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Recyclization of Polysubstituted Pyridinium Salts

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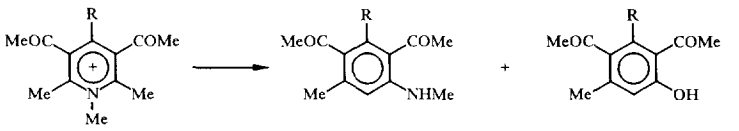
Abstract: 3,5-Diacetyl- and 3,5-dicyano-1,2,6-trimethylpyridinium perchlorates are converted by recyclization into N,5-dimethylanilines and 2-methylaminopyridines, respectively.

Pyridinium ring nucleophilic transformations are well known[1]. The recyclization of pyridinium salts into monosubstituted anilines[2] is predominant among the pyridine ring rearrangements to carbocycles. Preparation of some polyfunctional anilines using the pyridinium salts available from Hantzsch pyridines is briefly noted[3]. Now these studies are extended to the novel series of pyridinium salts.

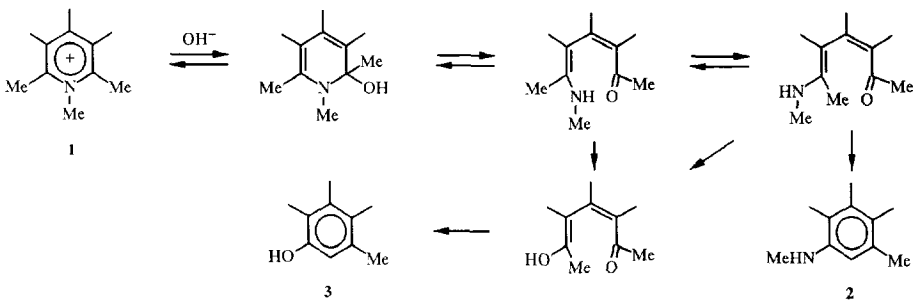
The first recyclization of Hantzsch type pyridinium compounds into benzene derivatives was demonstrated[4] by conversion of 3,5-diacetyl-1,2,4,6-tetramethylpyridinium with alkali into 2,4-diacetyl-3,5-dimethylphenol. Indeed, we isolated 2,4-diacetyl-N,3,5-trimethylaniline as a minor product when the above recyclization was repeated. Further investigations with 1,2,6-trimethylpyridinium salt **1a** resulted in the preparative isolation of N,5-dimethyl aniline **2a** as a main product (85%). Aniline formation after recyclization was diminished and accompanied by the phenol formation when pyridinium substrates containing a substituent at 4-C atom were used. Thus, 4-phenylpyridinium (perchlorates were everywhere used) **1b** in alkaline medium afforded the mixture of aniline **2b** and phenol **3b**. Aimed at the preparation of aniline derivatives other 3-aryl-N-methylanilines **2c-e** were also isolated:



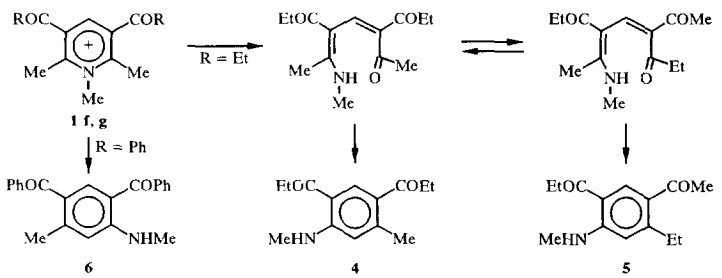
a) R = H; b) R = C_6H_5; c) R = 4-$NO_2C_6H_4$; d) R = 2-$MeOC_6H_4$; e) R = 2-$F_2CHOC_6H_4$

The recyclization of pyridinium salts in alkaline medium involves the addition of nucleophile to 2-C atom, the C-N bond cleavage of α-hydroxy amine formed, and intramolecular crotonic condensation of the acyclic intermediate. The whole process results in the benzene ring formation.

Addition of the nucleophile would take place at both pyridine α-C atoms of symmetrical pyridinium salts, and C-N bond cleavage would proceed as ionic or electrocyclic process. Intramolecular condensation of the primary acyclic intermediate affords the aniline derivative but the hydrolytic elimination of acyclic intermediate amino function leads to the phenol formation.



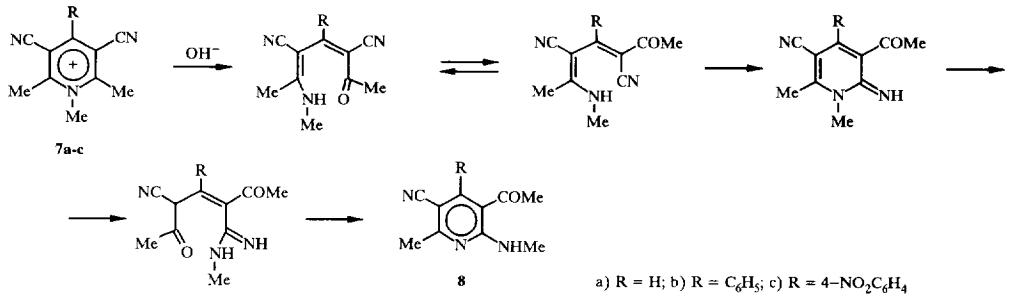
The acyclic intermediate is a relatively long-living product capable of transforming the conformation. For the very reason not only acetyl group formed after the C-N bond cleavage, but also carbonyl group of the substituent at 3-C atom would be a participant in the benzene ring formation. It is confirmed by isolation of 5-methyl and 5-ethyl substituted N-methylanilines **4** and **5** in ratio 1 : 1 after recyclization of the 3,5-dipropionylpyridinium **1f**:



Contrary to it, recyclization of 3,5-dibenzoyl-1,2,4-trimethylpyridinium (**1g**) under the same conditions afforded only 2,4-dibenzoyl-N,5-dimethylaniline (**6**). It means that the benzoyl group did not take part in this process.

Structure of isomeric anilines **4** and **5** was established on the basis of spectral studies. Comparison of aniline **4** control and decoupled NMR spectra showed doublet splitting disappearance of CH_3 group signal (2.60 ppm, J = 0.72 Hz) after high field aromatic 6-H proton (6.52 ppm) irradiation. Observed spin-spin coupling is in agreement with interaction of aromatic proton and *ortho*-CH_3 group. Therefore, the signal at 2.60 ppm is assigned to aniline **4** 5-CH_3 group. Similar spin coupling of 5-CH_3 group and 6-H proton was also observed for aniline **2a**. Mass spectrum of the aniline **5** confirmed the presence of the $COCH_3$ group (m/z 43), whereas in the spectrum of aniline **4** only COC_2H_5 (m/z 57) fragment was found.

The contribution of pyridinium ring 3,5-substituents in recyclization has been already shown by O.Mumm[5] when he obtained 3-acetyl-5-ethoxycarbonyl-1,4,6-trimethylpyrid-2-one by the treatment of 3,5-diethoxycarbonyl-1,2,4,6-tetramethylpyridinium with sodium hydroxide. We tried to use methylamine or morpholine as nucleophiles instead of alkali in Mumm's experiment but failed to get the target aniline and phenol (3-acetyl-5-ethoxycarbonyl-1,4,6-trimethylpyridin-2-one was obtained in 75-77% yield). It means that pyridone ring formation from acyclic intermediate proceeds by the intramolecular interaction of methylamino and ester functions.

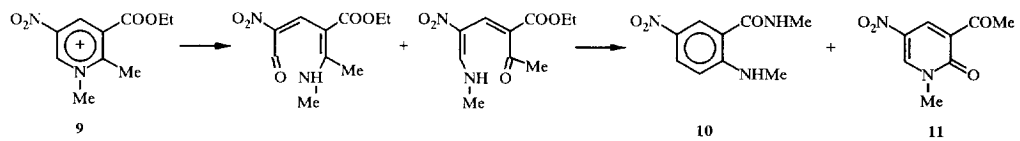


7a-c

8

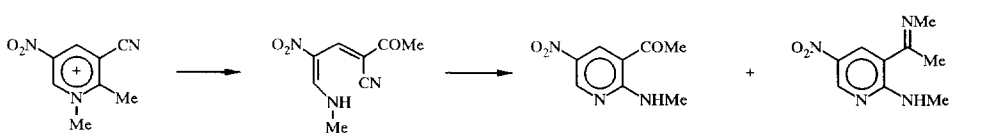
a) R = H; b) R = C_6H_5; c) R = 4-$NO_2C_6H_4$

Upon treatment with alkali 3,5-dicyano-1,2,6-trimethylpyridinium salt **7** underwent two successive ring-opening ring-closure processes, the final recyclization affording the 2-methylaminopyridines **8**. The first ring opening by the hydroxyl ion followed by the intramolecular interaction of the CH_3NH and CN groups gave the intermediate 2-iminopyridine. Dimroth rearrangement of the latter included the second ring-opening ring-closure process.



9 10 11

Addition of the hydroxyl ion to both α-C atoms of symmetric pyridinium salts generates the same acyclic intermediate while the asymmetric pyridinium derivatives depending on the C-N (2-C—N or 6-C—N) bond cleavage would give the different products. Thus, 3-ethoxycarbonyl-5-nitropyridinium derivative **9** treated with $MeNH_2$ solution affords pyridone **11** and 5-nitroanthranilic acid derivative **10** (amide formation due to the excess of $MeNH_2$). Formation of the pyridone is predominant, yields of products isolated are rather low.



12 13 14

Recyclization of the 3-cyano-5-nitropyridinium salt **12** by methylamine produces 3-acetylpyridine **13** in the mixture with methylimino derivative **14** (detected by PMR). 3-[1-(Methylimino)ethyl]pyridine **14** without isolation was converted to pyridine **13** by means of hydrolysis.

Recyclization products resulted from 2-C—N bond cleavage of the compounds **9** and **12** being predominant demonstrated that the more hindered 2-C atom has been drawn into ring transformation while the accessible 6-C atom took part in this process to a lesser degree. Pyridinium ring opening through cleavage of the both C-N bonds would be assumed, but the reverse ring closure by interaction of aldehyde group with methylamino moiety of the acyclic intermediate proceeds rather than change of the conformation.

Experimental

^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer using TMS as an internal standard. Mass spectra were obtained at 70 eV on a MAT 112 S spectrometer. IR spectra were recorded on a Specord IR 75 spectrometer. Melting points were determined on a Boethius heating block.

All new compounds gave the consistent elemental analysis.

The pyridinium perchlorates were obtained from methylation of the appropriate pyridines with dimethylsulfate at 60-80°C followed by anion exchange with sodium perchlorate.

3.5-Dipropionyl-1,2,6-trimethyl pyridinium perchlorate (1f): m.p. 160-163 °C, ^{1}H NMR (DMSO-d_6) 1.05 (t, J = 7.1 Hz, 6H), 2.70 (s, 6H), 3.02 (k, 4H), 4.06 (s, 3H), 8.86 (s, 2H).

1,2-Dimethyl-3-ethoxycarbonyl-5-nitropyridinium perchlorate (9): m.p. 84-85 °C, ^{1}H NMR (CD_3COOD): 1.47 (t, J = 7.0 Hz, 3H), 3.20 (s, 3H), 4.53 (s, 3H), 4.39 (k, 2H), 6.36 (d, J = 2.5 Hz, 1H), 6.56 (d, 1H).

1.2-Dimethyl-3-cyano-5-nitropyridinium perchlorate (12): m.p. 238-240 °C (decomp), ^{1}H NMR (acetone-d_6): 3.31 (s, 3H), 4.85 (s, 3H), 9.95 (d, J = 2.4 Hz, 1H), 10.38 (d, 1H).

N,5-Dimethyl-2,4-diacylanilines from 3,5-diacyl-1,2,6-trimethylpyridinium perchlorates 1a-g. General procedure. To the solution of 10 mmol perchlorate **1** in 20-30ml of 50% ethanol 50mmol of NaOH in 10ml of 50% ethanol was added with stirring. Reaction mixture was stirred at room temperature or refluxed for appropriate time, then the recyclization product was filtered off or the reaction mixture diluted with water, extracted with ether, evaporated and product was isolated by means of chromatography.

2,4-Diacetyl-N,5-dimethylaniline (2a), (room t°, 1h), yield 85%, m.p. 142- 143 °C (ethanol); ^{1}H NMR ($CDCl_3$): 2.56 (s, 3H, 2-$COCH_3$), 2.59 (s, 3H, 4-$COCH_3$), 2.61 (d J = 0.73 Hz, 5-CH_3), 2.96 (d J-5.1 Hz, 3H, 1-$NHCH_3$), 6.48 (d, J = 0.73 Hz, 1H, 6-H), 8.29 (s, 1H, 3-H), 9.19 (br.s., 1H, 1-$NHCH_3$); IR ($CHCl_3$): 1660 (CO), 3320 (NH); MS: 205 (44, M^+), 190 (100).

2,4-Diacetyl-N,5-dimethyl-3-phenylaniline (2b), (reflux, 1h, isolation by preparative TLC, eluent - hexane:$CHCl_3$:ethyl acetate 1:1:1); yield 19%, m.p. 133-134 °C (ethanol); ^{1}H NMR(CCl_4): 1.75 (s, 6H), 2.38 (s, 3H), 3.04 (d, J = 5.0 Hz, 3H), 6.50 (s, 1H), 6.90 (br.s, 1H), 7.38 (m, 5H); IR (CCl_4): 1650 (CO), 3400 (NH); MS: 281 (92, M^+), 266 (100).

2,4-Diacetyl-5-methyl-3-phenyl phenol (3b), (formed and isolated beside the aniline **2b** from **1b**), yield 11%, m.p. 91-92 °C (ethanol); ^{1}H NMR ($CDCl_3$): 1.88 (s, 3H), 2.36 (s, 3H), 2.64 (s, 3H), 6.75 (s, 1H), 7.47 (m, 5H), 12.40 (s, 1H); MS: 268 (65, M^+), 253 (100).

2,4-Diacetyl-N,5-dimethyl-3-(p-nitrophenyl)aniline (2c), (heating at 60 °C for 5 min, isolation by flash chromatography, eluent - hexane:$CHCl_3$:ethyl acetate 4:4:1), yield 20%, m.p. 225-226 °C (ethanol); ^{1}H NMR (CD_3CN): 1.56 (s, 3H), 1.70 (s, 3H), 1.87 (s, 3H), 2.78 (s, 3H), 6.61 (s, 1H), 6.98 (s, 1H), 7.40 (d, J = 2.0 Hz, 2H), 8.17 (d, 2H); IR ($CDCl_3$): 1360, 1540 (NO_2), 1670 (CO), 3400 (NH); MS: 326 (74, M^+), 311(100).

2,4-Diacetyl-N,5-dimethyl-3-(o-methoxyphenyl)aniline (2d), (reflux, 20 min, isolation by flash chromatography, eluent - $CHCl_3$:ethyl acetate 9:1), yield 19%, m.p. 136-137 °C (ethanol); ^{1}H NMR (acetone-d_6): 1.63 (s, 3H), 1.70 (s, 3H), 2.07 (s, 3H), 2.81 (d, J = 5.0 Hz, 3H), 3.74 (s, 3H), 6.60 (s, 1H), 6.82 (br.s, 1H), 6.98- 7.49 (m, 4H); IR (CCl_4): 1680 (CO), 3400 (NH); MS: 311 (100, M^+).

2,4-Diacetyl-3-(o-difluoromethoxyphenyl)-N,5-dimethylaniline (2e), (reflux, 20 min, flash chromatography, eluent - $CHCl_3$:ethyl acetate 9:1), yield 41%, m.p. 106-107 °C (ethanol); ^1H NMR (CD_3OD): 1.67 (s, 3H), 1.78 (s, 3H), 2.22 (s, 3H), 2.80 (s, 3H), 6.72 (t, J = 73.7 Hz, 1H), 7.15-7.64 (m, 4H); IR (CCl_4): 1670 (CO), 3375 (NH); MS: 347 (100, M^+).

N,5-Dimethyl-2,4-dipropionylaniline (4) and 4-acetyl-5-ethyl-N-methyl-3-propionylaniline (5), (reflux, 5min, flash chromatography, eluent - hexane: $CHCl_3$:ethyl acetate 4:4:1); **5**, yield 45%, m.p. 65-66 °C (hexane); ^1H NMR ($CDCl_3$): 1.22 (t, J = 7.4 Hz, 3H), and 1.23 (t, J = 7.4 Hz, 3H), 2-$COCH_2CH_3$ and 5-CH_2CH_3; 2.56 (s, 3H, 4-$COCH_3$), 2.97 (d, J = 5.1 Hz, 3H, 1-$NHCH_3$), 3.01 (q, J = 7.4 Hz, 4H, 2-$COCH_2CH_3$ and 5-CH_2CH_3), 6.52 (s, 1H, 6-H), 8.33 (s, 1H, 3-H), 9.24 (br.s., 1H, 1-$NHCH_3$); IR($CHCl_3$): 1640 (CO), 3320 (NH); MS: 233 (58,M^+), 204 (100), 43(49, $COCH_3^+$). **4**, yield 45%, m.p. 56-57°C (hexane); ^1H NMR ($CDCl_3$): 1.21 (t, J = 7.0 Hz, 3H) and 1.23 (t, J = 7.0 Hz, 3H), 2,4-$COCH_2CH_3$, 2, 60 (d, J = 0.73 Hz, 3H, 5-CH_3), 2.92 (q, J = 7.0 Hz, 2H) and 3.01 (q, J = 7.0 Hz, 2H) 2,4-$COCH_2CH_3$, 2.95 (d, J = 5.0 Hz, 3H, 1-$NHCH_3$), 6.48 (d, J = 0.73 Hz, 1H, 6-H), 8.34 (s, 1H, 3-H), 9.20 (br.s., 1H, 1-$NHCH_3$); IR ($CHCl_3$): 1650 (CO), 3330 (NH); MS: 233 (18,M^+), 204 (100), 57 (5, $COC_2H_5^+$).

3,4-Dibenzoyl-N,5-dimethylaniline (6), (reflux, 15min, flash chromatography, eluent - $CHCl_3$), yield 95%, m.p. 120-121 °C (benzene + heptane, 1:4); ^1H NMR ($CDCl_3$): 1.85 (s, 3H), 2.94 (s, 3H), 6.56 (s, 1H), 7.19-7.53 (m, 10H), 7.95 (s,1H), 8.80 (br.s, 1H); IR (CCl_4): 1625 (CO), 3320 (NH); MS: 329 (79, M^+), 314 (100).

3-Acetyl-2-methylaminopyridines 8 were obtained from 3,5-dicyano-1,2,6-trimethylpyridinium perchlorates **7**a-c by NaOH in 50% ethanol following the procedure described for the recyclization of perchlorates **1**.

3-Acetyl-5-cyano-6-methyl-2-methylaminopyridine (8a), (reflux, 10 min), yield 53%, m.p. 224-225 °C ($CHCl_3$); ^1H NMR (CCl_4): 2.92 (s, 3H), 3.04 (s, 3H), 3.58 (d, J = 5.0 Hz, 3H), 8.63 (s, 1H), 10.00 (br.s, 1H); IR ($CHCl_3$):1650 (CO), 2225 (CN), 3310 (NH); MS: 189 (100,M^+).

3-Acetyl-5-cyano-6-methyl-2-methylaminopyridine (8b), (reflux, 10 min) yield 88%, m.p. 142-143 °C (ethanol); ^1H NMR (CCl_4): 1.53 (s, 3H), 2.62 (s, 3H), 3.05 (d, J = 5.0 Hz, 3H), 7.25-7.67 (m, 5H), 8.25 (br.s., 1H); IR (CCl_4): 1650 (CO), 2200(CN), 3330(NH); MS: 265 (100, M^+).

3-Acetyl-5-cyano-6-methyl-2-methylamino-4-(p-nitrophenyl)pyridine (8c), (heating at 60°, 5 min, flash chromatography, eluent - $CHCl_3$:ethyl acetate, 9:1), yield 55%, m.p. 208-209°C (ethyl acetate); ^1H NMR ($CDCl_3$): 1.63 (s, 3H), 2.62 (s, 3H), 7.52 (d, J = 8.5 Hz, 2H), 8.32 (d, 2H); IR (CCl_4): 1360, 1530 (NO_2), 1650 (CO), 2225 (CN), 3330 (NH); MS: 310 (100, M^+).

3-Acetyl-1-methyl-5-nitropyrid-2-one (11). To a solution of perchlorate **9** (0.49 g, 1.5 mmol) in 25 ml DMF 20 ml of methylamine (25% solution) was added. After being kept at room temperature for 72 h, the reaction mixture was acidified with dil. HCl and evaporated. The residue was subjected to flash chromatography, eluting with $CHCl_3$-ethyl acetate 1:1. 5-Nitroanthranilic acid derivative **10** was eluted first, yield 13%, m.p. 204 °C. Pyridone **11** was obtained in 37% yield, m.p. 152-153°C (ethanol). ^1H NMR (DMSO-d_6): 2.83 (s, 3H), 3.83 (s, 3H), 8.42 (d, J = 2.5 Hz, 1H), 9.71 (d, 1H); IR ($CHCl_3$): 1350, 1570 (NO_2), 1690 (CO); MS: 196 (69, M^+), 181 (100).

3-Acetyl-2-methylamino-5-nitropyridine (13). Pyridinium perchlorate **12** (0.42 g, 1.5 mmol) after being kept in 25 ml of methylamine (25% solution) for 96 h furnished a mixture of pyridines **13** and **14**. The solid was filtered off, then refluxed in 10 ml ethanol with addition of 1 ml conc. HCl untill dissolved. The clear solution was diluted with water, the precipitate collected and crystallized from etha-

nol afforded the pyridine **13**. Yield 53%, m.p. 170-171 °C. ^{1}H NMR (DMSO-d_6): 2.59 (s, 3H), 3.08 (s, 3H), 8.70 (d, J = 2.6 Hz, 1H), 9.04 (d, 1H), 9.46 (br.s., 1H); IR ($CHCl_3$): 1310, 1560 (NO_2), 1660 (CO), 3300 (NH); MS: 195 (100, M^+).

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