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# CHARACTERISTICS OF THE OXIDATIVE HYDROXYLATION REACTION OF 7-ALKYL-1,3,7-TRIAZAPYRENIUM SALTS

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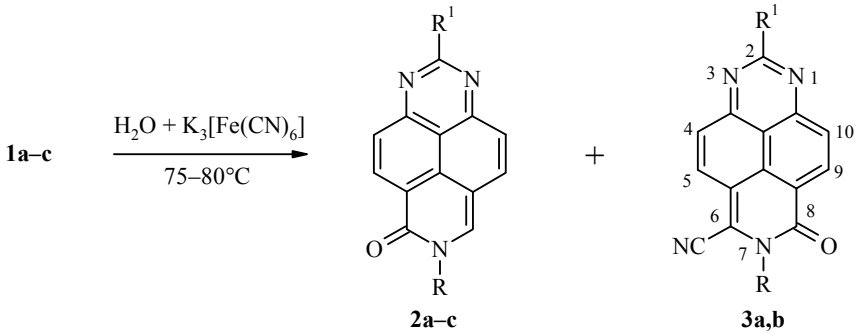
*The oxidative hydroxylation of 7-alkyl-1,3,7-triazapyrenium salts depends on the pH of the medium and the oxidant used. The products of monohydroxylation and dihydroxylation have been synthesized.*

**Keywords**: 7-alkyl-1,3,7-triazapyrenium salts, quaternization, oxidative hydroxylation.

The reaction of N-alkylpyridinium salts to the corresponding N-alkylpyridones was reported by Decker at the end of the 19th century [1] *via* the action of a basic solution of $K_3[Fe(CN)_6]$ and it became the standard method for their synthesis [2]. Subsequently this reaction was extended to many other heteroaromatic cations [3, 4]. The classical oxidant in this reaction remains an alkaline solution of potassium hexacyanoferrate(III) while oxygen [5] and other oxidants [6] are used rarely. An aqueous alkaline medium is generally used for the reaction conditions. Apart from the synthetic value of the reaction it is often used to determine the route of quaternization of heteroaromatic molecules which contain nonequivalent nitrogen atoms [7-10].

Preliminary results of a study of this reaction for 7-alkyl-1,3,7-triazapyrenium salts **1** showed that they give the expected 6-oxo derivatives using the system KOH–$K_3[Fe(CN)_6]$–$H_2O$ [11]. However, in continuing, we have obtained a series of novel results which are discussed in this work.




**a** R = Me, $R^1$ = H, **b** R = $R^1$ = Me, **c** R = Et, $R^1$ = H

The ability of salts **1a-c** to react when heated with an aqueous solution of $K_3[Fe(CN)_6]$ in the absence of alkali found by us is very unusual [12]. Under these conditions it was found that covalent hydration occurs with subsequent oxidation to give the 7-R-6-oxo-6,7-dihydro-1,3,7-triazapyrenes **2a-c**. However, the salts **1a,b**

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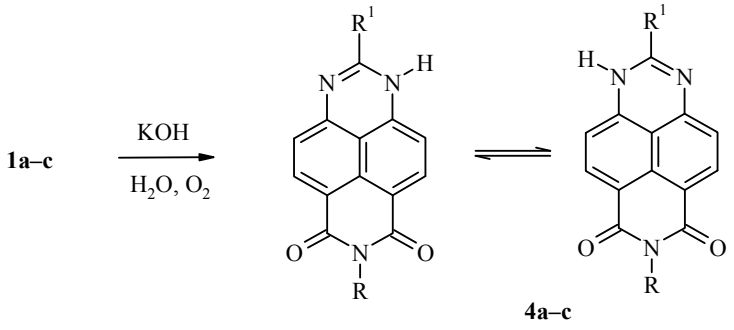
unexpectedly gave the 6-cyano-8-oxo derivatives **3a,b** in 15 and 17% yield respectively from the reaction product along with the main products **2a,b** while the salt **1c** gave only the amide **2c**.

This indicates that the much more nucleophilic cyanide ion, although present in low concentration, successfully competes with water molecules in the course of addition to the substrate cation. Thus, as it is clear that the cyano derivatives **3a,b** are not formed under the same conditions from amides **2a,b**, these products are the result of two parallel processes. The likely mechanism of formation of compounds **3a,b** includes a stepwise addition of nucleophiles to cations **1a,b** with subsequent oxidation involving the addition of cyanide ion in the first step and water in the second. The limiting step is evidently the oxidation process since, in both stages, it involves a neutral particle and not an anion as in the classically used Decker reaction [13]. The absence of cyanoamide **3c** as a result of the reaction of salt **1c** is not fully clear but it can be partially explained by the greater inductive effect and steric hindrance from the ethyl group when compared with a methyl.

Naturally, exchange of $K_3[Fe(CN)_6]$ for $MnO_2$ in the reaction of salts **1a-c** with water gives exclusively the 6-oxo derivatives **2a-c**. However, the best preparative method for their synthesis proved to be refluxing an alcohol solution of salts **1a-c** in the presence of $MnO_2$ when the yields of amides **2a-c** proved to be close to quantitative.

Kinetic studies of the Decker reaction [13, 14] have shown that this is a first order reaction in both the heterocyclic cation and the oxidant. However our attempt to speed up the oxidative hydroxylation process of salts **1a-c** in basic medium using $K_3[Fe(CN)_6]$ excess led to complete degradation of the reaction mixture. Excluding the $K_3[Fe(CN)_6]$ (i.e. carrying out the reaction of salts **1a-c** by heating with an excess of aqueous KOH solution) somewhat unexpectedly gave the products of double oxidative hydroxylation which were the 7-alkyl-6,8-dioxo-1,6,7,8-tetrahydro-1,3,7-triazapyrenes **4a-c**.

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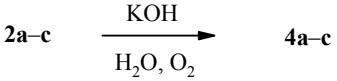
Evidently this process occurs *via* two consecutive hydroxylation-oxidation stages. As it was not possible to stop the process at the first stage the second hydroxylation proceeds more easily than the first. The oxidation of the pseudobase anions in the conversion of **1a-c** to the dioxo derivatives **4a-c** likely occurs through the action of atmospheric oxygen. Compounds **4a-c** can be considered as perimidines with acceptor substituents in positions 6 and 7. It is known that similar anions are extremely readily oxidized [15]. In a specific experiment we have shown that compounds **4a-c** are irreversibly oxidized by a basic solution of $K_3[Fe(CN)_6]$ and this explains our unsuccessful hydroxylation attempt in the presence of an excess of this oxidant.

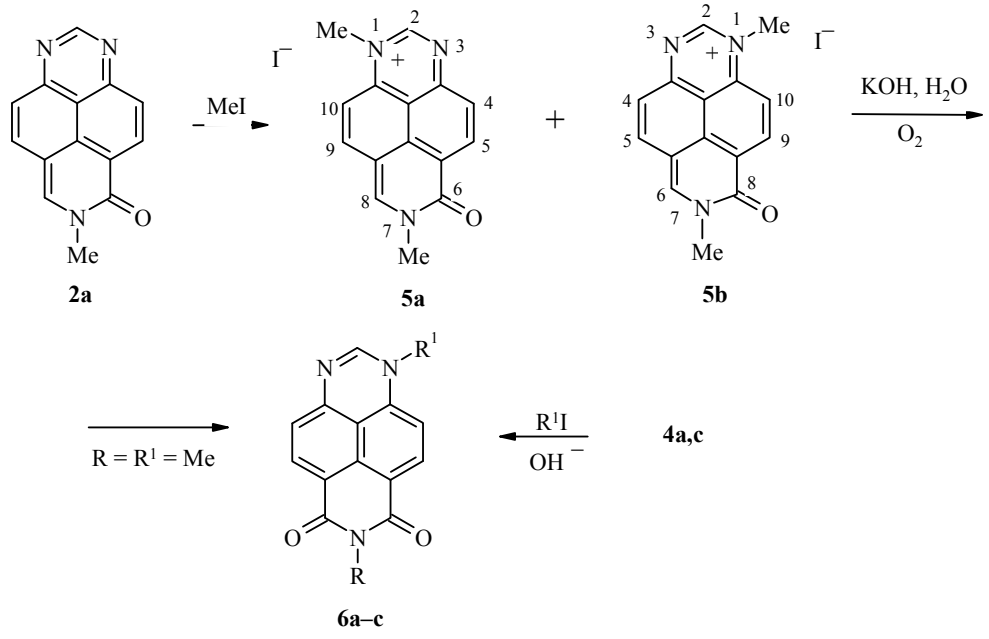
A feature of the $^1H$ and $^{13}C$ NMR spectra of compounds **2a-c** in DMSO-$d_6$ is their symmetry as a result of their rapid degenerate prototropic annular tautomerism on the NMR time scale (see Experimental).

We have also found that heating amides **2a-c** in aqueous alkali leads to a second oxidative hydroxylation to give the already known 7-alkyl-6,8-dioxo-1,6,7,8-tetrahydro-1,3,7-triazapyrenes **4a-c**.



Evidently the conversion of amides **2a-c** to imides **4a-c** involves the nucleophilic addition of $OH^-$ to the azadienone fragment of the **2a-c** molecules with subsequent oxidation of the anionic intermediate by atmospheric oxygen.

Having aimed to prepare the hydroxylation product at positions 2 and 6 of the triazapyrene ring we then undertook a quaternization of amide **2a** using methyl iodide. This occurs nonselectively to give a mixture of the two salts 1,7-dimethyl-6-oxo-6,7-dihydro-1,3,7-triazapyrenium iodide (**5a**) and 1,7-dimethyl-8-oxo-7,8-dihydro-1,3,7-triazapyrenium iodide (**5b**) in the ratio 5: 3 (from $^1$H NMR spectroscopic data).




**2a** **5a** **5b**

**6a–c**

6 **a** R = $R^1$ = Me, **b** R = Et, $R^1$ = Me, **c** R = $R^1$ = Et

Despite the efficient delocalization of the positive charge between the N-1 and N-7 atoms of cations **5a** and **5b** the oxidative hydroxylation of their mixtures occurs exclusively at the α-position of the pyridine fragment in the molecule to give the single compound 1,7-dimethyl-6,8-dioxo-1,6,7,8-tetrahydro-1,3,7-triazapyrene (**6a**).

Compound **6a** was also prepared by a counter synthesis *via* methylation of imide **4a** in basic medium. Its analogs (compounds **6b** and **6c**) were prepared by alkylation of imide **4c**.

Hence hydroxylation of 7-alkyl-1,3,7-triazapyrenium salts shows a series of features and allows the synthesis of a variety of derivatives of this heterocycle depending on the reaction conditions.

## EXPERIMENTAL

$^1$H and $^{13}$C NMR spectra were recorded on Bruker-200 (200 MHz) and Bruker DRX-500 (75 MHz) instruments respectively using DMSO-$d_6$ and with TMS as internal standard. The assignment of proton signals was carried out using the double resonance method. IR spectra were taken on a Varian 800 FT-IR instrument. Monitoring of the reaction course and the purity of the synthesized compounds was carried out by TLC on Silufol UV-254 plates. The identity of compounds prepared by different methods was proved by the absence of a depression of melting point for mixed samples and by comparison of their IR spectra.

**Reaction of Salts 1a-c in the System KOH–$H_2O$ (General Method)**. The corresponding 7-alkyl-1,3,7-triazapyrenium salt **1a-c** (1 mmol) was added to an 20% aqueous KOH solution (20 ml) and stirred vigorously at 75-80ºC for 4 h. The reaction mixture was extracted with 1-butanol (3×20 ml), the extract washed with a small amount of water, and solvent was evaporated under reduced pressure to 3-5 ml. The precipitated crystals were filtered off, washed with a small amount of alcohol, and dried.

**7-Methyl-6,8-dioxo-1,6,7,8-tetrahydro-1,3,7-triazapyrene (4a)**. Yield 0.193 g (77%). Yellow crystals; mp > 350ºC (1-butanol). IR spectrum, thin layer, ν, $cm^{-1}$: 2900-3300 (N–H), 1644 (C=O), 1583 (ring). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.37 (3H, s, $NCH_3$); 7.00, 8.17 (4H, two d, AB system, $^3J$ = 8.2, H-4(10), 5(9)); 12.40 (1H, br. s, N–H). $^{13}$C NMR spectrum, δ, ppm: 26.46, 110.28, 111.57, 119.20, 129.83, 133.70, 147.86, 149.09, 162.87. Found, %: C 66.69; H 3.58; N 16.88. $C_{14}H_9N_3O_2$. Calculated, %: C 66.93; H 3.61; N 16.72.

**2,7-Dimethyl-6,8-dioxo-1,6,7,8-tetrahydro-1,3,7-triazapyrene (4b)**. Yield 0.198 g (75%). Yellow crystals; mp > 350ºC (1-butanol). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.39 (3H, s, 2-$CH_3$); 3.33 (3H, s, $NCH_3$); 6.79, 8.13 (4H, two d, AB system, $^3J$ = 8.4, H-4(10), 5(9)); 12.42 (1H, br. s, NH). Found, %: C 67.83; H 4.30; N 15.97. $C_{15}H_{11}N_3O_2$. Calculated, %: C 67.92; H 4.18; N 15.84.

**7-Ethyl-6,8-dioxo-1,6,7,8-tetrahydro-1,3,7-triazapyrene (4c)**. Yield 0.196 g (74%). Yellow crystals; mp > 350ºC (1-butanol). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.18 (3H, t, $^3J$ = 7.3, $C\underline{H}_3CH_2$); 4.08 (2H, q, $^3J$ = 7.3, $CH_3C\underline{H}_2$); 7.00, 8.31 (4H, two d, AB system, $^3J$ = 8.2, H-4(10), 5(9)); 8.14 (1H, s, H-2); 12.50 (1H, br. s, NH). Found, %: C 67.81; H 4.29; N 16.03. $C_{15}H_{11}N_3O_2$. Calculated, %: C 67.92; H 4.18; N 15.84.

**Reaction of Salts 1a-c in the System $MnO_2$–$C_2H_5OH$–$H_2O$ (General Method)**. A mixture of the corresponding salt **1a-c** (1 mmol), $MnO_2$ (0.087 g, 10 mmol), and 96% ethanol (15 ml) was refluxed for 1 h, the hot mixture filtered, and the precipitate on the filter was washed with hot alcohol (10 ml). Solvent was evaporated to signs of crystallization and the precipitated compounds **5a-c** formed on cooling were filtered off and dried.

**7-Methyl-6-oxo-6,7-dihydro-1,3,7-triazapyrene (2a)**. Yield 0.230 g (98%). Yellow crystals; mp 260-262ºC (1-butanol) agreeing with data in [12].

**2,7-Dimethyl-6-oxo-6,7-dihydro-1,3,7-triazapyrene (2b)**. Yield 0.241 g (97%). Yellow crystals; mp 280-282ºC (1-butanol) agreeing with data in [12].

**7-Ethyl-6-oxo-6,7-dihydro-1,3,7-triazapyrene (2c)**. Yield 0.244 g (98%). Dark-orange crystals; mp 338-340ºC (ethyl acetate) agreeing with data in [11].

**Reaction of Compounds 2a-c in the system KOH–$H_2O$ (General Method)**. The corresponding compound **2a-c** (1 mmol) was added to an 20% aqueous KOH solution (20 ml) and stirred at 75ºC for 2.5 h. The separation of products **4a-c** was carried out by the method reported above. Yield of compounds: **4a** 0.198 g (79%); **4b** 0.204 g (77%), **4c** 0.201 g (76%).

**Quaternization of 7-Methyl-6-oxo-6,7-dihydro-1,3,7-triazapyrene (2a)**. Methyl iodide (0.453 g, 3 mmol) was added to a solution of compound **2a** (0.235 g, 1 mmol) in absolute acetonitrile (20 ml) and refluxed for 4 h. The acetonitrile was distilled to a volume of 3-5 ml and the product was filtered off, washed with a small amount of benzene, and dried in air.

According to $^1$H NMR data the reaction product (0.309 g, 82%) is a mixture of the isomeric salts: 1,7-dimethyl-6-oxo-6,7-dihydro-1,3,7-triazapyrenium iodide (**5a**) and 1,7-dimethyl-8-oxo-7,8-dihydro-1,3,7-triazapyrenium iodide (**5b**) in the ratio 5: 3.

**1,7-Dimethyl-6-oxo-6,7-dihydro-1,3,7-triazapyrenium Iodide (5a)**. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.96 (3H, s, 7-$NCH_3$); 4.31 (3H, s, 1-$NCH_3$); 7.80, 8.77 (2H, two d, AB system, $^3J$ = 9.0, H-5,4); 8.22, 9.12 (2H, two d, AB system, $^3J$ = 9.4, H-9,10); 9.54 (1H, s, H-8); 9.73 (1H, s, H-2).

**1,7-Dimethyl-8-oxo-7,8-dihydro-1,3,7-triazapyrenium Iodide (5b)**. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.96 (3H, s, 7-$NCH_3$); 4.26 (3H, s, 1-$NCH_3$); 7.85, 8.86 (2H, two d, AB system, $^3J$ = 9.4, H-5,4); 8.17, 9.05 (2H, two d, AB system, $^3J$ = 9.0, H-9,10); 9.39 (1H, s, H-6); 9.73 (1H, s, H-2).

**1,7-Dimethyl-6,8-dioxo-1,6,7,8-tetrahydro-1,3,7-triazapyrene (6a)**. A. The mixture of salts **5a** and **5b** (0.376 g, 1 mmol) was added to an 20% aqueous KOH solution (15 ml) and heated to 75ºC for 1 h. $K_3[Fe(CN)_6]$ (1.68 g, 5 mmol) was added and stirred for a further 2 h at this temperature. After cooling, the mixture was extracted with butanol (3×20 ml), the butanol solution was washed with a small amount of water, and evaporated to 3-5 ml. The crystals formed after cooling were filtered off, washed with a small amount of alcohol, and dried in air. Yield of compound **6a** 0.219 g (83%). Light-yellow crystals; mp > 350ºC (1-butanol). IR spectrum, thin layer, ν, $cm^{-1}$: 1639 (C=O), 1580 (ring). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.36 (3H, s, 1-$NCH_3$); 3.60 (3H, s, 7-$NCH_3$); 6.95, 8.34 (2H, two d, AB system, $^3J$ = 8.3, H-10,9); 7.18, 8.37 (2H, two d, AB system, $^3J$ = 8.3, H-4,5); 8.29 (1H, s, H-2). Found, %: C 63.95; H 4.07; N 15.00. $C_{15}H_{11}N_3O_2$. Calculated, %: C 64.05; H 3.94; N 14.94.

B. 7-Methyl-2,6-dioxo-1,6,7,8-tetrahydro-1,3,7-triazapyrene (**4a**) (0.25 g, 1 mmol) and methyl iodide (0.453 g, 3 mmol) were added to an 10% aqueous solution of KOH (20 ml). The mixture was refluxed for 3 h, solvent was distilled off, the residue was extracted with butanol (3×20 ml), and the extract was washed with a small amount of water and then evaporated to 3-5 ml volume. The crystals formed on cooling were filtered off, washed with a small amount of alcohol, and dried in air. Yield of compound **6a** 0.204 g (77%).

**7-Ethyl-1-methyl-6,8-dioxo-1,6,7,8-tetrahydro-1,3,7-triazapyrene (6b)** was prepared using method B for compound **6a**. Treatment of 7-ethyl-2,6-dioxo-1,6,7,8-tetrahydro-1,3,7-triazapyrene (**4c)** (0.279 g, 1 mmol) with methyl iodide (0.453 g, 3 mmol) gave compound **6b** (0.206 g, 74%). Brown crystals, mp > 350ºC (1-butanol). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.20 (3H, t, $^3J$ = 7.3, 7-$NCH_2C\underline{H}_3$ ); 3.62 (3H, s, 1-$NCH_3$); 4.11 (2H, q, $^3J$ = 7.3, 7-$NC\underline{H}_2CH_3$); 6.98, 8.42 (2H, two d, AB system, $^3J$ = 8.2, H-10,9); 7.22, 8.39 (2H, two d, AB system, $^3J$ = 8.2, H-4,5); 8.26 (1H, s, H-2). Found, %: C 68.55; H 4.77; N 14.86. $C_{16}H_{13}N_3O_2$. Calculated, %: C 68.81; H 4.69; N 15.04.

**1,7-Diethyl-6,8-dioxo-1,6,7,8-tetrahydro-1,3,7-triazapyrene (6c)** was prepared using method B for compound **6a**. Treatment of compound **4c** (0.279 g, 1 mmol) with ethyl iodide (0.468 g, 3 mmol) gave compound **6c** (0.222 g, 76%). Light-yellow crystals, mp > 350ºC (1-butanol). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.20 (3H, t, $^3J$ = 7.0, 7-$NCH_2C\underline{H}_3$); 1.38 (3H, t, $^3J$ = 7.0, 1-$NCH_2C\underline{H}_3$); 4.12 (4H, m, N(7)(N(1))–$C\underline{H}_2CH_3$); 7.08, 8.39 (2H, two d, AB system, $^3J$ = 8.2, H-10,9); 7.20, 8.37 (2H, two d, AB system, $^3J$ = 8.2, H-4,5); 8.30 (1H, s, H-2). Found, %: C 69.88; H 4.98; N 14.16. $C_{17}H_{15}N_3O_2$. Calculated, %: C 69.61; H 5.15; N 14.33.

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