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HETEROCYCLIC ANALOGS OF PLEIADENE. 73.* INTRAMOLECULAR CYCLIZATION OF CINNAMOYL- AND *o*-CHLOROBENZOYLPERIMIDINES

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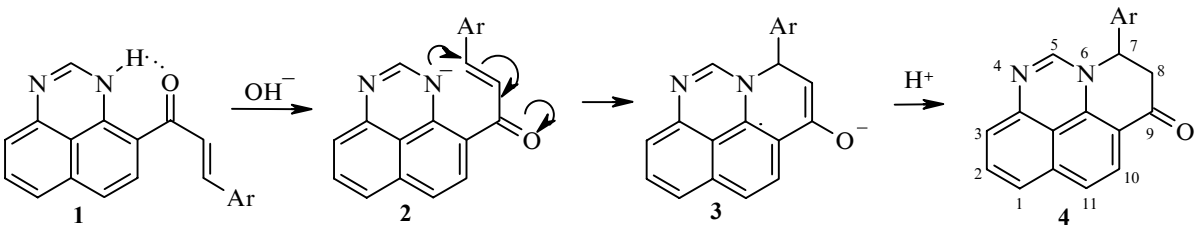
We have carried out the intramolecular cyclization of the anions of 4(9)- and 6(7)-cinnamoylperimidines and also of 4(9)-o-chlorobenzoylperimidine. These partially hydrogenated pyrido- and quino[1,2,3-cd]perimidines were obtained for the first time. Their ^{1}H NMR spectroscopic features are discussed.

Keywords: acylperimidines, perimidine, intramolecular cyclization.

We have previously developed two methods for the synthesis of perimidine chalcones and also shown that the cyclization of 6(7)-cinnamoylperimidines under the action of $AlBr_3$ is accompanied by dearylation to give 6-hydroxy-1,3-diazapyrene [1]. Under these conditions, 4(9)-cinnamoylperimidine does not react.

The aim of this work was to study the possible cyclization of the anions of 4(9)- and 6(7)-cinnamoyl- and also *o*-chlorobenzoylperimidines which could build onto the perimidine six-membered rings at the *peri*-6,7 and 1,9 positions.

It was found that heating the 4(9)-cinnamoylperimidines **1** in aqueous alcoholic base gave the 7-aryl-7,8-dihydro-9H-pyrido[1,2,3-*cd*]perimidin-9-ones cyclization products **4**. This conversion evidently occurs *via* an intramolecular Michael reaction *via* the anions **2** and **3**.



a Ar = Ph; **b** Ar = *p*-BrC_6H_4

Previously, similar compounds not containing a substituent at position 7 have been obtained by the intramolecular acylation of β-(perimidin-1-yl)propionic acids in PPA [2, 3]. Attempts to dearylate compound **4** with $AlBr_3$ were not successful.

* For Communication 72 see [1].

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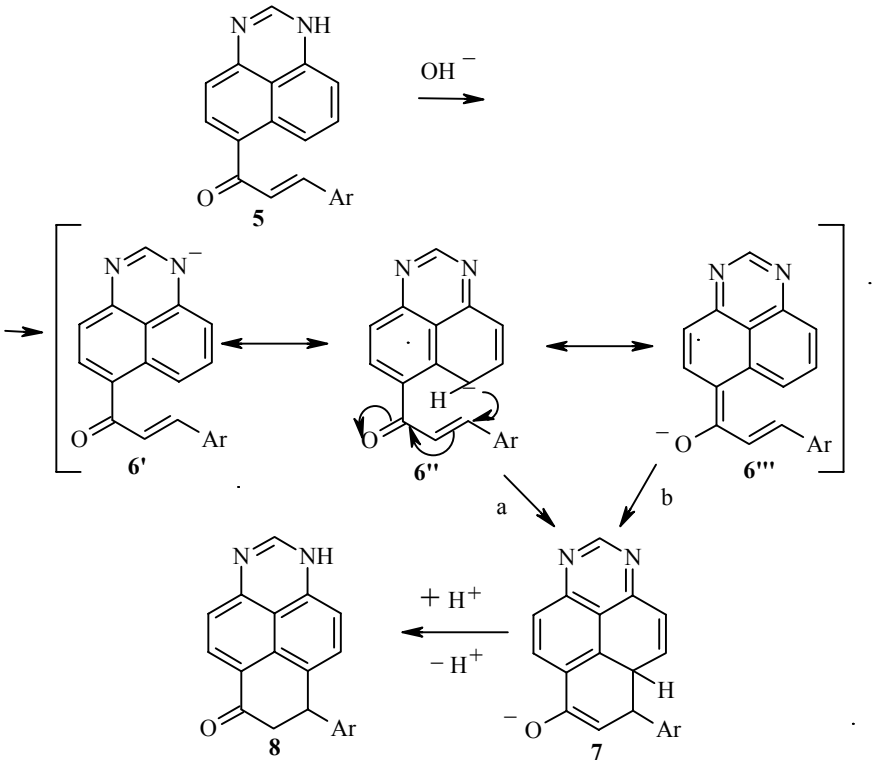
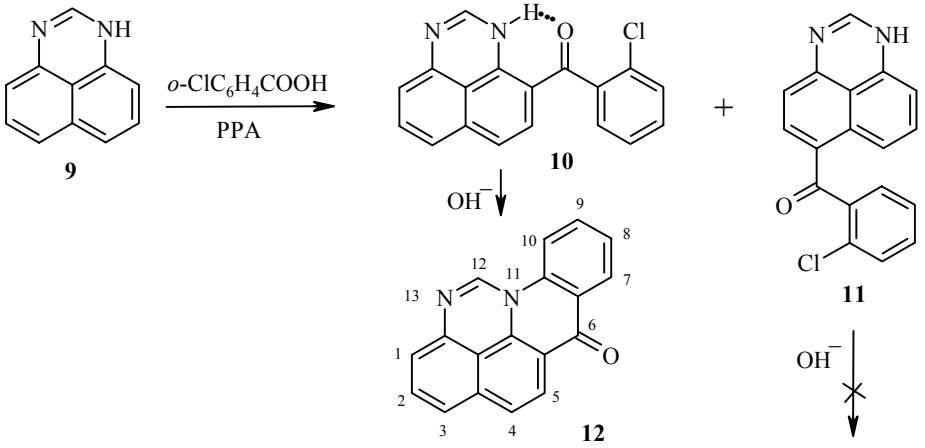
The perimidine N-anion is ambidentate and, when reacting with allyl- and benzylhalides, it behaves as a C_4 [4] and with chalcone as a C_6-nucleophile [5]. In this connection we propose a possible cyclization of the 6(7)-cinnamoylperimidines under conditions of base catalysis. Actually, the reaction occurs but under more rigid conditions when compared with the 4(9)-isomer (refluxing with KOH in ethylene glycol). It was interesting that the reaction can occur both as a nucleophilic addition of the C_6-anion at the double bond (structure **6''** route a) and also *via* a synchronous mechanism as an electrocyclic reaction (structure **6'''** route b).



a Ar = Ph; **b** Ar = *p*-BrC_6H_4

In both cases the aromaticity of the quinazoline fragment of the molecule is preserved. After protonation and rearrangement of the intermediates **7** the 8(6)-aryl-6(8)-oxo-1,6,7,8-tetrahydro-1,3-diazapyrenes **8** are formed and these have been obtained previously by us *via* another route [1].

In connection with the synthesis of compounds **4** and **8** it was also of interest to prepare their benzo analogs from the corresponding *o*-chlorobenzoylperimidines. These were obtained by the acylation of perimidine **9** with *o*-chlorobenzoic acid in PPA. As in other, similar examples [6] conditions of kinetic control (80-85°C) give a mixture of 4(9)- **10** and 6(7)-isomers **11** with the latter predominating and under thermodynamically controlled conditions (130-135°C) the single reaction product is the 4(9)-*o*-chlorobenzoylperimidine. Attempts to cyclize the isomer **10** by refluxing in aqueous alcoholic base gave only the starting material. We propose that the reaction takes place by an S_N2 aromatic mechanism and, since the starting compound is activated only by the carbonyl group, needs more forcing conditions for it to occur. In fact, refluxing 4(9)-*o*-chlorobenzoylperimidine (**10**) with base in ethylene glycol converts it over one hour to the 6H-quino[1,2,3,-*cd*]perimidin-6-one (**12**).



However, the 6(7)- isomer **11** does not participate in a similar reaction, even under prolonged refluxing with base in ethylene glycol.

The ^{1}H NMR spectrum of compound **10** in DMSO-d_6 shows a number of features. Firstly, the signal for the proton at position 2 appears as a doublet (J = 3.0 Hz) due to interaction with the NH group proton (upon heating to 60°C the signal is broadened but the doublet structure is retained). Together with the sharp signals for the aromatic protons of the perimidine ring this points not only to a slow chemical exchange of the NH, but also to the absence of annular NH-prototropy, even in such a polar solvent. In other words, compound **10** exists exclusively as the 9- tautomer and the NH proton is found in a split interaction with the carbonyl group and the solvent. Secondly, when compared with compound **4** and with 9-acetylperimidine (see the Experimental section), the signal for the 8-H proton is shifted to higher field by 0.6 ppm. In our opinion this is due to the impossibility on the grounds of steric hindrance of a coplanar positioning of the chlorophenyl group relative the perimidine ring, as a result of which the given proton is partially shielded by it. The close value of the chemical shifts of the 8-H protons in 9-acetylperimidine and compounds **4**, differing in the spatial position of the carbonyl group, points to the absence of an anisotropic effect in both cases. But if, in the first compound this is explained by conformational immobility of the carbonyl due to intramolecular hydrogen bonding, then in compound **4** it is the result of a non-planar structure for the carbonyl group contained in the ring. In any case, the flattening of the molecule upon changing to compound **12** leads to a low field shift of the 8-H signal (δ 8.23 ppm against 7.44 in 9-acetylperimidine and 7.47 ppm in compound **4b**). The diastereotopic protons of the methylene group in compound **4** appear as a double doublet with a characteristic spin-spin coupling.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker WP-200 (200 MHz) instrument with TMS internal standard. Signal assignments were made using a double resonance method. IR Spectra were recorded on a UR-20 instrument. Monitoring of the course of the reaction and the purity of the synthesized materials was made using Silufol UV-254 plates and column chromatography was carried out on Chemapol L 40/100 silica gel.

7-Phenyl-7,8-dihydro-9H-pyrido[1,2,3-*cd*]perimidin-9-one (4a). A mixture of 4(9)-cinnamoylperimidine (0.6 g, 2 mmol), isopropanol (10 ml), water (3 ml), and KOH (0.7 g) was refluxed for 40 min, diluted with water, and filtered. The precipitate was dissolved in a minimum amount of benzene and chromatographed through a small layer of silica gel with benzene eluent. The yield of compound **4a** after evaporation of solvent was 0.14 g (23%) as yellow crystals; mp 157-159 (benzene–petroleum ether). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, J (Hz): 2.99 (1H, dd, $J_{8H^aH^b(gem)}$ = 16.2, $J_{8H^a7H(cis)}$ = 2.8, 8-H^a); 3.46 (1H, dd, $J_{8H^bH^a(gem)}$ = 16.2,

$J_{8H^b7H(trans)}$ = 6.4, 8-H^b); 5.73 (1H, dd, $J_{78^a(cis)}$ = 2.8, $J_{78^b(trans)}$ = 6.4, 7-H); 7.02 (1H, dd, J_{32} = 7.6, J_{31} = 0.6, 3-H); 7.09 (1H, d, J_{1110} = 8.9, 11-H); 7.32 (1H, dd, J_{12} = 7.9, J_{13} = 0.6, 1-H); 7.35 (5H, m, C_6H_5); 7.38 (1H, d, J_{1011} = 8.9, 10-H); 7.55 (1H, dd, J_{23} = 7.6, J_{21} =7.9, 2-H); 7.94 (1H, s, 5-H). Found, %: C 80.30; H 4.46; N 9.19. $C_{20}H_{14}N_2O$. Calculated, %: C 80.52; H 4.73; N 9.39.

7-*p*-Bromophenyl-7,8-dihydro-9H-pyrido[1,2,3-*cd*]perimidin-9-one (4b). A mixture of 4(9)-*p*-bromocinnamoylperimidine (0.67 g, 2 mmol), ethanol (5 ml), water (2.5 ml), and KOH (0.7 g) was refluxed for 40 min and diluted with water. The dry precipitate was dissolved in a minimum amount of benzene, refluxed with silica gel, filtered, and the benzene was evaporated. Yield 0.16 g (28%) as yellow crystals; mp 94-96°C (octane). ^{1}H NMR spectrum (acetone-d_6), δ, ppm, *J* (Hz): 3.03 (1H, dd, $J_{8H^aH^b(gem)}$ = 16.2, $J_{8H^a7H(cis)}$ = 3.4, 8-H^a); 3.44 (1H, dd, $J_{8H^bH^a(gem)}$ = 16.2, $J_{8H^b7H(trans)}$ = 6.4, 8-H^b); 5.75 (1H, dd, $J_{78^a(cis)}$ = 3.4, $J_{78^b(trans)}$ = 6.4, 7-H); 7.03 (1H, dd, J_{32} = 7.7, J_{31} = 0.9, 3-H); 7.10 (1H, d, J_{1110} = 8.5, 11-H); 7.36 (1H, dd, J_{12} = 8.1, J_{13} = 0.9, 1-H); 7.39 (2H, d, *J* = 8.5, 2'- and 6'-H C_6H_4); 7.47 (1H, d, J_{1011} = 8.5, 10-H); 7.54 (1H, dd, J_{23} = 7.7, J_{21} = 8.1, 2-H); 7.57 (2H, d, *J* = 8.5, 3'- and 5'-H, C_6H_4); 7.77 (1H, s, 5-H). Found, %: C 63.92; H 3.65; N 7.22. $C_{20}H_{13}BrN_2O$. Calculated, %: C 63.68; H 3.47; N 7.43.

8(6)-Aryl-6(8)-oxo-1,6,7,8-tetrahydro-1,3-diazapyrene (8a and 8b). A mixture of 6(7)-cinnamoylperimidine or 6(7)-*p*-bromocinnamoylperimidine (1 mmol) and KOH (5 mmol) in ethylene glycol (5 ml) was refluxed for 3 h, cooled, poured into water (~30 ml), extracted with ethyl acetate (4 × 5 ml), and solvent evaporated at reflux until turbidity was seen. The precipitated solid formed on cooling was filtered off and dried to give 8(6)-phenyl-6(8)-oxo-1,6,7,8-tetrahydro-1,3-diazapyrene (**8a**) (83%) as orange crystals; mp 156-157°C (ethyl acetate). The yield of 8(6)-*p*-bromophenyl-6(8)-oxo-1,6,7,8-tetrahydro-1,3-diazapyrene (**8b**) was 82%, yellow orange crystals; mp 168-170°C (ethyl acetate). Both samples did not give a depression of melting point when mixed with samples prepared by us from the alternative route [1].

Acylation of Perimidine Using *o*-Chlorobenzoic Acid. A. A mixture of perimidine (0.68 g, 4 mmol), *o*-chlrorbenzoic acid (0.94 g, 6 mmol) and PPA (10 g) was heated to 130-135°C and held with stirring at the same temperature for 2 h. The reaction mass was cooled to 80°C and poured into cold water (50 ml) with vigorous stirring. After basification with ammonia to pH ~ 8 the precipitate was filtered off, washed with water, and dried. The dried precipitate was treated with ethyl acetate (20 ml) and, together with the precipitate, was transferred to a chromatography column with silica gel (50 g). It was eluted with ethyl acetate, collecting the first yellow colored fraction. Evaporation of solvent gave 4(9)-*o*-chlorobenzoylperimidine (**10**) (0.6 g, 49%) as yellow crystals; mp 225-227°C (benzene–petroleum ether). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 6.86 (1H, d, J_{87} = 9.0, 8-H); 7.01 (1H, d, J_{78} = 9.0, 7-H); 7.12 (1H, br. d, J_{65} = 7.7, J_{64} << 1, 6-H); 7.35 (1H, br. d, J_{45} = 8.1, J_{46} << 1, 4-H); 7.50-7.60 (4H, m, C_6H_4); 7.64 (1H, br. t, J_{56} + J_{54} = 15.8, 5-H); 8.01 (1H, d, $J_{2\text{-NH}}$ = 3.0, 2-H); 12.57 (1H, br. s, NH). Found, %: C 70.66; H 3.64; N 9.02. $C_{18}H_{11}ClN_2O$. Calculated, %: C 70.48; H 3.61; N 9.13.

B. A mixture of perimidine (0.34 g, 2 mmol), *o*-chlorobenzoic acid (0.47 g, 3 mmol), and PPA (7 g) was stirred at 80-85°C for 3 h, poured with vigorous stirring into cold water (~ 30 ml), basified with ammonia to pH ~ 8, and the precipitate was filtered off, washed with water, and dried. It was then treated with ethyl acetate (5 ml) and, together with the precipitate, transferred to a chromatography column with silica gel. Initial elution with ethyl acetate gave a first fraction and with a mixture of ethyl acetate and ethanol (10:1) gave a second (both fractions were yellow in color).

Evaporation of solvent from the first fraction gave compound **10** (0.025 g, 4%) which did not depress the melting point of a sample prepared as described in method A.

The second fraction gave 6(7)-*o*-chlorobenzoylperimidine (0.41 g, 67%) as yellow orange crystals; mp 220-221°C (benzene–ethanol). ^{1}H NMR spectrum (DMSO-d_6; reported as the 6-tautomer), δ, ppm, *J* (Hz): 6.43 (1H, br. d, J_{45} = 8.1, 4-H); 6.92 (1H, br. d, J_{98} = 7.3, 9-H); 7.31 (1H, J_{54} = 8.1, 5-H); 7.4-7.5 (4H, m, C_6H_4); 7.57 (1H, br. t, J_{87} + J_{89} = 16.3, 8-H); 7.73 (1H, s, 2-H), 8.72 (1H, br. d, J_{78} = 9.0, 6-H). Found, %: C 70.29; H 3.41; N 9.22. $C_{18}H_{11}ClN_2O$. Calculated, %: C 70.48; H 3.61; N 9.13.

4(9)-Acetylperimidine was prepared by method [6]. ^{1}H NMR spectrum ($CDCl_3$)*, δ, ppm, *J* (Hz): 2.56 (3H, s, CH_3CO); 6.99 (1H, d, J_{78} = 9.1, 7-H); 7.11 (1H, dd, J_{45} = 7.6, J_{46} = 1.1, 4-H); 7.26 (1H, dd, J_{65} = 8.1, J_{64} = 1.1, 6-H); 7.44 (1H, d, J_{87} = 9.1, 8-H); 7.51 (1H, dd, J_{54} = 7.6, J_{56} = 8.1, 5-H); 7.68 (1H, d, $J_{2\text{-NH}}$ = 3.1, 2-H); 12.60 (1H, br. s, NH···O=).

6H-Quino[1,2,3-*cd*]perimidin-6-one (12). A mixture of 4(9)-*o*-chlorobenzoylperimidine (0.5 g, 16 mmol), calcined potassium hydroxide (0.4 g, 7 mmol), and ethylene glycol (4 ml) was heated to reflux (when a red colored solution was formed) and refluxed for 1 h. The reaction mixture was cooled and poured into cold water (30 ml) and the precipitate was filtered off, washed with water, and dried. Yield 0.26 g (60%) as yellow brown crystals; mp 282-283°C (benzene–ethanol). ^{1}H NMR spectrum (CD_3CN), δ, ppm, *J* (Hz): 7.24 (1H, br. d, J_{12} = 7.3 , 1-H); 7.33 (1H, dd, J_{87} = 8.1, J_{89} = 6.8, 8-H); 7.37 (1H, s, 12-H); 7.52 (1H, d, J_{45} = 9.0, 4-H); 7.53 (1H, dd, J_{21} = 7.3, J_{23} = 8.1, 2-H); 7.60 (2H, m, 3-H and 10-H); 7.72 (1H, dd, J_{98} = 6.8, J_{910} = 7.7, 9-H); 8.23 (1H, d, J_{54} = 9.0, 5-H); 8.34 (1H, dd, J_{78} = 8.1, J_{79} = 0.9, 7-H). Found, %: C 79.69; H 3.44; N 10.62. $C_{18}H_{10}N_2O$. Calculated, %: C 79.99; H 3.73; N 10.36.

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* ^{1}H NMR spectrum of this compound is published for the first time.