Synthesis and Reactivity of *N*-[(α-Acetoxy)-4-pyridylmethyl]-3,5-dimethylbenzamide

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The synthesis of *N*-[(α-acetoxy)-4-pyridylmethyl]-3,5-dimethylbenzamide (**4**) and its reactivity are described. Since the acetoxy is a good leaving group, **4** gives S_N processes easily.

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In our previous paper (1), we reported that the reaction of *N*-(4-pyridylmethyl)-3,5-dimethylbenzamide *N*-oxide (**1**) (2) with acetic anhydride at 140° yielded dimerization compounds (**2** and **3**). However, the treatment of **1** with acetic anhydride at 100° gave *N*-[(α-acetoxy)-4-pyridylmethyl]-3,5-dimethylbenzamide (**4**). The infrared (ir) spectrum of **4** showed absorption bands for amide and ester groups. The nmr spectrum showed signals at δ 2.10 (s, 3H, $COCH_3$), 2.25 (s, 6H, $2CH_3$-aromatic), 6.95 (s, 1H, CH), 7.00-7.30 (m, 5H, 3H-phenyl, 2H-β-pyridine), 7.40 (m, 1H, NH), 8.40 (d, 2H, 2H-α-pyridine in the AA'BB' pattern). The mass spectrum gave fragments at m/e 298 (M^+), 239 (M^+-$OCOCH_3$), 133 ($C_9H_9O^+$), 105 ($C_8H_9^+$).

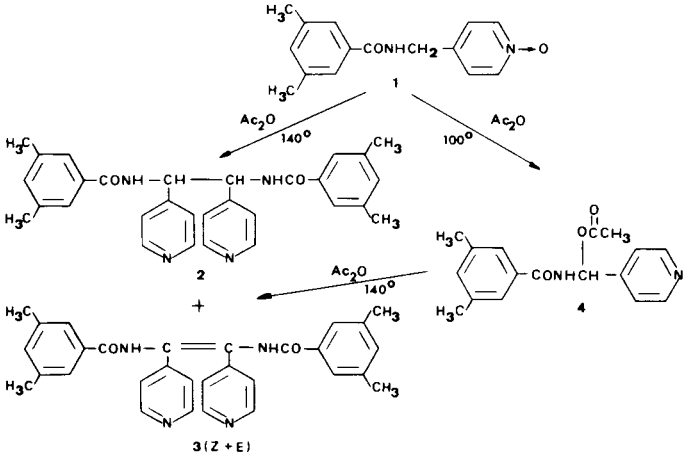

Figure 1

The formation of **4** must follow the mechanism generally accepted in the literature (3) for the reaction of 4-substituted pyridine *N*-oxides with acetic anhydride. The initial step involves acetylation of the *N*-oxide function to form **5** which, by migration of a proton, would form the anhydrobase (**6**). The anhydrobase would give **4** by an intramolecular rearrangement *via* the ion pair **7**.

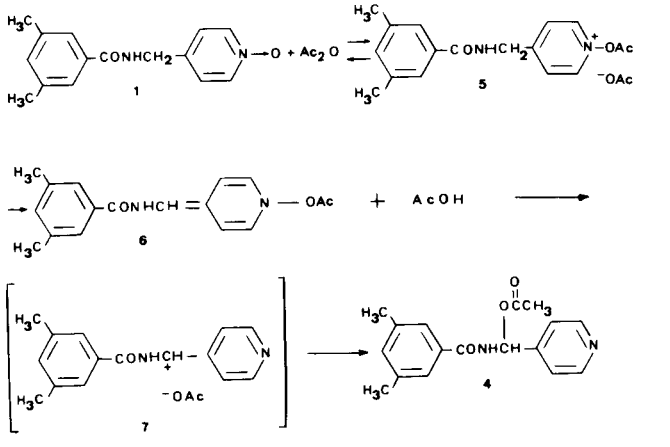

Figure 2

In the thin-layer chromatography (tlc) of **4** with benzene:ethanol 9:1 as the eluent, three compounds were observed (R*f* = 0.28, 0.18 and 0.14, respectively). To isolate and identify these products, column chromatography over silica gel with benzene:ethanol 9:1 as the eluent was used yielding three substances of which only one proved to be the compound of R*f* 0.28.

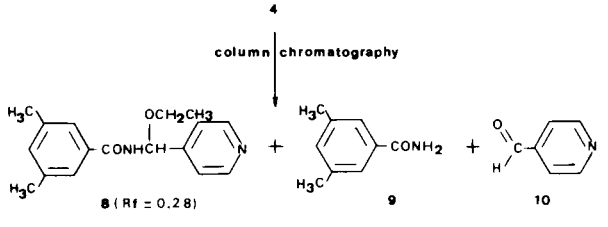

Figure 3

N-[(α-Ethoxy)-4-pyridylmethyl]-3,5-dimethylbenzamide (**8**) (R*f* = 0.28) was thus obtained. The infrared (ir) spectrum showed absorption for amide and ether groups. The nmr spectrum showed peaks at δ 1.30 (t, 3H, CH_3-ether), 2.30 (s, 6H, $2CH_3$-ether), 2.30 (s, 6H, $2CH_3$-aromatic), 3.80 (q, 2H, CH_2), 6.60 (s, 1H, CH), 7.20 (s, 1H, H *para*-phenyl), 7.45 (s, 2H, 2H *ortho*-phenyl), 7.55 (d, 2H, 2H β-pyridine), 8.60 (d, 2H, 2H α-pyridine). The mass spectrum gave fragments at m/e 284 (M^+), 255 (M^+-C_2H_5), 240 ($M^+C_2H_4O$), 133 ($C_9H_9O^+$), 105 ($C_8H_9^+$).

On further elution of the column, a mixture of **8** and iso-

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nicotinic aldehyde (**10**) (tlc with standard) was identified. On the last elution, 3,5-dimethylbenzamide (**9**) (R*f* = 0.21) was obtained.

The hydrolysis of **4** with dimethylformamide-water yielded *N*-[(α-hydroxy)-4-pyridylmethyl]-3,5-dimethylbenzamide (**11**) (R*f* = 0.14). The ir spectrum of **11** showed absorption bands for hydroxyl and amide groups. The nmr spectrum showed peaks at δ 2.40 (s, 6H, $2CH_3$), 7.05 (s, 1H, CH), 7.30 (s, 1H, H *para*-phenyl), 7.40 (s, 2H, 2H *ortho*-phenyl), 8.45 (d, 2H, 2H β-pyridine), 8.90 (d, 2H, 2H α-pyridine). The mass spectrum of **11** gave the fragments at m/e 256 (M^+), 149 ($C_9H_{11}NO^+$), 133 ($C_9H_9O^+$), 107 ($C_6H_5NO^+$).

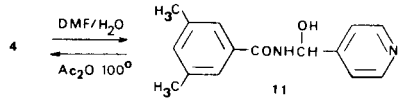

Figure 4

To confirm the structural relation between **4** and **11**, acetylation of **11** with acetic anhydride was carried out and **4** was obtained in quantitative yield. The hydrolysis of **11** gave **9** (R*f* = 0.21) and **10**, which was identified by its picrate and phenylhydrazone.

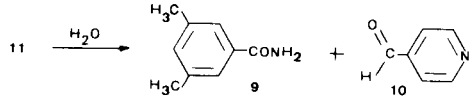

Figure 5

These experimental results suggest that from **4** (R*f* = 0.18), compounds **8** (R*f* = 0.28) and **11** (R*f* = 0.14) were formed in the tlc by alcoholysis and hydrolysis reactions of the acetoxy group. However, a different result is observed when **4** is chromatographed in a column over silica gel

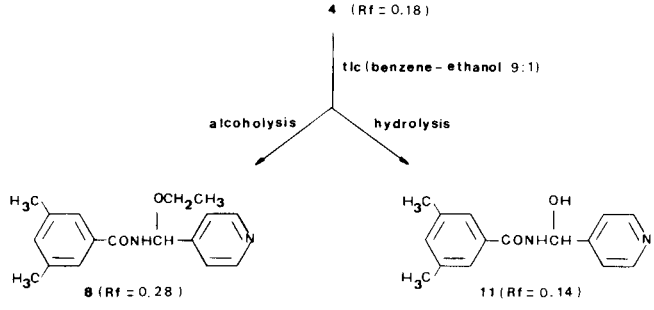

Figure 6

using the same eluent as was used with tlc. Compound **11** could not be obtained, but its hydrolysis products (**9** and **10**) could be prepared.

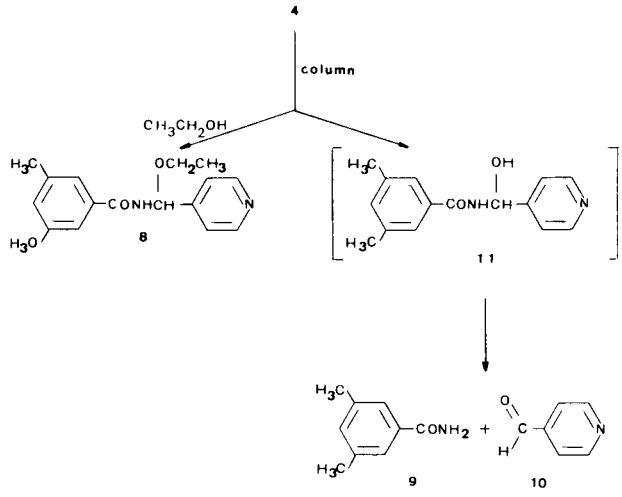

Figure 7

In order to confirm the extension of the alcoholysis of **4**, this compound was treated with ethanol and isopropyl alcohol yielding **8** and **12**, respectively.

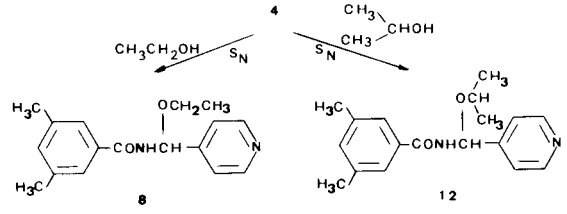

Figure 8

When **4** was treated with acetic anhydride under reflux for 1.5 hours, **2** and **3** were obtained (40% and 20% yield, respectively). This result confirms that **4** is an intermediate in the reaction of *N*-(4-pyridylmethyl)-3,5-dimethylbenzamide *N*-oxide with acetic anhydride as was proposed in our previous paper (1).

EXPERIMENTAL

The melting points were obtained on a Büchi apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer (potassium bromide disc). Nmr spectra were determined with a Varian T-60A 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 analysis were performed by Centro Nacional de Química Orgánica, Madrid. Column chromatography was performed on Merck Kieselgel 60, 0.063-0.200 mm. The thin layer chromatography (tlc) system used silica gel (60, F 254, Merck) with benzene:ethanol 9:1 as eluent.

N-[(α-Acetoxy)-4-pyridylmethyl]-3,5-dimethylbenzamide (**4**).

A solution of **1** (5 g, 0.02 mole) in 50 ml of acetic anhydride was refluxed at 100° for 20 minutes. The solution was cooled to room temperature, the precipitate (**4**) was purified by crystallization in ether/*n*-hexane (3 g, 52%), mp 133-135°; ir: ν 3280 (NH), 1730 cm^{-1} (C=O, ester); nmr (deuteriochloroform): 60 MHz δ 2.10 (s, 3H, $COCH_3$), 2.25 (s, 6H, $2CH_3$), 6.95 (s, 1H, CH), 7.00-7.30 (m, 5H, 3H-phenyl, 2H β-pyridine), 7.40 (m, 1H, NH), 8.40 ppm (d, 2H, 2H α-pyridine); ms: m/e 298 (M^+), 239 (16), 133 (100), 105 (36), 79 (10), 77 (10).

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.43; H, 6.08; N, 9.39. Found: C, 68.34; H, 6.04; N, 9.10.

Chromatography of **4**.

Compound **4** (4 g) was chromatographed on a silica gel column with benzene:ethanol 9:1 as eluent, affording the following products.

Compound **8** (R*f* = 0.28, benzene:ethanol 9:1) was obtained (1 g, 26%), mp 99-100° (cyclohexane); ir: ν 3260 (NH), 1650 (C=O), 1600, 1520 (aromatic), 1100 cm^{-1} (C-O-C); nmr (deuteriochloroform): 90 MHz 1.30 (t, 3H, CH_3-ether), 2.30 (s, 6H, $2CH_3$-ar), 3.80 (q, 2H, CH_2), 6.60 (s, 1H, CH), 7.20 (s, 1H, H *para*-phenyl), 7.45 (s, 2H, 2H *ortho*-phenyl), 7.55 (d, 2H, 2H β-pyridine), 8.60 ppm (d, 2H, 2H α-pyridine); ms: m/e 284 (M^+), 255 (19), 240 (23), 133 (100), 108 (10) 105 (18).

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.97; H, 7.04; N, 9.79. Found: C, 72.15; H, 7.15; N, 9.61.

On further elution of the column, a mixture (2 g) of **8** and **10** (tlc with standard) was obtained. On further elution of the column, **9** was obtained (R*f* 0.21, benzene:ethanol 9:1) (1 g, 50%), mp 133° (cyclohexane) (4).

N-[(α-Hydroxy)-4-pyridylmethyl]-3,5-dimethylbenzamide (**11**).

To a solution of **4** (1.5 g, 5 mmoles) in dimethylformamide, was added water at room temperature, the white needles which formed were filtered. The yield was 1.28 g (99%) of **11**, mp 146-148°; ir: ν 3240 (NH), 3200-2700 (OH), 1640 (C=O), 1600, 1525 (aromatic), 1330, 1050 cm^{-1} (C-O); nmr (trifluoracetic acid): 90 MHz δ 2.40 (s, 6H, $2CH_3$), 7.05 (s, 1H, CH), 7.30 (s, 1H, H *para*-phenyl), 7.40 (s, 2H, 2H *ortho*-phenyl), 8.45 (d, 2H, 2H β-pyridine), 8.90 ppm (d, 2H, 2H α-pyridine); ms: m/e 256 (M^+), 149 (64), 133 (100), 107 (75), 105 (60), 77 (40).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.20; H, 6.28; N, 10.70.

Hydrolysis of **11**.

A solution of **11** in water was heated under reflux for 2 hours. The solution was cooled to room temperature and a white precipitate formed; the crystals were filtered. Recrystallization from cyclohexane afforded 0.7 g of **9**.

To a 10 ml portion of the above aqueous solution was added 2 ml of phenylhydrazine and the resulting precipitate was collected. Recrystallization from ethanol gave the phenylhydrazone of isonicotinic aldehyde (**10**), mp 178-179° (4).

Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.30. Found: C, 72.78; H, 5.61; N, 21.04.

To a 10 ml portion of the above aqueous solutions was added 5 ml of picric acid. The mixture was cooled and the collected precipitate was recrystallized from water, giving the picrate of isonicotinic aldehyde (**10**), mp 168-169° (4).

Anal. Calcd. for $C_{12}H_8N_4O_8$: C, 42.86; H, 2.40; N, 16.66. Found: C, 43.11; H, 2.39; N, 16.77.

Reaction of **11** with Acetic Anhydride.

A solution of **11** (2 g, 8 mmoles) in 20 ml of acetic anhydride was refluxed at 100° for 20 minutes. The solution was cooled to room temperature, the precipitate (**4**) was purified by crystallization in ether/*n*-hexane (2 g, 87%), mp 133-135°.

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

A solution of **4** (4 g, 0.013 mole) in 40 ml of absolute ethanol was refluxed for 5 hours, the solvent was evaporated *in vacuo* giving a solid (**8**), mp 99-100° (cyclohexane). The yield was 3 g (79%).

N-[(α-Isopropoxy)-4-pyridylmethyl]-3,5-dimethylbenzamide (**12**).

A solution of **4** (5 g, 0.017 mole) in 50 ml of isopropanol was refluxed for 5 hours, the solvent was evaporated *in vacuo* giving an oil, which was chromatographed over silica gel using benzene-isopropanol 9:1 as the eluent to yield 2.5 g (50%) of **12**, mp 84-85° (cyclohexane); ir: ν 3240 (NH), 1640 (C=O), 1600, 1520 (aromatic), 1090 cm^{-1} (C-O-C); nmr (deuteriochloroform): ppm 1.20 (m, 6H, O-C-$(CH_3)_2$), 2.30 (s, 6H, 2 CH_3-aromatic), 3.90 (m, 1H, -CH-$(Me)_2$), 6.50 (s, 1H, CH-Py), 7.00 (s, 1H, H *para-phenyl), 7.10-7.30 (m, 4H, 2H ortho*-phenyl, 2H β-pyridine), 8.30 (d, 2H, 2H α-pyridine).

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.45; H, 7.43; N, 9.38. Found: C, 72.70; H, 7.25; N, 9.54.

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REFERENCES AND NOTES

(1) M. F. Braña and M. L. L. Rodriguez, *Tetrahedron Letters*, **21** 3923 (1980).

(2) P. D. G. Jalón, E. Gonzales, A. Idoipe, M. R. M. Larrañaga and M. F. Braña, *Arzneim.-Forsch.*, **29**, 1704 (1979).

(3) S. Oae and K. Ogino, *Heterocycles*, **6**, 583 (1977).

(4) J. R. A. Pollock and R. Stevens, "Dictionary of Organic Compounds", Eyred Spott Swoode, London, 1965.