Reaction of *N*-(2-Pyridylmethyl)-3,5-dimethylbenzamide and *N*-(3-Pyridylmethyl)-3,5-dimethylbenzamide *N*-Oxides With Acetic Anhydride

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As a continuation of our work on the reaction of *N*-pyridylmethyl-3,5-dimethylbenzamide *N*-oxides with acetic anhydride, we now report a study of the reaction of *N*-(2-pyridylmethyl)-3,5-dimethylbenzamide *N*-oxide (**5**) and *N*-(3-pyridylmethyl)-3,5-dimethylbenzamide *N*-oxide (**6**) with acetic anhydride. Compound **5** gave *N,N'*-di(3,5-dimethylbenzoyl)-1,2-di(2-pyridyl)ethenediamine (**7**) and 3,5-dimethylbenzamide (**8**). Compound **6** afforded three products formulated as 2-acetoxy-3-(3,5-dimethylbenzoylaminomethyl)pyridine (**12**), 3-(3,5-dimethylbenzoylaminomethyl)-2-pyridone (**13**) and 5-(3,5-dimethylbenzoylaminomethyl)-2-pyridone (**14**). Analytical and spectral data are presented which support the structures proposed.

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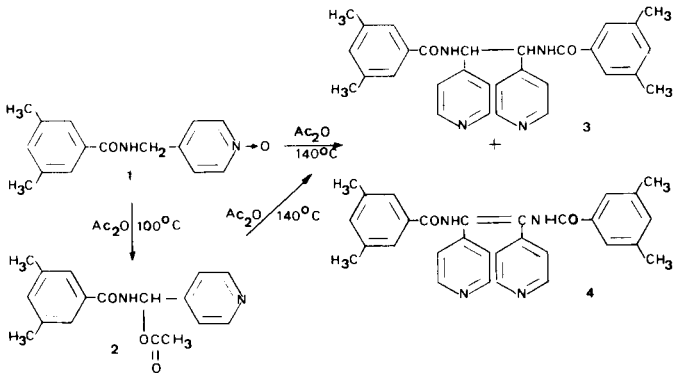
In previous publications (1,2) we reported that the reaction of *N*-(4-pyridylmethyl)-3,5-dimethylbenzamide *N*-oxide (**1**) with acetic anhydride yielded the compounds formulated as *N*-[(α-acetoxy)-4-pyridylmethyl]-3,5-dimethylbenzamide (**2**), *N,N'*-di(3,5-dimethylbenzoyl)-1,2-di(4-pyridyl)ethylenediamine (**3**) and a mixture of the *Z* and *E* isomers of *N,N'*-di(3,5-dimethylbenzoyl)-1,2-di(4-pyridyl)-ethenediamine (**4**).

Figure 1

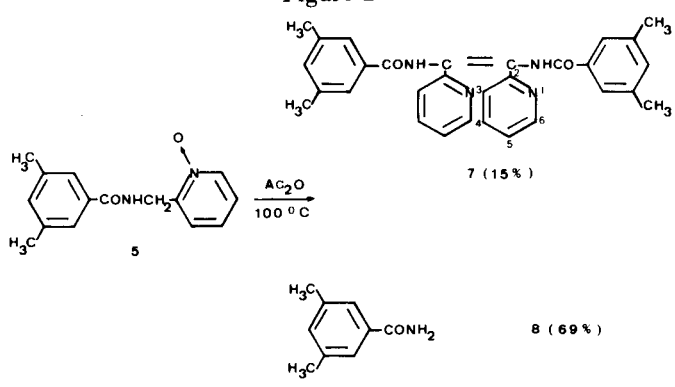


The theoretical interest of this reaction led us to carry out the reaction of *N*-(2-pyridylmethyl)-3,5-dimethylbenzamide *N*-oxide (**5**) and *N*-(3-pyridylmethyl)-3,5-dimethylbenzamide *N*-oxide (**6**) with acetic anhydride in order to study the effect of *N*-substitution on the reactivity.

The treatment of **5** with acetic anhydride afforded the *N,N'*-di(3,5-dimethylbenzoyl)-1,2-di(2-pyridyl)ethenediamine (**7**) in 15% yield when the residue of reaction was treated with ethyl acetate.

The mass spectrum of **7** showed a molecular peak at 476. The infrared (ir) spectrum exhibited an absorption band for amide group. The nmr spectrum showed signals at δ 2.20 (s, $4CH_3$, 12H), 6.90 (m, 2H *para*-phenyl, $2H_3$ and $2H_5$-pyridine, 6H), 7.50 (m, 4H *ortho*-phenyl, $2H_4$-pyridine,

Figure 2



2NH, 8H), 8.85 (m, $2H_6$-pyridine, 2H).

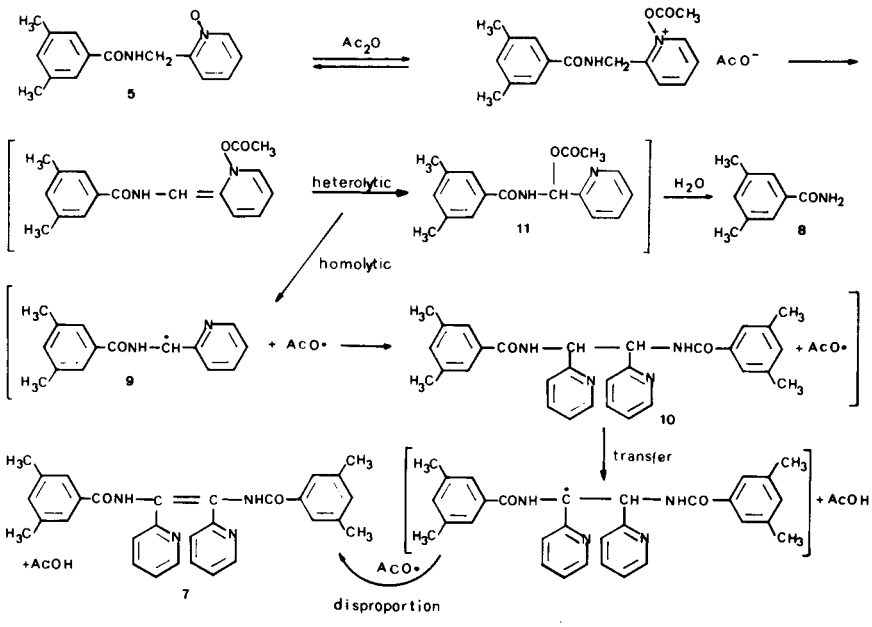
The ethyl acetate solution was chromatographed on a column of silica gel eluted with benzene/ethanol (9:1) to give 3,5-dimethylbenzamide (**8**) in 69% yield.

The fact that **7** and **8** were isolated seems to suggest that homolytic and heterolytic processes are competing in this reaction (Scheme 1). The homolytic cleavage process gave rise to radicals **9**, dimerization of which explains the formation of **10**. The latter, in a transfer reaction followed by a radical disproportionation process would give rise to **7**. The major reaction proceeds *via* an heterolytic process, which, by an intramolecular rearrangement *via* "ion pair" would give unisolated **11**, that for chromatography on a column would hydrolize into 3,5-dimethylbenzamide (**8**).

In the reaction of **6** with acetic anhydride three compounds, **12**, **13** and **14** were isolated. These were separated by column chromatography over silica gel using benzene:ethanol (9:1) as the eluent.

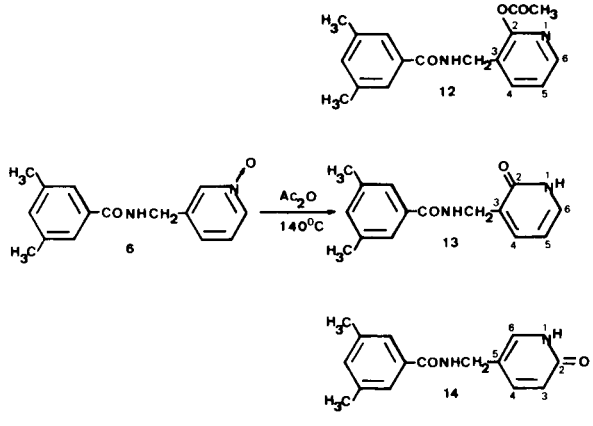
On the first elution, 2-acetoxy-3-(3,5-dimethylbenzoylaminomethyl)pyridine (**12**) [Rf = 0.42, benzene:ethanol (9:1)] was obtained. The infrared (ir) spectrum showed absorption for amide and ester groups. The nmr spectrum

Scheme 1



showed signals at δ 2.20 (s, $COCH_3$, 3H), 2.30 (s, $2CH_3$-aromatic, 6H), 4.60 (s, CH_2, 2H), 6.20 (t, H_5-pyridine, 1H), 7.10 (s, H *para*-phenyl, 1H), 7.20 (s, 2H *ortho*-phenyl, 2H), 7.30 (m, H_4 and H_6-pyridine, 2H).

Figure 3

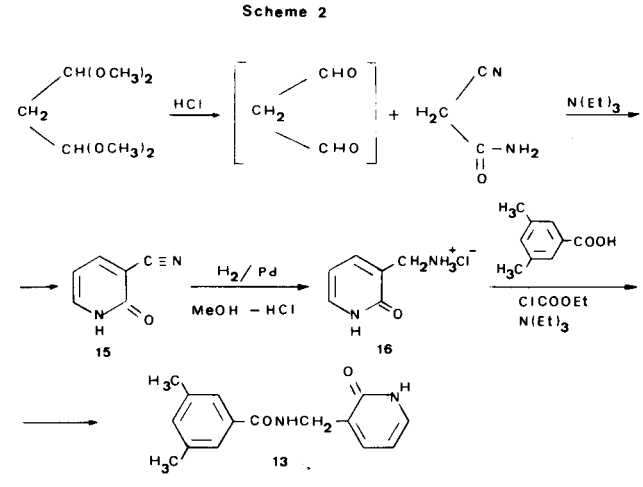


On further elution of the column 3-(3,5-dimethylbenzoylaminomethyl)-2-pyridone (**13**) [Rf = 0.28, benzene:-ethanol (9:1)] was isolated. The infrared (ir) spectrum showed absorption bands for amide and pyridone groups. The nmr spectrum showed peaks at δ 2.30 (s, $2CH_3$, 6H), 4.30 (s, CH_2, 2H), 6.20 (t, H_5-pyridone, 1H), 7.10 (s, H *para*-phenyl, 1H), 7.40 (m, H_4 and H_6-pyridone, 2H), 7.50 (s, 2H *ortho*-phenyl, 2H).

The identity of the product **13** was determined unequivocally as shown in Scheme 2.

The synthesis of 3-cyano-2-pyridone (**15**) was carried out

Scheme 2



following the method of Protopopova (3). Catalytic hydrogenation of **15** gave **16**, which was allowed to react with 3,5-dimethylbenzoic acid in presence of ethyl chloroformate and triethylamine to give **13**. The two samples of **13** prepared from **6** or **15** proved to be identical (mp, ir, nmr).

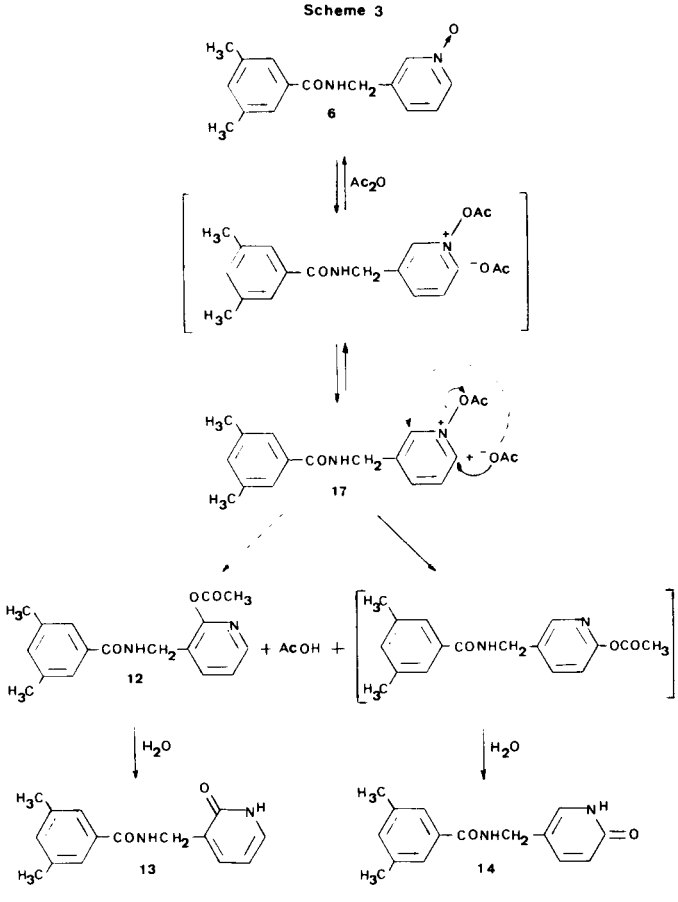
On further elution of the column, 5-(3,5-dimethylbenzoylaminomethyl)-2-pyridone (**14**) [Rf = 0.14, benzene:-ethanol (9:1)] was obtained. The infrared (ir) spectrum showed absorption bands for amide and pyridone groups. The nmr spectrum showed peaks at δ 2.40 (s, $2CH_3$, 6H), 4.30 (m, CH_2, 2H), 6.30 (d, H_3-pyridone, 1H), 7.10 (s, H *para*-phenyl, 1H), 7.50 (m, 2H *ortho*-phenyl, H_4 and H_6-pyridone, 4H).

These experimental results are similar to those reported in the literature (4) from the reaction of heteroaromatic *N*-oxides with alkyl substituents at β-position with acylat-

ing agents.

The general mechanism (Scheme 3) proceeds *via* an intermolecular rearrangement involving the nucleophilic attack of acetate anion at α-ring carbon on *N*-acetoxypyridinium ion (**17**) with the subsequent 1,2-elimination of acetic acid to give **12**, **13** and **14**.

Scheme 3



Finally, the behavior of *N*-oxides of *N*-(2-pyridylmethyl)-3,5-dimethylbenzamide (**5**) and *N*-(4-pyridylmethyl)-3,5-dimethylbenzamide (**1**) with acetic anhydride is alike, because both give rise to reactions of radicalic dimerization. However, with the *N*-oxide of *N*-(3-pyridylmethyl)-3,5-dimethylbenzamide (**6**), the reactions taking place on the α-position of the pyridine ring.

EXPERIMENTAL

The melting points were obtained on a Büchi apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer (potassium bromide disc). The nmr spectra were determined with a Varian T-60 or a Bruker WH 90 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian Model MAT 711 spectrometer. The elemental analyses were performed by Centro Nacional de Química Orgánica, Madrid. Column chromatography was performed on Merck Kieselgel 60, 0.063-0.200 mm.

Reaction of *N*-(2-pyridylmethyl)-3,5-dimethylbenzamide *N*-Oxide (**5**) With Acetic Anhydride.

A solution of **5** (5 g, 0.02 mole) in 40 ml of acetic anhydride was heated at 100° for 20 minutes and then evaporated under reduced pressure. The residue was treated with ethyl acetate, the precipitate **7** was purified by crystallization in benzene-ethyl acetate (0.7 g, 15%), mp 238-240°; ir (potassium bromide): 3000 (NH), 1650 (C=O), 1600, 1580, 1520 cm^{-1} (aromatic); nmr (deuteriochloroform): 60 MHz δ 2.20 (s, $4CH_3$, 12H), 6.90 (m, 2H *para*-phenyl, $2H_3$ and $2H_5$-pyridine, 6H), 7.50 (m, 4H *ortho*-phenyl, $2H_4$-pyridine, 2NH, 8H), 8.85 (m, $2H_6$-pyridine, 2H); ms: 476 (M^+), 327 (100), 298 (15), 249 (24), 133 (79), 105 (50), 79 (19), 77 (11).

Anal. Calcd. for $C_{30}H_{28}N_4O_2$: C, 75.60; H, 5.92; N, 11.75. Found: C, 75.80; H, 5.96; N, 11.86.

The ethyl acetate solution was removed *in vacuo* and the residue was chromatographed on a silica gel column with benzene:ethanol (9:1) as the eluent, affording **8** (2 g, 69%), mp 133° (cyclohexane) (133° in the reference 2).

Reaction of *N*-(3-Pyridylmethyl)-3,5-dimethylbenzamide *N*-Oxide (**6**) With Acetic Anhydride.

A solution of **6** (10 g, 0.04 mole) in 70 ml of acetic anhydride was refluxed for 1.5 hours. The acetic anhydride was evaporated *in vacuo* giving an oil, which was chromatographed over silica gel using benzene:-ethanol (9:1) as the eluent, affording the following products:

The first fraction, compound **12** [Rf = 0.42, benzene:ethanol (9:1)] was obtained (1 g, 9%), mp 167° (ethyl acetate); ir (potassium bromide): 3167 (NH), 1685 (C=O ester), 1660 (C=O amide), 1580, 1560 (aromatic), 1270 cm^{-1} (C-O ester); nmr (d-acetone 99.5% + S_2C): 90 MHz δ 2.20 (s, $COCH_3$, 3H), 2.30 (s, $2CH_3$, 6H), 4.60 (s, CH_2, 2H), 6.20 (t, H_5-pyridine, 1H), 7.10 (s, H *para*-phenyl, 1H), 7.20 (s, 2H *ortho*-phenyl, 2H), 7.30 (m, H_4 and H_6-pyridine, 2H).

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.43; H, 6.08; N, 9.39. Found: C, 68.14; H, 6.12; N, 9.32.

The second fraction, compound **13** [Rf = 0.28, benzene:ethanol (9:1)] was obtained (2.1 g, 21%), mp 218-220° (methanol-water); ir (potassium bromide): 3270 (NH), 3000-2500 (OH α-pyridone), 1650 (C=O pyridone), 1630 (C=O amide), 1600, 1560, 1540 cm^{-1} (aromatic); nmr (d-acetone 100% + S_2C): 90 MHz δ 2.30 (s, $2CH_3$, 6H), 4.30 (s, CH_2, 2H), 6.20 (t, H_5-pyridone, 1H), 7.10 (s, H *para*-phenyl, 1H), 7.40 (m, H_4 and H_6-pyridone, 2H), 7.50 (s, 2H *ortho*-phenyl, 2H).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.00; H, 6.39; N, 10.72.

The third fraction, compound **14** [Rf = 0.14, benzene:ethanol (9:1)] was obtained (1 g, 10%), mp 195-197° (water); ir (potassium bromide): 3380 (NH), 3200-2500 (OH α-pyridone), 1680 (C=O pyridone), 1650 (C=O amide), 1600, 1530 cm^{-1} (aromatic); nmr (d-acetone 99% + S_2C): 90 MHz δ 2.40 (s, $2CH_3$, 6H), 4.30 (m, CH_2, 2H), 6.30 (d, H_3-pyridone, 1H), 7.10 (s, H *para*-phenyl, 1H), 7.50 (m, 2H *ortho*-phenyl, H_4 and H_6-pyridone, 4H).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.27; H, 6.31; N, 10.63.

On further elution of the column, compound **6**, [Rf = 0.12, benzene:-ethanol (9:1)] was isolated (1.3 g, 13%) mp 168-169° (water).

3-Cyano-2-pyridone (**15**).

A solution of malonaldehyde dimethyl acetal (8.2 g, 0.05 mole) in 20 ml of 0.5 *N* hydrochloric acid was heated at 50° for 20 minutes. The reaction mixture was basified with triethylamine (8 ml) and cyanoacetamide (4.5 g, 0.05 mole) was added. After the mixture was stirred at room temperature for 2 hours, at 60° for 2 hours and at 100° for 1 hour. The solvent was evaporated *in vacuo*, the residue was treated with diethyl ether-ethanol, the precipitate was washed with diethyl ether-ethanol to give 3.45 g (57%) of **15**, mp 224-225° (ethanol) (224° in the reference 3).

3-(3,5-Dimethylbenzoylaminomethyl)-2-pyridone (**13**).

A mixture of 7.1 g (0.06 mole) of **15**, 500 ml of ethanol, 17 ml of 2 *N* hydrochloric acid and 5 g of 10% palladium/carbon was hydrogenated in a Parr shaker. The catalyst was removed by filtration, and the filtrate was

concentrated *in vacuo* to give 6.0 g (63%) of **16**, mp 181-184°. This material was used in the next step without further purification.

A solution of 1.5 g (0.01 mole) of 3,5-dimethylbenzoic acid, 2 g (0.02 mole) of triethylamine in 25 ml of anhydrous acetone was stirred and cooled at 10°. Ethyl chloroformate (1.1 g, 0.01 mole) was added and the temperature was maintained at 10° for 1 hour. Compound **16** (1.6 g, 0.01 mole) in 10 ml of water was then added. The mixture was stirred at room temperature for 1 hour. The acetone was evaporated, the solution was made alkaline with 3 *N* aqueous sodium hydroxide. The triethylamine was evaporated *in vacuo*, the precipitate **(13)** was purified by crystallization in methanol-water (1 g, 39%), mp 218-220°. All the analytical data for the 3-(3,5-dimethylbenzoylaminomethyl)-2-pyridone so obtained are identical with those of compound **13**.

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