, and crystallized from dioxane to give 0.28 g (80%) of product.

Nitration of 2-Methylaceperimidine. A solution of 0.21 ml (5 mmole) of HNO_3 (sp. gr. 1.5) in 3 ml of acetic acid was added dropwise to a solution of 1.04 g (5 mmole) of aceperimidine Ib in 100 ml of glacial acetic acid. When the mixture was heated to 80°, the precipitate that had formed dissolved. The mixture was heated at 70–80° for 3 h, after which it was cooled and neutralized with ammonia. The precipitate was removed by filtration, washed with water, and dried. The mixture of nitro compounds was extracted with chloroform and separated with a chromatographic column (filled with Al_2O_3, elution with $CHCl_3$) to give 0.45 g (36%) of 4-nitro-2-methylaceperimidine (IIb) with mp 265-266° (from dioxane). ν_{N-H} 3325 cm^{-1}. λ_{max} 480 nm, log ε 4.4. PMR spectrum, δ, ppm: 2.38 (s, CH_3), 3.02 (s, CH_2CH_2), 6.71 (d, 4-H), 7.14 (d, 5-H), 7.4 (s, 8-H). Found %: C 66.0; H 4.5; N 16.6. $C_{14}H_{11}N_3O_2$. Calculated %: C 66.4; H 4.3; N 16.6. The second reaction product was 4,9-dinitro-2-methylaceperimidine (IIIb) [0.1 g (7%)], which darkened and charred from 245 to 260° (from DMF). ν_{N-H} 3325 cm^{-1}. λ_{max} 485 nm, log ε 3.75. Found %: C 56.2; H 3.7; N 18.5. $C_{14}H_{10}N_4O_4$. Calculated %: C 56.4; H 3.4; N 18.8.

Nitration of 1,2-Dimethylaceperimidine. A solution of 0.3 ml (7 mmole) of HNO_3 (sp. gr. 1.5) in 3 ml of acetic acid was added dropwise to a solution of 0.78 g (3.5 mmole) of aceperimidine Id in 12 ml of glacial acetic acid. When the mixture was heated to 70°, the precipitated nitrate gradually dissolved to give a dark-red solution. The solution was stirred at 70–80° for 3 h, after which it was cooled and neutralized with ammonia. The precipitate was removed by filtration, washed with water, and dried. Separation with a chromatographic column gave, initially, 0.07 g (8%) of 1,2-dimethyl-9-nitroaceperimidine (IId) with mp 169-170° (from ethanol) (Found %: C 66.8; H 4.9; N 15.6. $C_{15}H_{13}N_3O_2$. Calculated %: C 67.4; H 4.9; N 15.7) and then 0.42 g of 1,2-dimethyl-4-nitroaceperimidine with mp 220-222° (from dioxane). λ_{max} 465 nm, log ε 3.98. Found %: C 67.2; H 4.6; N 16.0. $C_{15}H_{13}N_3O_2$. Calculated %: C 67.4; H 4.9; N 15.7.

LITERATURE CITED

1. V. I. Sokolov, A. F. Pozharskii, I. S. Kashparov, A. G. Ivanov, and B. I. Ardashev, Khim. Geterotsikl. Soedin., 558 (1974).
2. I. S. Kashparov, Master's Dissertation [in Russian], Rostov State University, Rostov-on-Don (1971).
3. I. H. Richmond, Six-membered Heterocyclic Nitrogen Compounds with Three Condensed Rings, New York (1958), p. 518.
4. A. F. Pozharskii and E. N. Malysheva, Khim. Geterotsikl. Soedin., 103 (1970).
5. V. I. Minkin, I. I. Zakharov, and L. L. Popova, Khim. Geterotsikl. Soedin., 1552 (1971).