Reaction of *N*-(4-Pyridylmethyl)-3,5-dimethylbenzamide *N*-Oxide with Acidic Compounds in the Presence of Acetic Anhydride: Discussion of the Mechanism

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The mechanism of *N*-(4-pyridylmethyl)-3,5-dimethylbenzamide *N*-oxide with acidic compounds in the presence of acetic anhydride is presented.

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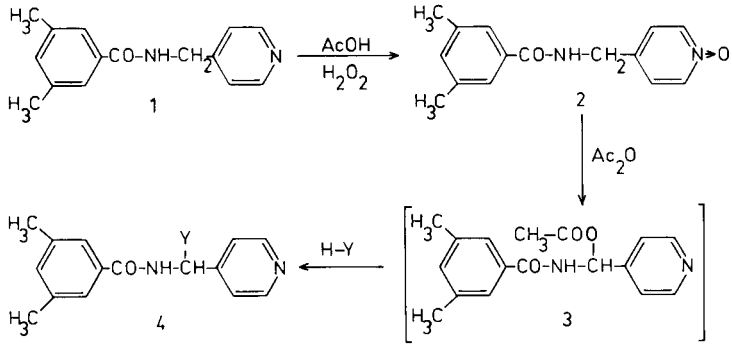
Due to the therapeutic interest [1] of Picobenzide **1** we have published several papers with the object to increase its activity by the functionalitation of the methylene group [2-12]. The best method to carry out this matter consists in the reaction of the *N*-oxide **2** with active methylene compounds in the presence of the acetic anhydride (Scheme 1). This paper presents a general discussion of the mechanism of this type of reaction.

To begin with, in previous papers [5-7] we have demonstrated that the α-acetoxyderivative **3** is the intermediate in the reaction of the *N*-oxide with acidic hydrogen compounds. The substitution of the acetoxy group mainly may occur by a classical S_N mechanism or by an elimination-addition reaction *via* the acylimine **5** (Scheme 2).

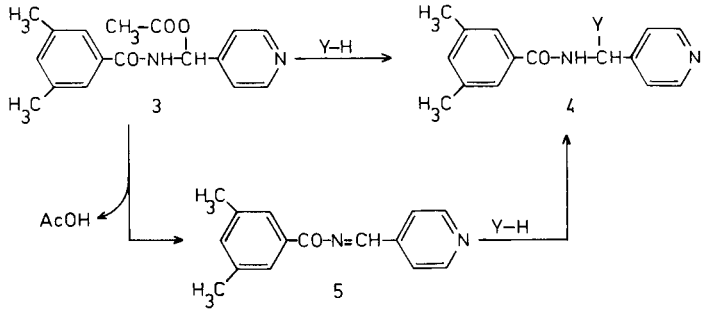
Considering the elimination-addition mechanism we have tried to trap **5** by the addition of dienes. We have not detected the corresponding cycloaddition compounds in any of these experiments.

As an indirect procedure and in order to confirm the above results and that the reaction does not take place *via* **5**, we have synthesized the α-acetoxy derivative **8** (Scheme 3), which could not give the acylimine intermediate since the amide moiety nitrogen has been substituted.

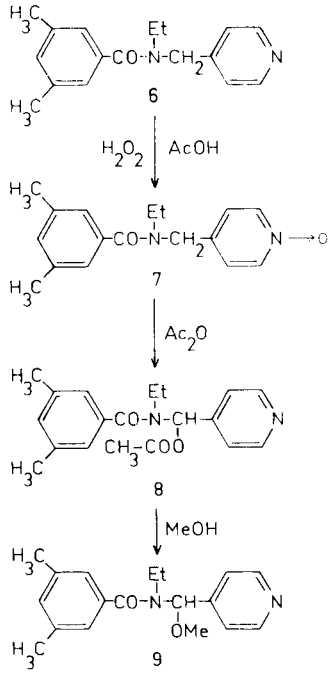
Scheme 1



Scheme 2



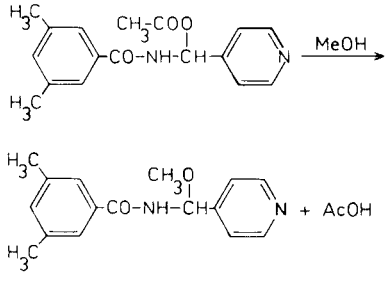
Scheme 3



N-Ethyl-*N*-(4-pyridilmethyl)-3,5-dimethylbenzamide **6** was obtained by the direct reaction of 3,5-dimethylbenzoyl chloride with *N*-ethyl-*N*-(4-pyridylmethyl)amine. The oxidation of **6** with hydrogen peroxide in acetic acid provided the *N*-oxide **7**. Treatment of **7** with acetic anhydride at 100° [3] gave *N*-ethyl-*N*-[(α-acetoxy)-4-pyridylmethyl]-3,5-dimethylbenzamide **8**. Reaction of **8** with methanol afforded the corresponding substitution compound, *N*-ethyl-*N*-[(α-methoxy)-4-pyridylmethyl]-3,5-dimethylbenzamide **9**. This result shows that the reaction that is our object of study presumably occurs by a simple S_N displacement process.

Proton nmr was the best method to study the kinetic of alcoholysis of **3**. Infrared and ultraviolet spectroscopy were unsuitable since no significant changes were observed during the course of the reaction. Loss of the acetoxy signal and appearance of signals due to products were clearly visible in the nmr spectrum and was ideal for our study.

Scheme 4



By ^{1}H nmr, loss of the acetoxy protons at 2.1 ppm, appearance of a singlet at 3.4 ppm due to the methoxy group and appearance of a methyl signal at 1.9 ppm for acetic acid were clearly discernable during the methanolysis of **3**.

This transformation can be carried out in a range of temperatures between 25° and 64°. Our study was carried out in methanol-d_4 at room temperature using the signal at 2.1 ppm and as a reference the signal at 2.3 ppm which corresponds to the methyl groups attached to the aromatic ring.

Figure 1 shows a plot of the reaction of **3** with methanol-d_4 as a function of time based on signal at 2.1 ppm. Under

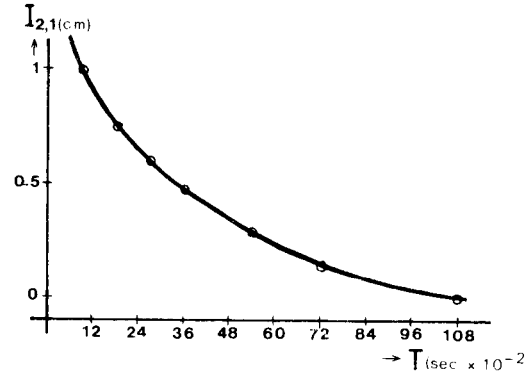


Figure 1

pseudo-first-order conditions, good straight line (correlation coefficient 0.9990) was obtained to 85% completion. From this plot, value of $k_{obs} = 1.1 \times 10^{-4}$ s^{-1} was calculated.

Although on the basis that in a solvolysis, the kinetics alone, does not distinguish the S_N2 type of mechanism from the S_N1 type, the fact that in the reaction of **8** with ethanol does not give the substitution compounds (probably due to steric restrictions in the transition state), seems to suggest that the substitution of the acetoxy group occurs by a S_N2 mechanism.

EXPERIMENTAL

Melting points were obtained in open capillary on a Büchi 510 and are uncorrected. The ir spectra were determined on a Perkin-Elmer 781 spectrophotometer (potassium bromide disc). The ^{1}H and ^{13}C nmr spectra were recorded on a Varian T60A (60 MHz) and Varian FT-80A spectrometers, respectively. The elemental analyses were performed by "Centro Nacional de Química Orgánica", Madrid.

N-[(α-Acetoxy)-4-pyridylmethyl]-3,5-dimethylbenzamide (**3**) was obtained according to the literature method [3].

N-Ethyl-*N*-(4-pyridylmethyl)-3,5-dimethylbenzamide (**6**).

To a solution of 3,5-dimethylbenzoyl chloride (8.9 g, 0.05 mole) in chloroform (50 ml) was added *N*-ethyl-*N*-(4-pyridylmethyl)amine (6.8 g, 0.05 mole) in 15 ml of chloroform. The mixture was refluxed for 3 hours. The solvent was evaporated under reduced pressure and the residue was treated with 10% hydrochloric acid and ether. The aqueous phase was basified, extracted with chloroform and dried over magnesium sulfate.

The solvent was evaporated under reduced pressure to give **6** in 55% yield, bp 166-170° (0.03 mm Hg); ir (potassium bromide): ν 1640 (C=O), 1600, 1475 (Ar) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.9 (t, 3H, CH_3-ethyl, J = 7 Hz), 2.1 (s, 6H, $2CH_3$-Ar), 3.3 (q, 2H, CH_2-ethyl, J = 7 Hz), 4.4 (s, 2H, CH_2-pyridine), 6.8 (s, 3H, H_2, H_4 and H_6-phenyl), 6.9 (d, 2H, H_3 and H_5-pyridine, J = 6 Hz), 8.3 (d, 2H, H_2 and H_6-pyridine, J = 6 Hz) ppm.

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 75.81; H, 7.44; N, 10.74.

N-Ethyl-*N*-(4-pyridylmethyl)-3,5-dimethylbenzamide *N*-Oxide (**7**).

To a solution of **6** (16.5 g, 0.06 mole) in glacial acetic acid (250 ml) was added hydrogen peroxide (30 ml, 30% w/v). The solution was heated at 100° and the completion of the reaction was determined by tlc. The solvent was evaporated under reduced pressure and 250 ml of water was added. The solvent was evaporated again and the residue was alkalinized with 10% sodium hydroxide, extracted with chloroform and dried over anhydrous magnesium sulphate and evaporated. The yield was 10.4 g (63%), mp 102-104° (benzene); ir (potassium bromide): ν 1630 (C=O), 1600, 1475 (Ar), 1220 (N→O) cm^{-1}; ^1H nmr (deuteriochloroform): 1.0 (t, 3H, CH_3-ethyl, J = 7 Hz), 2.2 (s, 6H, $2CH_3$-Ar), 3.1 (q, 2H, CH_2-ethyl, J = 7 Hz), 4.4 (s, 2H, CH_2-pyridine), 6.8 (s, 3H, H_2, H_4 and H_6-phenyl), 7.0 (d, 2H, H_3 and H_5-pyridine, J = 6 Hz), 7.9 (d, 2H, H_2 and H_6-pyridine, J = 6 Hz) ppm.

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.08; N, 9.85. Found: C, 71.45; H, 6.73; N, 9.81.

N-Ethyl-*N*[(α-acetoxy)-4-pyridylmethyl]-3,5-dimethylbenzamide (**8**).

A solution of **7** (2.84 g, 0.01 mole) in 20 ml of acetic anhydride was heated at 70-75° for 1.5 hour. The solvent was evaporated under reduced pressure providing an oil. Column chromatography (benzene/ethyl acetate 8:2) afforded **8** in 60% yield, mp 65-66° (hexane); ir (potassium bromide): ν 1755 (C=O, ester), 1655 (C=O, amide), 1600, 1450 (Ar) cm^{-1}; ^1H nmr (deuteriochloroform): 1.0 (t, 3H, CH_3-ethyl, J = 7 Hz), 2.1 (s, 3H, CH_3CO), 2.2 (s, 6H, $2CH_3$-Ar), 2.8-3.6 (m, 2H, CH_2-ethyl), 6.9 (m, 2H, CH, H_4-phenyl), 7.1-7.3 (m, 4H, H_2 and H_6-phenyl, H_3 and H_5-pyridine), 8.4 (d, 2H, H_2 and H_6-pyridine, J = 5 Hz) ppm.

Anal. Calcd. for $C_{19}H_{22}N_2O_3$: C, 69.91; H, 6.79; N, 8.58. Found: C, 69.64; H, 7.01; N, 8.54.

N-Ethyl-*N*[(α-methoxy)-4-pyridylmethyl]-3,4-dimethylbenzamide (**9**).

A solution of **8** (4.7 g, 0.14 mole) in 30 ml of methanol was refluxed for 9 hours. The solvent was evaporated under reduced pressure giving **9** in 50% yield, mp 79-82° (hexane); ir (potassium bromide): ν 1650 (C=O), 1600, 1450 (Ar) cm^{-1}; ^1H nmr (deuteriochloroform): 0.9 (t, 3H, CH_3-ethyl), 2.2 (s, 6H, $2CH_3$-Ar), 2.9-3.3 (m, 2H, CH_2-ethyl), 3.3 (s, 3H, OCH_3), 6.8-6.9 (m, 4H, H_2, H_4 and H_6-phenyl, CH), 7.2 (d, 2H, H_3 and H_5-pyridine, J = 5 Hz), 8.3 (d, 2H, H_2 and H_6-pyridine, J = 5 Hz) ppm; ^{13}C nmr (deuteriochloroform): 13.22 (CH_3-ethyl), 20.10 ($2CH_3$-Ar), 36.01 (CH_2-ethyl), 54.55 (OCH_3), 86.94 (CH), 120.26 (C_3 and C_5-pyridine), 123.29 (C_2 and C_6-phenyl), 130.19 (C_1-phenyl), 135.32 (C_4-phenyl), 137.19 (C_3 and C_5-phenyl), 146.07 (C_4-pyridine), 148.94 (C_2 and C_6-pyridine), 171.90 (C=O).

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.31; H, 7.23; N, 9.28.

NMR Study of the Reaction Kinetics: d_4-Methanolysis.

In a typical experiment, 0.075 g (0.25 mmole) of **3** was placed in a 5-mm nmr tube. At time = 0s, 0.5 ml of methanol-d_4 was added *via* syringe, and the tube was shaken to dissolve **3**. The signals at 1.9, 2.1 and 2.3 ppm were integrated every 15 minutes during the first hour, every 30 minutes during the second hour and finally every hour.

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