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# DERIVATIVES AND REACTIONS OF GLUTACONALDEHYDE—XIII†

## REGIOSPECIFIC RING OPENING OF 3-SUBSTITUTED PYRIDINES

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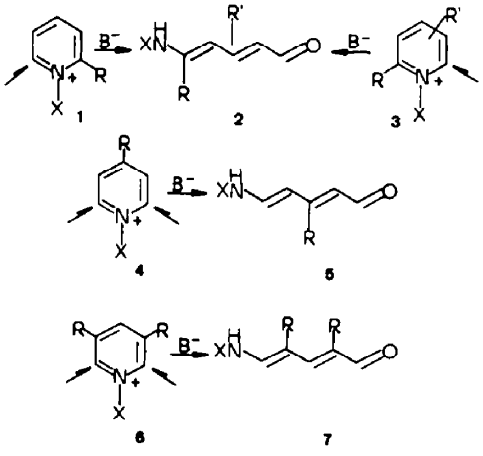
**Abstract**—A number of nucleophilic ring openings of 3-substituted pyridinium salts have been reinvestigated and summarized. The structure of the resulting stable glutaconaldehyde derivatives was investigated in detail by $^1$H NMR. It has been concluded that in general nucleophilic pyridinium ring openings are highly regiospecific. In each case investigated to date a single product was isolated, as a result of attack by the nucleophile at only one of the pyridine $\alpha$-positions. With the OH ion as the only nucleophile, attack occurs at the pyridine C-2, while larger nucleophiles such as amines and carbanions attack at the pyridine C-6. This was found to be the case for a variety of 3-substituted pyridines such as 3-methyl-, 3-methoxy-, 3-cyano-, 3-chloro-pyridine.

A number of pyridine ring openings[1] have been reported since the discovery of the classical ring opening reactions of pyridinium salts.[2,3] Pyridinium compounds react easily with nucleophiles and the reactions are in many cases followed by ring opening, resulting in the formation of glutaconaldehyde derivatives. Most of the reported examples, in which stable glutaconaldehyde derivatives have been isolated[1] have been carried out with the unsubstituted pyridine, but some substituted pyridines have also been ring opened with nucleophiles to give correspondingly substituted stable glutaconaldehyde derivatives, however in many cases without confirmation of the structure.[8,14]

As the regioselectivity of these ring openings which are of preparative value apparently have never been acknowledged and summarized before the present work was undertaken.

For substrates such as 2- and 6-substituted pyridines **1** and **3**, and the symmetrical **4** and **6** no problems concerning the regioselectivity arise as only one product is possible, namely compounds **2**, **5** or **7**:

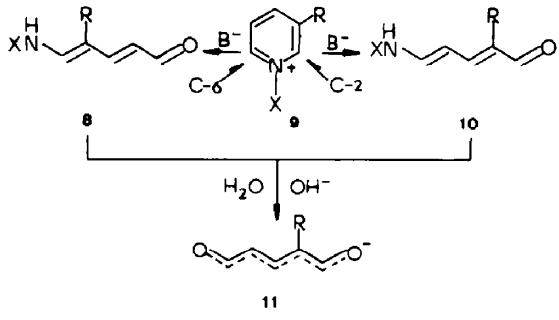


Scheme 1.

†Part XII, see *Tetrahedron* **37**, 789 (1981).

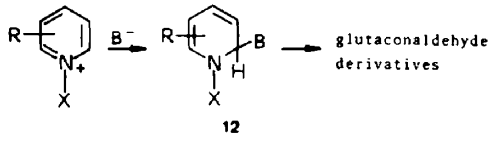
‡Attack at the pyridine C-4 by a nucleophile usually does not give a ring opening product.

However unsymmetrical pyridines such as 3- and 3,4- and 3,5-disubstituted pyridines may react‡ at either pyridine C-2 or C-6 giving rise to two different glutaconaldehyde derivatives **8** and **10**:



Scheme 2.

If the amino aldehyde **8** or **10** is hydrolysed the glutaconaldehyde anion **11** is formed, this anion will subsequently give two products upon acylation.[4] The mechanism of these ring openings which often is complicated[11] has not been investigated in the present work, but before any ring opening will take place an intermediate[5] such as **12** is involved.[17]



Scheme 3.

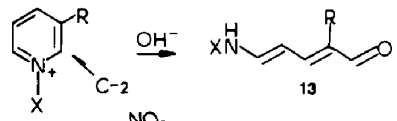
For the pyridine series it is known, that in 3-alkyl pyridines nucleophilic substitution will take place at C-2, for example with phenyllithium.[6]

The preference for nucleophilic attack at pyridine C-2 is well documented. Kuthan *et al.*[7] have carried out an HMO calculation for 3-methylpyridine and concludes that nucleophilic attack takes place in the order C-2 > C-6 > C-4. However the calculated values here also suggest

that there should only be a small difference between the preference for attack at C-2 or C-6.†

Similar results could be expected for nucleophilic reactions in the pyridinium series giving rise to a mixture[11] of 2- and 4-substituted glutaconaldehyde derivatives. However as will be seen from the assignments of structures to the glutaconaldehyde derivatives actually isolated and reported in Scheme 4, there is usually a difference in preference for attack at either C-2 or C-6 in the pyridinium series.

A. Reactions with $OH^-$ alone:



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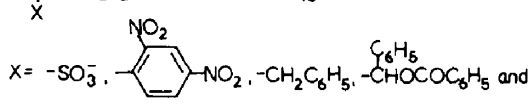
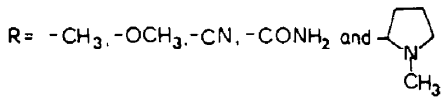
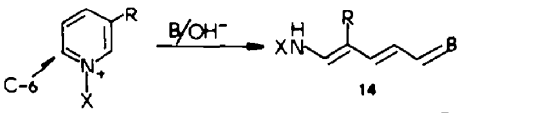




B. Reactions with other nucleophiles:



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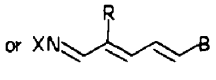

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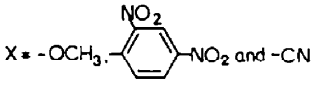
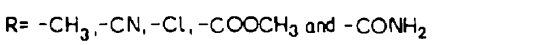
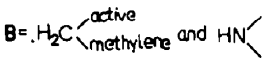






Reported examples of nucleophilic ring opening of 3-substituted pyridines, see for reactions A. refs. 4,8,10,11,12,13 and 16, for reactions B. see refs. 11,14 and 15.

Scheme 4.

## RESULTS

Scheme 4 gives a compilation of the preparative useful results for past and present ring openings of unsymmetrically substituted pyridines, while Scheme 7 gives the result of the new work. As seen from Scheme 4 usually a single product is isolated in each case, sometimes in high yields, excluding the formation of isomers. Scheme 4 further demonstrates that there is a preference for attack by the OH ion at pyridine C-2 while larger nucleophiles such as amines and carbon ions react at C-6. It is significant that the reactions in Scheme 4 apparently are independent of the electronic effects of the pyridine-3-substituent, thus both 3-methyl-, 3-chloro- as well as 3-cyanopyridines react with anilines at C-6, while the OH ion usually reacts at C-2 in these pyridines.

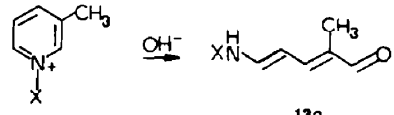
†The HMO calculation such as the one cited[7] does not account for steric as well as solvent effects.

Part of this effect is probably steric, while the electronegativity of the pyridine N-substituent seems to be less important. Another explanation of these results could be that only one of the possible ring opened products is stable.[17]

Only glutaconaldehyde derivatives of type **13** are formed when a pyridinium compound is treated with the OH ion alone. Thus Becher[4] demonstrated that the Baumgarten ring opening of 3-methyl and 3-methoxypyridinium-1-sulfonates yielded products from reaction at the pyridine C-2. Analogous results were obtained by Kuhn and Teller[13] for 3-cyano-pyridinium salts which with the OH ion yielded type **13** compounds from reaction at the pyridine C-2.

In a series of papers Moracci *et al.*[11] have demonstrated, that the ring opening of pyridinium derivatives with electro-negative 3-substituents with nucleophiles also followed the general scheme, thus amines give products corresponding to reaction at C-6, while the OH ion is found to attack at C-2 or C-6, but only attack at C-2 actually results in ring opening and isolation of a stable glutaconaldehyde derivative. 3-Methylpyridinium salts with a number of *para* substituted benzoyl vinyl N-substituents was also ring opened[12] at C-2 by the OH ion only.

Also N-(2,4-dinitrophenyl) pyridinium salts were opened at C-2 by the OH ion as demonstrated for the nicotinic amide derivatives by Autherhof and Weinmann.[10] Tamura *et al.*[8a] showed that the corresponding 3-methylpyridine could ring open with aqueous base, and a reinvestigation of the glutaconaldehyde product demonstrated this to be a result of ring opening at the pyridine C-2;



13a

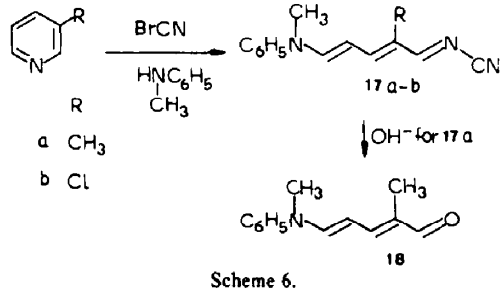
X = 2,4-dinitrophenyl

Scheme 5.

Thus in all cases reaction of a pyridinium salt with the OH ion only yields glutaconaldehyde derivatives according to Scheme 4.

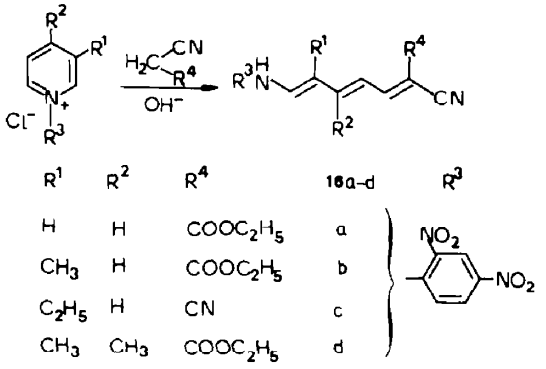
On the other hand, when the ring opening is performed in the presence of another nucleophile such as an aliphatic or an aromatic amine or a compound containing an active methylene group, the pyridine usually reacts at C-6.

This was demonstrated by Schneckenburger *et al.*[15] for a number of 3-substituted N-methoxypyridinium perchlorates which in all cases with various nucleophiles and aqueous base ring opened at the pyridine C-6. This is also the case[14] where we have investigated the $^1H$ NMR spectra of the glutaconaldehyde products **17** and **18**:



Scheme 6.

Again it was demonstrated that the ring opening had taken place at the pyridine C-6 as expected. Previously Tamura *et al.*[8b] have ring opened 2,4-dinitrophenylpyridinium chloride with an active methylene compound present, however without assigning a structure for the product. We have reinvestigated and substantiated this reaction as the following Scheme shows:



| $R^1$ | $R^2$ | $R^4$ | 16a–d | $R^3$ |
|---|---|---|---|---|
| H | H | $COOC_2H_5$ | a | 2,4-dinitrophenyl |
| $CH_3$ | H | $COOC_2H_5$ | b | |
| $C_2H_5$ | H | CN | c | |
| $CH_3$ | $CH_3$ | $COOC_2H_5$ | d | |

Scheme 7.

The $^1$H NMR spectra of the glutaconaldehyde products **16** in each case confirmed that the reactions were regiospecific as only product arising from the least steric hindered pyridine C-6 position was found.

All assignments of $^1$H-NMR spectra reported were performed as previously described.[9]

The assignment of the structure to the glutaconaldehyde derivatives **16a–d** was carried out by decoupling experiments in the 270 MHz $^1$H-NMR spectra, as described for compound **16d**. In compound **16d** coupling N–H and H–5 was seen as a doublet at $\delta$ 10.43 ppm, thus, irradiation at $\delta$ 10.43 ppm (broad singlet) resulted in the appearance of a sharp singlet at $\delta$ 7.71 ppm.

Decoupling of the doublet at $\delta$ 8.25 ppm gave a singlet at $\delta$ 6.58 ppm, while decoupling at $\delta$ 7.71 ppm resulted in the formation of a broad singlet at $\delta$ 10.43 ppm. Finally irradiation at the $\delta$ 8.25 ppm doublet resulted in the formation of a singlet at $\delta$ 6.58 ppm, this gives the combination for H-1 and H-2 as well as for NH and H-5.

It was of great help in our assignment of the H-1 and H-5 protons that the aldehyde **18** could be prepared by the method of Hafner and Asmus[14] as the $^1$H NMR spectra of this aldehyde was well known.[9] Both 60 MHz and 270 MHz spectra were used and decoupling in the 270 MHz spectra were performed in some cases.

## CONCLUSION

It can be concluded that nucleophilic attack followed by *ring opening of 3-substituted pyridinium compounds, which give stable glutaconaldehyde derivatives*, usually are regiospecific. Using the OH ion as the only nucleophile reaction generally occurs at the pyridine C-2, independent of the pyridine C-3 substituent as well as the N-substituent. Reaction with other nucleophiles results exclusively in attack at the pyridine C-6. This may therefore have practical value for the synthesis of substituted pentadienes.

## EXPERIMENTAL

*Instrumentation.* $^1$H-NMR: Joel JNM-PMX 60 and Bruker HX 270. M.p. Büchi apparatus (uncorrected). MS. Varian MAT 311 A. 70 eV at resolution 5000 (Grant No. 5111-3809, the Danish Natural Science Research Council). IR Perkin Elmer 580. UV. Varian CARY 219.

All compounds were prepared as described in the refs. For a review of preparative methods, see Ref. 1.

*2-Methyl-5-(2,4-dinitroanilino)-2,4-pentadienal* **13**. This was prepared according to the procedure of Grigoreva and Gintse Mp. 164–6° (d). (Litt[16] m.p. 161°). IR(KBr): 1660, (CHO); $^1$H NMR ($CDCl_3$) $\delta$: 10.45 (1H, s, N–H), 9.42. (1H, s, $H^1$), 8.82 (1H, d, $J_{ab}$ = 3Hz, $H^a$), 8.41 (1H, dd, $J_{ab}$ = 3Hz, $J_{bc}$ = 10 Hz, $H^b$) 7.89 (1H, d, $J_{4,5}$ = 12.5 Hz, $H^5$), 7.75 (1H, d, $J_{bc}$ = 10 Hz, $H^c$), 7.10 (1H, d, $J_{4,5}$ = 12.5 Hz, $H^4$), 3.38 (3H, s, C–$CH_3$).

*2-Cyano-7-(2,4-dinitroanilino)-heptatrienoic acid ethyl ester* (**16a**). Pyridine (1.62 ml, 0.02 mole) and 2,4-dinitrochlorobenzene (4.04 g, 0.02 mole) was stirred at 70° for 30 min. The mixture crystallized, whereupon abs EtOH (50 ml) was added, followed by ethyl cyanoacetate (3.13 ml, 0.02 mole). To the clear soln was then added NaOH (2.4 ml (33%), 0.02 mole) and the mixture refluxed for 2 hr. After cooling to room temp, the dark red ppt was isolated and washed with water, EtOH and diethyl ether, yield of **16a** 5.2 g (73%) m.p. 220–2° d. MS peak match, calc. for $C_{16}H_{14}N_4O_6$: 358.0913, Found: 358.0959. IR (KBr): 2217 cm$^{-1}$ (CN).

$^1$H NMR ($CD_3COCD_3$) $\delta$: 10.55 (1H, s, N–H), 902 (1H, d, $J_{ab}$ = 27 Hz, $H^a$), 8.48 (1H, dd, $J_{ab}$ = 2.7 Hz, $H_{b,c}$ = 9.5 Hz, $H^b$), 8.05 (1H, d, $J_{12}$ = 12.9 Hz, $H^1$), 7.94 (1H, d, $J_{4,4}$ = 11.7 Hz, $H^5$), 7.83 (1H, d, $J_{bc}$ = 9.5 Hz, $H^c$), 7.43 (1H, dd, $J_{2,3}$ = 11.2, $J_{3,4}$ = 13.9, $H^3$), 6.76 (1H, dd, $J_{1,2}$ = 12.9 Hz, $J_{2,3}$ = 11.2 Hz, $H^2$), 6.65 (1H, dd, $J_{3,4}$ = 13.9 Hz, $J_{4,5}$ = 11.7 Hz, $H^4$), 4.28 (2H, q, $J$ = 7.2 Hz, O–$CH_2$), 1.31 (3H, t, $J$ = 7.2 Hz, $CH_2$–$CH_3$).

*2-Cyano-6-methyl-7-(2,4-dinitroanilino)-hepatrienoic acid ethyl ester* (**16b**). This was prepared as above, yield 5.4 g (73%), m.p. 197–8° d. MS. peak match, calc. for $C_{17}H_{16}N_4O_6$: 372.1069, Found: 372.1069. IR (KBr): 2217 cm$^{-1}$ (CN).

$^1$H-NMR (DMSO-$d_6$) $\delta$: 10.59 (1H, s, N–H), 8.85 (1H, d, $J_{a,b}$ = 2.17 Hz, $H^a$), 8.45 (1H, dd, $J_{ab}$ = 2.7, $J_{bc}$ = 9.5 Hz, $H^b$), 7.87 (1H, d, $J_{12}$ = 12.0 Hz, $H^1$), 7.77 (1H, s, $H^5$); 7.75 (1H, d, $J_{bc}$ = 9.5 Hz, $H^c$), 7.16 (1H, d, $J_{2,3}$ = 12.3 Hz, $H^3$), 6.93 (1H, dd, $J_{1,2}$ = 12.0 Hz, $J_{2,3}$ = 12.3 Hz, $H^2$), 4.25 (2H, q, $J$ = 7.0 Hz, O–$CH_2$), 2.19 (3H, s = C–$CH_3$), 1.27 (3H, t, $J$ = 7.0 Hz, $CH_2$–$CH_3$).

*2 - Cyano - 6 - ethyl - 7 - (2,4 - dinitroanilino) - heptatrienonitrile* (**16c**). This was prepared as above from 3 - ethylpyridine (2.24 ml, 0.02 mole), 2,4-dinitrochlorobenzene (4.04 g, 0.02 mole) and malodinitrile (1.32 g 0.02 mole), yield 1.5 g (22%), m.p. 184–5° d. MS. peak match, calc. for $C_{16}H_{13}N_5O_4$: 339.0967, Found: 339.0979.

$^1$H-NMR (DMSO-$cl_6$) $\delta$: 10.38 (1H, s, N–H), 8.88 (1H, d, $J_{ab}$ = 2.7 Hz, $H^a$), 8.69 (1H, s, $H^5$), 8.49 (1H, dd, $J_{ab}$ = 2.7 Hz, $J_{ab}$ = 9.3 Hz, $H^b$), 8.12 (1H, d, $J_{1,2}$ = 11.6 Hz, $H^1$), 7.94 (1H, d, $J_{bc}$ = 9.3 Hz, $H^c$), 7.37 (1H, d, $J_{2,3}$ = 14.3 Hz, $H^3$), 6.57 (1H, dd, $J_{12}$ = 11.6 Hz, $J_{2,3}$ = 14.3 Hz, $H^2$), 1.12 (3H, $J$) = 7.6 Hz, $CH_2$–$CH_3$).




Scheme 8. Numbering used for the $^1$H NMR spectra of the glutaconaldehyde derivatives reported here.

2 - *Cyano* - 5,6 - *dimethyl* - 7 - (2,4 - *dinitroanilino*) *heptatrienoic acid ethylester* (**16d**). This was prepared as above, yield 2.7 g (35%), m.p. 175–6° d. MS. peak match calc. for $C_{18}H_{18}N_4O_6$: 386.1226, Found: 386.1235. IR (KBr): 2217 $cm^{-1}$ (CN).

$^1$H-NMR (-DMSO.d6) $\delta$: 10.43 (1H, s, N–H), 8.84 (1H, d, $J_{ab}$ = 2.7 Hz, $H^a$), 8.35 (1H, dd, $J_{ab}$ = 2.7 Hz, $J_{ab}$ = 95 Hz, $H^b$) 8.25 (1H, d, $J_{1,2}$ = 12.3 Hz, $H^1$), 7.83 (1H, d, $J_{bc}$ = 9.5 Hz, $H^c$), 7.71 (1H, s, $H^5$), 6.58 (1H, d, $J_{12}$ = 12.3 Hz, $H^2$), 4.21 (2H, q, $J$ = 7.0 Hz, O–C$H_2$), 2.31 (3H, s, =C–C$H_3$), 1.99 (3H, s, =C–C$H_3$), 1.23 (3H, t, $J$ = 7.0 Hz m $CH_2$–C$H_3$).

2 - *Methyl* - 5 - [*N* - *methylanilino*] - *pentadien* - (2,4)-*yliden* - 1 - *cyanid* (**17a**). Prepared according to the procedure of Hafner and Asmus,[14] m.p. 149–149.5° (Litt.[14] m.p. 145–6°. IR (KBr): 2185 $cm^{-1}$ (CN) UV (abs. EtoH): $\lambda_{max}$ (log $\epsilon$): 444.8 nm (4.89), 266.8 nm (3.84).

$^1$H-NMR ($CDCl_3$) $\delta$: 8.32 (1H, s, $H^1$), 7.46 (1H, d, $J_{4,5}$ = 12.4 Hz, $H^5$), 7.27 (5H, m, phenyl), 7.04 (1H, d, $J_{3,4}$ = 12.4, $H^3$), 5.74 (1H, dd, $J_{3,4}$ = 12.4; $H^4$), 3.45 (3H, s, N–C$H_3$), 1.90 (3H, s, C–C$H_3$).

2 - *Chloro* - 5 - [N - *methylanilinol* - *pentadien* - (2,4) - *yliden* - 1 - *cyanid* (**17b**). Prepared according to the procedure of Hafner and Asmus,[14] m.p. 185–6° (Litt[14] m.p. 185–6°). IR (KBr): 2160 $cm^{-1}$ (CN) UV (absELOH): $\lambda_{max}$ (log $\epsilon$): 453.4 nm (4.91), 263.2 nm (3.79) $^1$H-NMR ($CDCl_3$) $\delta$: 8.60 (1H, s, $H^1$), 8.10 (1H, d, $J_{4,5}$ = 12.0, $H^5$), 7.75 (1H, d, $J_{3,4}$ = 12.0, $H^3$), 7.45 (5H, m, phenyl), 5.95 (1H, dd, $J_{3,4}$ = $J_{4,5}$ = 12.0, $H^4$), 3.52 (3H, s, N–C$H_3$).

2 - *Methyl* - 5 - N - *methylanilino* - 2,4 - *pentadienal*, (**18**). Prepared according to Hafner and Asmus.[14] The product was an oil which was distilled in a "Kugelrohr" apparatus, this gave a yellow oil b.p. 170° (0.02 mm Hg) which crystallized after storage in the freezer, crystals m.p. 83–88° (Litt.[14] 86°). IR (KBr): 1655 $cm^{-1}$ (CHO).

$^1$H-NMR ($CDCl_3$) $\delta$: 9.30 (1H, s, $H^1$), 7.30 (1H, d, $J_{4,5}$ = 12.0 $H^5$), 7.20 (5H, m, phenyl), 6.95 (1H, d, $J_{3,4}$ = 12.0, $H^3$), 5.68 (1H, dd, $J_{3,4}$ = $J_{4,5}$ = 12.0, $H^4$), 3.37 (3H, s, N–C$H_3$), 1.82 (3H, s, C–C$H_3$).

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