# HETEROCYCLIC ANALOGS OF PLEIADIENE

## XII.* REDUCTION OF THE C = N BOND IN PERIMIDINES AND PERIMIDINIUM SALTS. SYNTHESIS AND PROPERTIES OF SOME 2,3-DIHYDRO DERIVATIVES OF PERIMIDINE AND ACEPERIMIDINE

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2,3-Dihydro derivatives of perimidine were obtained in high yields by the action of lithium aluminum hydride or sodium borohydride on perimidinium salts and 1,3-dialkylperimidones.

The reduction of nitrogenous heteroaromatic compounds, particularly their quaternary salts, with complex metal hydrides is a good method for the preparation of their 2,3-dihydro derivatives [2, 3]. The present paper is devoted to the utilization of this reaction for the synthesis of little studied 2,3-dihydroperimidines.

2,3-Dihydroperimidines that do not contain substituents attached to the nitrogen atoms can be obtained as a result of the reaction of 1,8-diaminonaphthalene with various aldehydes (for example, see [4, 5]).

It is disadvantageous to obtain N-substituted 2,3-dihydroperimidines of the III and IV type in this manner because of the relatively low accessibility of N-substituted 1,8-diaminonaphthalenes. Up to now three compounds of this group have been described: 1-(2-hydroxyethyl)-2,3-dihydroperimidine, 1,3-dimethyl-2,3-dihydroperimidine (IIIa), and 1,3-dimethyl-2,3-dihydroaceperimidine (IVa). The first of these was obtained by reduction of ethyl 1-perimidinylacetic acid with lithium aluminium hydride, while IIIa and IVa were obtained as a result of the action of aqueous alkali on the corresponding perimidinium salts (I and II) [6].

We have confirmed the data in [4] in regard to the fact that the C = N bond in 1-substituted perimidines is not reduced by sodium borohydride but is reduced by lithium aluminum hydride to mono-N-substituted perimidines of the XI type.

Quaternary perimidinium (I) and aceperimidinium (II) salts are readily hydrogenated in practically quantitative yields by lithium aluminum hydride in ether and sodium borohydride in water.

N,N-Disubstituted 2,3-dihydroperimidines (III and IV) are also readily formed in the reduction of perimidones V or VII with lithium aluminum hydride.

The $\beta$ and $\gamma$ bands with maxima at 335 and 235 nm that are peculiar to perimidines are retained in the UV spectra of hydrogenated perimidines III and IV, but the $\alpha$ band at 400 nm, which is considered to be responsible for the yellow color of perimidines [7], vanishes. The disappearance of this band for 2,3-dihydroperimidines is in agreement with its interpretation based on the results of MO calculations for the $\pi-\pi^*$ electron transition from the naphthalene portion of the molecule to the heteroring [7, 8].

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*See [1] for communication XI.

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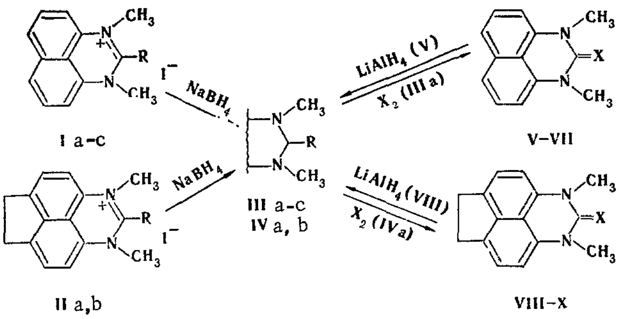
It is known that 1,8-bis(dimethylamino)naphthalene is one of the strongest neutral bases (p$K_a$ 12.34) [9] and is advertised by chemical firms as "the proton sponge." Despite the close structural similarity between 1,8-bis(dimethylamino)naphthalene and the 1,3-dimethyl-2,3-dihydroperimidines that we obtained, the basicity of the latter is sharply depressed, and the p$K_a$ in 50% alcohol is ~3.9. This attests to the fact that, in contrast to noncoplanar (for steric reasons) 1,8-bis(dimethylamino)naphthalene, the nitrogen atoms in III and IV are to a considerable degree coplanar with the naphthalene ring due to the binding effect of the methylene bridge. As a result, conjugation of the unshared electron pairs of the two nitrogen atoms with the aromatic $\pi$ system is reinforced, and this is accompanied by a decrease in the basicity.



a R=H; b R=$CH_3$; c R=$C_6H_5$; V, VIII X=O; VI, IX X=S; VII, X X=Se

XI

As a consequence of their lowered basicities 2,3-dihydroperimidines form unstable hydrolyzable hydrochlorides. However, in contrast to the similarly constructed benzimidazolines [3], they can be converted to methiodides XII by the action of methyl iodide in DMF at 100°C.

In contrast to benzimidazoles [3], 2,3-dihydroperimidines III and IV (and, to a somewhat lesser degree, XI) are stable in air and do not change on prolonged storage and on heating in $CCl_4$. In addition, they are readily oxidized by iodine to starting perimidinium salts I and II; on heating with oxygen, sulfur, and selenium they form structures of the V–X type.

## EXPERIMENTAL

All of the starting compounds were obtained by the methods in [6, 10, 11].

The ionization constants were measured by potentiometric titration of 0.01 N solutions of the compounds in 50% aqueous alcohol with a 0.01 N HCl solution with an LPU-01 potentiometer at 20 ± 1°. The IR spectra were recorded with a UR-20 spectrometer. The PMR spectrum was obtained with a PE-2305 spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The UV spectra of $10^{-3}$ to $10^{-4}$ M solutions of the compounds in methanol were recorded with an SF-4A spectrophotometer.

1-Methyl-2,3-dihydroperimidine (XI). A 2.7-g (0.015 mole) sample of 1-methylperimidine was added to a solution of 2.3 g (0.06 mole) of $LiAlH_4$ in 75 ml of absolute ether, and the mixture was stirred and refluxed for 1 h. The colorless solution was then cooled, 10 ml of water was added, and the mixture was stirred for another 5-10 min. The ether layer was separated, the ether was evaporated, and the residual viscous oil was vacuum dried over $P_2O_5$ and vacuum distilled to give 1.9 g (70%) of a product with bp 170° (2 mm). $\nu_{NH}$ 3370 cm$^{-1}$ (broad, strong; mineral oil), 3410 cm$^{-1}$ (broad, strong; chloroform). PMR spectrum (12% solution in $CDCl_3$): $\delta$ 2.78 (N–$CH_3$, singlet), 4.05 (N–$CH_2$, singlet), 6.25-7.40 (aromatic, complex multiplet). UV spectrum, $\lambda_{max}$, nm (log $\varepsilon$): 232 (4.66), 331 (4.08). Found: C 78.2; H 6.3; N 15.4%. $C_{12}H_{12}N_2$. Calculated: C 78.2; H 6.5; N 15.2%. The picrate was obtained as crimson crystals with mp 230° (from alcohol). Found: N 17.2%. $C_{12}H_{12}N_2 \cdot C_6H_3N_3O_7$. Calculated: N 17.0%.

General Method for the Preparation of 1,3-Dimethyl-2,3-dihydro Derivatives of Perimidine and Aceperimidine. A) A 0.01-mole sample of the appropriate methiodide (I or II) was added with stirring to a solution of 1.1 g (0.03 mole) of $LiAlH_4$ in 50 ml of absolute ether. In the case of the perimidine derivatives, the yellow color of the solution vanished instantaneously. The mixture was refluxed and stirred for

30 min, after which it was cooled to room temperature and carefully decomposed with 5 ml of water. The ether layer was separated, and the water layer was extracted twice with 40-ml portions of ether. The ether was evaporated from the combined ether extracts, and the crystalline residue was dried at 50° and crystallized from alcohol. The yields were close to quantitative. The $R_f$ values of III and IV were ~0.85 ($Al_2O_3$, chloroform).

B) A 10-mmole sample of $NaBH_4$ was added with stirring at 30° in the course of 10 min to a solution of 5 mmole of salt I or II in 150 ml of water, after which the mixture was stirred for another 30 min. The precipitated dihydro derivative was removed by filtration and crystallized. The yields were close to quantitative.

C) A 0.01-mole sample of 1,3-dimethylperimidone or 1,3-dimethylaceperimidone was added to a solution of 0.03 mole of $LiAlH_4$ in 50 ml of absolute ether, and the mixture was refluxed with stirring for 1.5 h. The 2,3-dihydroperimidines were isolated as in method A. The yields were close to quantitative. Compound IIIa had mp 150° (from alcohol) [6] and $pK_a$ 3.77. UV spectrum, $\lambda_{max}$, nm (log ε): 233 (4.64), 330 (4.01).

Compound IVa had mp 152-153° (from alcohol) [6] and $pK_a$ 3.89. UV spectrum, $\lambda_{max}$, nm (log ε): 232 (4.62), 338 (4.01).

Methods A and B were used to obtain 1,2,3-trimethyl-2,3-dihydroperimidine (IIIb) [mp 125-126°, $pK_a$ 3.86. UV spectrum, $\lambda_{max}$, nm (log ε): 234 (4.68), 335 (4.12). Found: C 79.3; H 7.8; N 12.7%. $C_{14}H_{16}N_2$. Calculated: C 79.2; H 7.6; N 12.7%]; 1,3-dimethyl-2-phenyl-2,3-dihydroperimidine (IIIc) [mp 176-177°, $pK_a$ 3.75. UV spectrum, $\lambda_{max}$, nm (log ε): 236 (4.63), 350 (4.19). Found: C 83.2; H 6.8; N 10.1%. $C_{19}H_{18}N_2$. Calculated: C 83.2; H 6.6; N 10.2%] and 1,2,3-trimethyl-2,3-dihydroaceperimidine (IVb) [mp 146-147°. Found: C 80.5; H 7.5; N 12.0%. $C_7H_{18}N_2$. Calculated: C 80.6; H 7.6; N 11.8%; $pK_a$ 3.96. UV spectrum, $\lambda_{max}$, nm (log ε): 234 (4.68), 335 (4.12)].

Methiodide. A 6.4-g (0.045 mole) sample of methyl iodide was added carefully at 100° to a solution of 3 g (0.015 mole) of IIIa in 5 ml of DMF, and the mixture was held at 100° for 2 h. It was then cooled, 25 ml of ether was added, and the colorless crystals of methiodide XII with mp 160-161° (from alcohol–ether) were removed by filtration. The yield was 4.1 g (80%). Found: I 36.9; N 8.2%. $C_{14}H_{17}N_2$. Calculated: I 37.3; N 8.2%.

Oxidation of 1,3-Dimethyl-2,3-dihydroperimidine (IIIa). A) A solution of 0.2 g (1 mmole) of IIIa in 10 ml of alcohol was mixed with a solution of 0.26 g (1 mmole) of iodine in 10 ml of ether, and the mixture was refluxed for 20 min. The solvent was evaporated, and the residual methiodide (Ia) was crystallized from alcohol to give 0.29 g (90%) of a product with mp 269-270° (from alcohol) [6].

B) A 1-g (5 mmole) sample of dihydroperimidine IIIa was heated in a stream of oxygen at 150° for 30 min. The melt was refluxed with 10 ml of chloroform, after which the mixture was filtered, and the filtrate was passed through a column containing aluminum oxide (elution with benzene). The yield of perimidone V with mp 209° (from alcohol) [6] was 0.86 g (80%).

The oxidation of IVa was carried out similarly to give Xa with mp 212-213° (from acetic acid) [6] in 78% yield.

Reaction of IIIa and IVa with Sulfur. A mixture of 1.5 mmole of perimidone IIIa or IVa and 0.1 g (3 mmole) of finely ground powdered rhombic sulfur was held at 130° for 1 h. The melt was then dissolved in 10 ml of chloroform, and the solution was passed through a column containing aluminum oxide (elution with chloroform) to give VI with mp 189-190° (from alcohol) in 90% yield. $\nu_{C=S}$ 1100 $cm^{-1}$ (chloroform). Found: C 68.5; H 5.5; N 12.0%. $C_{13}H_{12}N_2S$. Calculated: C 68.3; H 5.3; N 12.3%. The yield of thione VI with mp 129-130° (from alcohol) was 90%. Found: C 71.0; H 5.1; N 12.2%. $C_{15}H_{14}N_2S$. Calculated: C 71.2; H 5.1; N 12.6%.

Reaction of Perimidines IIIa and IVa with Selenium. A mixture of 3 mmole of IIIa or IVa with 0.8 g (10 mmole) of powdered selenium was heated at 160° for 1.5 h, after which the temperature was raised to 200°, and the mixture was cooled to room temperature. The dark-red melt was dissolved in 10 ml of chloroform, and the solution was passed through a column containing $Al_2O_3$ (elution by chloroform) to give the selenoxo derivative with mp 120-121° (from heptane) in 90% yield. Found: C 56.7; H 4.4; N 10.2%. $C_{13}H_{12}N_2Se$. Calculated: C 56.6; H 4.4; N 10.2%. The yield of X with mp 116-117° (from heptane) was 89%. Found: C 59.5; H 4.3%. $C_{15}H_{14}N_2Se$. Calculated: C 59.8; H 4.7%.

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