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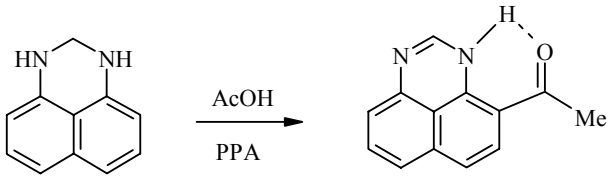
SYNTHESIS OF 2,3-DIHYDROPERIMIDINE KETONES

I. V. Borovlev[1]* and O. P. Demidov[1]

Ketones derived from unsubstituted 2,3-dihydroperimidine were obtained by the selective reduction of the corresponding acylperimidines. The direct acylation of 2,3-dihydroperimidine in PPA is accompanied by dehydrogenation and leads to 4(9)-acylperimidines. The spectral characteristics of these products were discussed.

Keywords: sodium borohydride, 2,3-dihydroperimidine, perimidine, polyphosphoric acid, acylation.

In previous work, we showed that the electrophilic C-acylation by carboxylic acids in PPA is characteristic not only for perimidines [1] but also for 1,3-dialkyl-2,3-dihydropyrimidines. This reaction proceeds under even milder conditions in the case of 1,3-dialkyl-2,3-dihydropyrimidines [2]. However, ketones of unsubstituted 2,3-dihydroperimidine have not been reported. It would be reasonable to assume that these compounds can be obtained analogously by the acylation of 2,3-dihydroperimidine **1**. However, the only reaction product obtained in an attempt to acetylate the compound **1** by acetic acid in PPA at 50°C was 4(9)-acetylperimidine (**2**). Since perimidines react under more vigorous conditions, we might assume that the reaction proceeds at C-4 with subsequent dehydrogenation.



1 **2**

We should note that facile dehydrogenation of 2,3-dihydroperimidines without substituents at C-2 by the action of even milder electrophiles has already been noted by Pozharskii et al. [3]. It is interesting that 1,8-diaminonaphthalene, which is isoelectronic to 2,3-dihydroperimidine, does not react with acids in PPA at 50°C but forms 2-R-4(9)-acylperimidines at 120°C [1].

Another possible pathway to obtain 4- and 6-acyl-2,3-dihydroperimidines is the mild reduction of the corresponding acylperimidines. While 4(9)-acetylperimidine (**2**) required for this purpose was obtained in PPA

* To whom correspondence should be addressed, e-mail: k-biochem-gcs@stavsu.ru.

[1]Stavropol State University, 355009 Stavropol, Russia.

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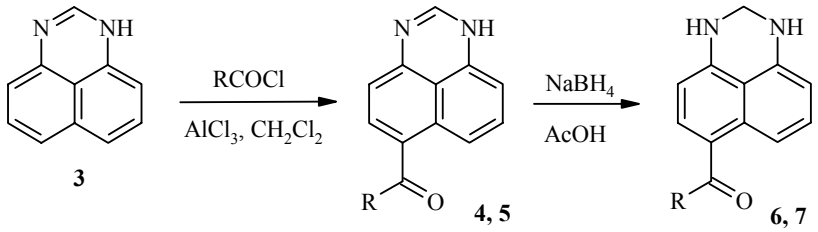
[1], 6(7)-acylperimidines **4** and **5** are more conveniently synthesized by the action of acid chlorides on perimidine **3** in dichloromethane in the presence of excess $AlCl_3$. In this case, the reaction proceeds selectively at C-6(7) in the perimidine system, which eliminates the necessity of separating the 4(9)- and 6(7)-isomers.

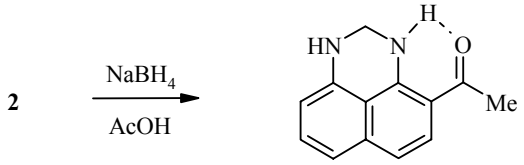
$NaBH_4$ is a convenient reducing agent for aldehydes and ketones to the corresponding alcohols as well as C=N and NO_2 groups and some other groups [4-6]. However, a particular feature of acylperimidines is the presence of two electrophilic sites: the carbonyl group and the *meso*-carbon atom in the heterocycle. We have found that the sodium borohydride reduction of 6(7)-acetyl- (**4**) and 6(7)-benzoylperimidine (**5**) in glacial acetic acid is regiospecific at C-2. The products of these reactions are 6-acyl-2,3-dihydroperimidines **6** and **7**, respectively.



3 **4, 5** **6, 7**

4, 6 R = Me; **5, 7** R = Ph

4(9)-Acetylperimidine (**2**) undergoes analogous reduction to give 4-acetyl-2,3-dihydroperimidine (**8**).



8

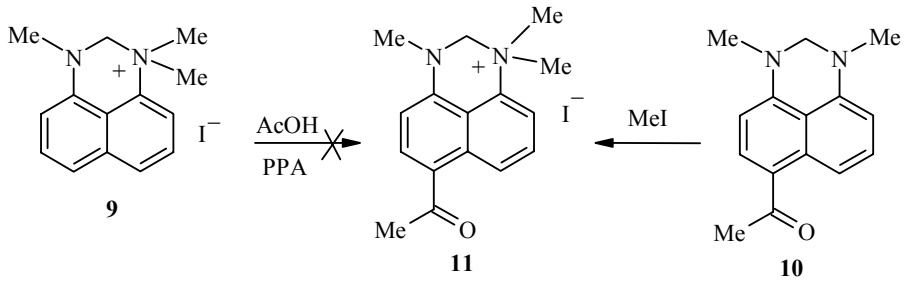
Somewhat unexpectedly, the carbonyl group in this action is not affected despite a significant excess of $NaBH_4$. Thus, this reaction was found to be a convenient method for the synthesis of previously unreported 4- and 6-acyl-2,3-dihydroperimidines.

An attempt to reduce acetylperimidines **2** and **4** by the action of $NaBH_4$ in alcohol gave tar formation. In this case, reduction of the carbonyl group accompanies the dehydration, while the quinoid compounds formed polymerize. If the possibility of dehydration is eliminated, for example, in the case of 6-acyl-2,3-dialkyl derivatives of perimidone and 2,3-dihydroperimidine, the reaction in ethanol proceeds normally at the carbonyl group [7].

It is interesting that attempts to introduce a second acetyl group into 4- (**8**) and 6-acetyl-2,3-dihydropermidine (**6**) by the action of acetic acid in PPA at 120°C always gave acetylperimidine **2**, i.e., the dehydrogenation proceeds more readily than repeated acylation.

In light of the specific features for the acylation of dihydroperimidines in PPA, we attempted to clarify whether these compounds react as the base or cation. For this purpose, we attempted to carry out the reaction of the reported 1,1,3-trimethyl-2,3-dihydroperimidinium cation (**9**) [8]. When the reaction of 1,1,3-trimethyl-2,3-dihydroperimidinium iodide with acetic acid in PPA was carried out under conditions for the acylation of 1,3-dimethyl-2,3-dihydroperimidine [2], we isolated only the starting salt as a perchlorate. This result indicated that, in contrast to perimidine [9], 2,3-dihydroperimidines are acylated only as the base.

Acetylated salt **11** was obtained upon the methylation of 6-acetyl-1,3-dimethyl-2,3-dihydroperimidine (**10**). As in the case of 1,3-dimethyl-6-nitro-2,3-dihydroperimidine [10] (and in contrast to the 6-bromo derivative [11]), quaternization proceeds exclusively at the nitrogen atom further from the acetyl group. This behavior is apparently due to the –M-effect of the acetyl group.



9 **11** **10**

A characteristic feature of the ^{1}H NMR spectra of the compounds **6**, **7**, and **11** is a downfield shift of the signal for H-7 due to deshielding by the carbonyl group oxygen (see Experimental). The chemical shifts of the two nonequivalent NH group protons differ by 3.86 ppm in the ^{1}H NMR spectrum of 4-acetyl-2,3-dihydroperimidine (**8**). The downfield shift of one of these protons unequivocally indicates intramolecular hydrogen bonding. The characteristic carbonyl group signal in the IR spectra of these products is shifted strongly toward lower frequencies and is seen at 1633-1630 cm^{-1}, which indicates considerable conjugation of the carbonyl group with the amino group.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Unity-300 spectrometer at 300 MHz with TMS as the internal standard. The assignment of the signals was carried out by a double resonance technique. The IR spectra were taken for vaseline mulls on a UR-20 spectrometer. Monitoring of the reaction course and purity of the products was carried out by thin-layer chromatography on Silufol UV-254 plates with ethyl acetate as the eluent. Column chromatography was carried out on Chemapol L 40/100 silica gel.

Samples of 2,3-dihydroperimidine **1** [12] and PPA [13] were obtained according to standard procedures.

Acetylation of 2,3-Dihydroperimidine 1 and its 4- (8) and 6-Acetyl Derivatives (6). A mixture of corresponding dihydroperimidine (1 mmol) and glacial acetic acid (1.5 mmol) in PPA (4 g) was stirred at 50°C for 5 h (for **1**) and at 120°C for 1 h (for **6** and **8**). The reaction mixture was poured into water and brought to pH 8 by adding ammonium hydroxide. The precipitate formed was filtered off, washed with water, dried, ground, and treated with 5 ml ethyl acetate. The solution obtained along with the insoluble precipitate was subjected to chromatography on a column packed with 50 g silica gel. The first yellow-green fraction was eluted with ethyl acetate. The solvent was distilled off to give 4(9)-acetylperimidine (**2**). The yields of **2** were 60% for **1**, 66% for **8**, and 63% for **6**. The IR spectrum of this product was identical to the spectrum of an authentic sample of ketone **2** [1].

Acylation of Perimidines (General Method). $AlCl_3$ (4 g, 20 mmol) was carefully added to a stirred, water-cooled suspension of perimidine (0.34 g, 2 mmol) in dichloromethane (5 ml)*. Then, the corresponding carboxylic acid chloride (0.4 ml, 6 mmol) was added dropwise, maintaining steady boiling. The reaction mixture was stirred for 1 h at room temperature. Water (8-10 ml) was added dropwise, maintaining uniform reflux. The remaining solvent was distilled off. Then, ammonium hydroxide was added to the aqueous suspension to bring it to pH 5-6. The precipitate was filtered off, treated with 50 ml hot 2-propanol containing 1 ml ammonium hydroxide. The insoluble residue was filtered off and the filtrate was evaporated off in vacuum. The residue was recrystallized.

6(7)-Acetylperimidine (4) was obtained in 94% yield (0.395 g) after recrystallization from ethyl acetate. The IR spectrum of this product was identical to the spectrum of an authentic sample of ketone **4** [1].

*The reaction proceeds less selectively when higher-boiling solvents were used.

6(7)-Benzoylperimidine (5) was obtained in 78% yield (0.45 g) after recrystallization from benzene. The IR spectrum of this product was identical to the spectrum of an authentic sample of ketone **5** [1].

Reduction of Acylperimidines (General Method). Sodium borohydride (30 mmol) was added with vigorous stirring over 30 min in portions to a solution of acylperimidine (5 mmol) in glacial acetic acid (10 ml) at room temperature. The mixture was stirred for an additional 30 min, poured into cold water (50 ml), and brought to pH 8 by adding aqueous NaOH. The precipitate was filtered off, washed with water, and dried. The product was purified by recrystallization from a suitable solvent with the addition of a small amount of silica gel.

6-Acetyl-2,3-dihydroperimidine (6) was obtained in 78% yield as yellow crystals; mp 134-135°C (benzene). IR spectrum, ν, cm^{-1}: 3320-3233 (NH), 1633 (C=O), 1580 (ring). ^{1}H NMR spectrum (acetone-d_6), δ, ppm (*J*, Hz): 2.56 (3H, s, CH_3); 4.56 (2H, br. s, CH_2); 5.89 (1H, br. s, H-1); 6.50 (1H, d, $J_{4,5}$ = 8.1, H-4); 6.59 (1H, dd, $J_{9,8}$ = 7.7, $J_{9,7}$ = 0.9, H-9); 6.64 (1H, br. s, H-3); 7.27 (1H, dd, $J_{8,9}$ = 7.7, $J_{8,7}$ = 8.5, H-8); 8.00 (1H, d, $J_{5,4}$ = 8.1, H-5); 8.57 (1H, dd, $J_{7,8}$ = 8.5, $J_{7,9}$ = 0.9, H-7). Found, %: C 73.37; H 5.55; N 13.06. $C_{13}H_{12}N_2O$. Calculated, %: C 73.57; H 5.70; N 13.20.

6-Benzoyl-2,3-dihydroperimidine (7) was obtained in 83% yield as yellow crystals; mp 130-131°C (benzene–hexane). IR spectrum, ν, cm^{-1}: 3320-3247 (NH), 1633 (C=O), 1580 (ring). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.10 (1H, br. s, H-1); 4.55 (2H, s, CH_2); 4.95 (1H, br. s, H-3); 6.41 (2H, m, H-4, H-9); 6.60 (1H, d, $J_{5,4}$ = 7.2, H-5); 7.30-7.55 (4H, m, H-8, *m*-H and *p*-H C_6H_5); 7.78 (2H, br. d, *o*-H C_6H_5); 7.99 (1H, d, $J_{7,8}$ = 8.6, H-7). Found, %: C 78.97; H 5.15; N 10.36. $C_{18}H_{14}N_2O$. Calculated, %: C 78.81; H 5.14; N 10.21.

4-Acetyl-2,3-dihydroperimidine (8) was obtained in 83% yield as pale-yellow crystals; mp 143-144°C (benzene–hexane). IR spectrum, ν, cm^{-1}: 3273 (NH); 1630 (C=O); 1607, 1567 (ring). ^{1}H NMR spectrum (acetone-d_6), δ, ppm (*J*, Hz): 2.53 (3H, s, CH_3); 4.70 (2H, br. s, CH_2); 6.11 (1H, br. s, H-1); 6.59 (1H, dd, $J_{9,8}$ = 7.7, $J_{9,7}$ = 0.9, H-9); 6.89 (1H, d, $J_{6,5}$ = 9.00, H-6); 7.01 (1H, dd, $J_{7,8}$ = 8.1, $J_{7,9}$ = 0.9, H-7); 7.32 (1H, dd, $J_{8,9}$ = 7.7, $J_{8,7}$ = 8.1, H-8); 7.64 (1H, d, $J_{5,6}$ = 9.00, H-5); 9.79 (1H, br. s, H-3). Found, %: C 73.28; H 5.85; N 13.42. $C_{13}H_{12}N_2O$. Calculated, %: C 73.57; H 5.70; N 13.20.

Attempt to Acetylate 1,1,3-trimethyl-2,3-dihydroperimidinium Iodide (9). A mixture of iodide **9** (0.4 g, 1.2 mmol), acetic acid (0.11 g, 1.8 mmol), and PPA (5 g) was stirred at 45-50°C for 5 h and then poured into water. 60% Perchloric acid (3 ml) was added to the solution obtained. The precipitate was filtered off, washed with water, and dried. The yield of 1,1,3-trimethyl-2,3-dihydroperimidine perchlorate was 0.24 g (64%) as colorless crystals; mp 212-213°C (water). This product was also obtained in 88% yield by treating iodide **9** in water with perchloric acid.

6-Acetyl-1,1,3-trimethyl-2,3-dihydroperimidinium Iodide (11). A mixture of 6-acetyl-1,3-dimethyl-2,3-dihydroperimidine (**10**) (0.24 g, 1 mmol), methyl iodide (0.19 ml, 3 mmol), and 5 ml ethanol was heated at reflux for 3 h. The solvent was evaporated until the solution became turbid. The crystalline precipitate formed upon cooling was filtered off and dried to give 0.27 g (73%) compound **11** as yellow-green crystals; mp 169-170°C (ethanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.68 (3H, s, CH_3CO); 3.31 (3H, s, 3-CH_3); 3.63 (6H, s, 1-$(CH_3)_2$); 5.20 (2H, s, CH_2); 7.05 (1H, d, $J_{4,5}$ = 8.5, H-4); 7.78 (1H, dd, $J_{8,9}$ = 7.8, $J_{8,7}$ = 8.8, H-8); 8.12 (1H, d, $J_{9,8}$ = 7.8, H-9); 8.34 (1H, d, $J_{5,4}$ = 8.4, H-5); 9.18 (1H, d, $J_{7,8}$ = 8.8, H-7). Found, %: C 50.50; H 4.94; N 7.06. $C_{16}H_{19}IN_2O$. Calculated, %: C 50.28; H 5.01; N 7.33.

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