Reaction of *N*-[(α-Acetoxy)-4-pyridylmethyl]-3,5-dimethylbenzamide with Alkyl Isocyanates

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Reaction of *N*-[(α-acetoxy)-4-pyridylmethyl]-3,5-dimethylbenzamide **3** with methyl and ethyl isocyanates afforded 1,3-dimethyl and 1,3-diethyl-4-(3,5-dimethylbenzoylamino)-2-oxoimidazolidine-5-spiro-4'-[1',4'-dihydro-1'-acetyl]pyridine **6a,b**, respectively. However, the reaction of **3** with isopropyl, *t*-butyl and phenyl isocyanates gave the corresponding *N,N'*-diurea and the dimerization compound **8**. The structure of **6a** was confirmed by crystal X-ray diffraction analysis.

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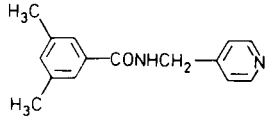
Picobenzide (**1**) [1] is a potent neuroleptic agent. In attempts to obtain compounds possessing superior pharmacological properties, we have synthesized and tested new derivatives of **1** by various modifications at the benzene [2,3] and pyridine rings [4] as well as at the methylene group [5-16].



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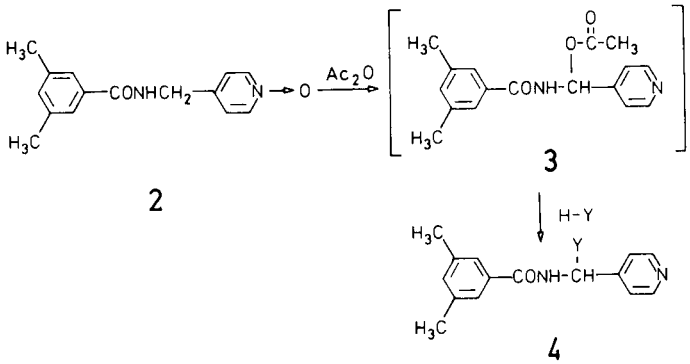
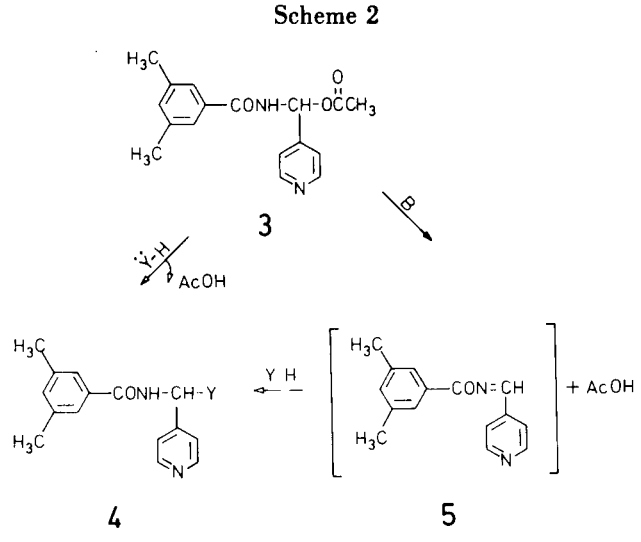
The best method to functionalize the methylene group consists on the reaction of the *N*-oxide **2** with compounds possessing active hydrogens in the presence of acetic anhydride or, alternatively, making react the intermediate acetoxy derivative **3** directly with the acidic compound (Scheme 1).

Scheme 1



Regarding the last procedure, the simplest explanation for the substitution of the acetoxy group would be by a classical S_N mechanism or by an elimination-addition reaction *via* the acylimine **5** (Scheme 2).

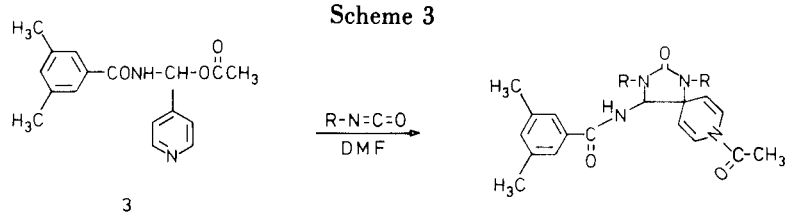
Scheme 2



Considering the elimination-addition mechanism, we have tried to trap the acylimine intermediate **5** with 2,3-dimethylbutadiene through a Diels-Alder reaction [17]; however, all attempts failed and we have not detected the corresponding cycloaddition product. Also, we tried the reaction with methyl isocyanate through a [2+2] cycloaddition reaction [18] but, instead of the cycloaddition product, the treatment of **3** at 100° with methyl isocyanate in DMF for 3 hours gave 1,3-dimethyl-4-(3,5-dimethylbenzoylamino)-2-oxoimidazolidine-5-spiro-4'-[1',4'-dihydro-1'-acetyl)pyridine (**6a**) in 44% yield. The structure of **6a** was established on the basis of elemental analysis, spectral data (see experimental section) and X-ray studies (Figure 1).

An additional fact that proved the structure of **6a** was obtained by catalytic hydrogenation. The reaction of **6a** with hydrogen over Pd/C gave *N*-[(α-methylamino)-4-pyridylmethyl]-3,5-dimethylbenzamide (**7**) in 71% yield.

Scheme 3



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6a R=CH$_3$
6b R=CH$_2$CH$_3$

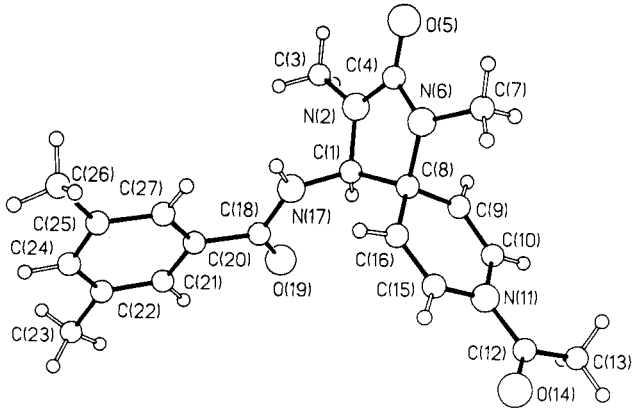
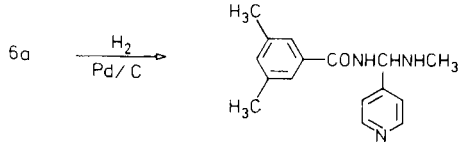


Figure 1

Scheme 4



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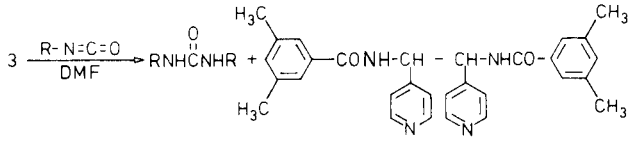
In order to know the extension of this reaction we have carried out the reaction of **3** with ethyl, isopropyl, *t*-butyl and phenyl isocyanates. The treatment of **3** with ethyl isocyanate gave rise to the formation of 1,3-diethyl-4-(3,5-dimethylbenzoylamino)-2-oxoimidazolidine-5-spiro-4'-[1',4'-dihydro-1'-acetyl]pyridine (**6b**). However, by carrying out the reaction of **3** with isopropyl, *t*-butyl and phenyl isocyanates, only the corresponding *N,N'*-diurea and the dimerization compound **8** [5] were obtained, perhaps due to steric hindrance.

Scheme 5



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EXPERIMENTAL

Melting points were measured in open capillary on a Büchi 510 apparatus and are uncorrected. The ir spectra were determined on a Perkin-Elmer 781 spectrophotometer (potassium bromide disc). The ^{1}H nmr spectra were recorded on a Varian T-60A (60 MHz), FT-80A (80 MHz) and GEQE 300w (300 MHz) spectrometers. The ^{13}C nmr spectra were obtained on a Varian FT-80A spectrometer. Elemental analysis were performed by "Centro Nacional de Química Orgánica", Madrid.

Reaction of **3** with Methyl and Ethyl Isocyanates.

A solution of 3 g (0.01 mole) of **3** [6] and 0.01 mole of alkyl isocyanate in 5 ml of DMF was heated at 100° for 3 hours. The solvent was removed under reduced pressure and the resulting oil was chromatographed on a silica gel column with toluene/ethanol (8:2) affording the compounds **6a** or **6b** in 44 and 46% yield respectively.

1,3-Dimethyl-4-(3,5-dimethylbenzoylamino)-2-oxoimidazolidine-5-spiro-4'-[1',4'-dihydro-1'-acetyl]pyridine (**6a**).

This compound was obtained as white crystals (benzene-cyclohexane), mp 225-227°; ir: ν 3260, 1695, 1660 (broad), 1620, 1600 cm^{-1}; ^{1}H nmr (deuteriochloroform): 300 MHz, δ 2.3 (s, 3H, CH_3CO), 2.4 (s, 6H, 2 CH_3-Ph), 2.5 (s, 3H, CH_3N), 2.8 (s, 3H, CH_3N), 4.9-5.1 (m, 2H, H_3 and H_5-dihydropyridine), 5.5 (d, 1H, H_4-imidazolidine, J = 8 Hz), 7.0 (t, 1H, NH), 7.2 (s, 1H, H_4-phenyl), 7.4 (s, 2H, H_2 and H_6-phenyl), 7.6 (m, 2H, H_2 and H_6-dihydropyridine); ^{13}C nmr (deuteriochloroform): δ 21.27 (q, 2CH_3-Ph, CH_3-acetyl), 28.42 (q, CH_3N), 29.19 (q, CH_3N), 59.61 (s, C-spiro), 72.02 (d, CH-imidazolidine), 102.90 (d, C_5-dihydropyridine), 106.48 (d, C_3-dihydropyridine), 125.21 (d, C_2 and C_6-phenyl), 128.35 (d, C_2 and C_6-dihydropyridine), 133.32 (s, C_1-phenyl), 133.68 (d, C_4-phenyl), 138.34 (s, C_3 and C_5-phenyl), 158.50 (s, -N-CO-N-), 166.63 (s), 168.05 (s) (CO-amide of CO-acetyl); ms: (m/e, relative intensity) 368 (M^+), 235 (M^+-C_9H_9O, 2), 219 (M^+-$C_9H_{11}NO$, 97), 176 (219-$COCH_3$, 31), 150 ($C_9H_9O^+$, 46), 108 (100).

Anal. Calcd. for $C_{20}H_{24}N_4O_3 \cdot \frac{1}{2}\ C_6H_6$: C, 67.79; H, 6.88; N, 13.75. Found: C, 67.30; H, 6.70; N, 13.80.

1,3-Diethyl-4-(3,5-dimethylbenzoylamino)-2-oxoimidazolidine-5-spiro-4'-[1',4'-dihydro-1'-acetyl]pyridine (**6b**).

This compound was obtained as white crystals (benzene-cyclohexane), mp 167-169°; ir: ν 3260, 1690, 1650, 1640, 1620, 1600 cm^{-1}; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 0.9-1.2 (m, 6H, 2 CH_3-ethyl), 2.1 (s, 3H, CH_3-acetyl), 2.2 (s, 6H, 2 CH_3-Ph), 2.7-3.2 (m, 4H, 2 CH_2-ethyl), 4.9-5.0 (m, 2H, H_3 and H_5-dihydropyridine), 5.4 (d, 1H, H_4-imidazolidine, J = 10 Hz), 6.8-7.4 (m, 6H, 3H-phenyl, NH, H_2 and H_6-dihydropyridine); ^{13}C nmr (deuteriochloroform): δ 13.01 (CH_3-ethyl), 15.56 (CH_3-ethyl), 21.26 (2 CH_3-Ph, CH_3-acetyl), 35.42 (CH_2-ethyl), 35.83 (CH_2-ethyl), 59.92 (C-spiro), 69.70 (CH-imidazolidine), 104.05 (C_5-dihydropyridine), 108.02 (C_3-dihydropyridine), 124.96 (C_2 and C_6-phenyl, C_2 and C_6-dihydropyridine), 133.40 (C_1-phenyl), 133.76 (C_4-phenyl), 138.50 (C_3 and C_5-phenyl), 157.85 (N-CO-N), 166.62, 167.79 (CO-amide or CO-acetyl); ms: (m/e, relative intensity) 396 (M^+), 263 (M^+-C_9H_9O, 2), 247 (M^+-$C_9H_{11}NO$, 94), 204 (247-CO-CH_3, 54), 149 ($C_9H_{11}NO^+$, 100), 133 ($C_9H_9O^+$, 70).

Anal. Calcd. for $C_{22}H_{28}N_4O_3 \cdot \frac{1}{2}\ C_6H_6$: C, 68.94; H, 7.17; N, 12.86. Found: C, 68.60; H, 7.21; N, 12.56.

Reaction of **3** with Isopropyl, *t*-Butyl and Phenyl Isocyanates.

A solution of 3 g (0.01 mole) of **3** [6] and 0.01 mole of alkyl isocyanate in 5 ml of DMF was heated at 100° for 3 hours. After cooling to room temperature, the formed precipitate was filtered off, giving *N,N'*-di(3,5-dimethylbenzoyl)-1,2-di(4-pyridyl)ethylenediamine (**8**) [5]. The solvent was removed under reduced pressure and the resulting oil was treated with hot ethanol to give the corresponding *N,N'*-diurea.

N-[(α-Methylamino)-4-pyridylmethyl]-3,5-dimethylbenzamide (**7**).

A solution of 2.5 g (6.5 mmoles) of **6a** in 50 ml of ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of Pd/C 10%. When the hydrogen absorption was finished, 50 ml of DMF was added and the catalyst was filtered off. The solution was evaporated under reduced pressure, and the residual oil was crystallized from ethanol to yield 0.7 g (29%) of **6a**. The mother liquors gave 1.2 g (72 %) of **7**, mp 210-212° (toluene); ir: ν 3340-3300, 1640, 1600, 1500 cm^{-1}; ^1H nmr (deuteriochloroform): 80 MHz, δ 2.2 (s, 6H, 2 CH_3-Ph), 2.5 (s, 3H, CH_3N), 6.1 (d, 1H, CH, J = 10 Hz), 7.0 (s, 1H, NH-amine), 7.2-7.4 (m, 5H, H_3 and H_5-pyridine, H_2, H_4 and H_6-phenyl), 8.1 (d, 1H, NH-amide, J = 10 Hz), 8.4 (d, 2H, H_2 and H_6-pyridine, J = 3 Hz); ^{13}C nmr (deuteriochloroform): δ 20.70 (2 CH_3-Ph), 33.50 (CH_3-N), 66.29 (CH), 121.91 (C_3 and C_5-pyridine), 124.88 (C_2 and C_6-phenyl), 132.69 (C_1-phenyl), 133.56 (C_4-phenyl), 138.06 (C_3 and C_5-phenyl), 146.31 (C_4-pyridine), 149.76 (C_2 and C_6-pyridine), 168.44 (CO); ms (m/e, relative intensity) 254 (M^+-CH_3, 6), 238 (M^+-CH_3-NH_2, 5), 133 ($C_9H_9O^+$, 100), 105 ($C_8H_9^+$, 30).

Anal. Calcd. for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60. Found: C, 71.58; H, 7.35; N, 15.62.

Crystal X-ray Diffraction Analysis of **6a**.

Needle-shaped crystals were grown from benzene/dichloromethane; $C_{20}H_{24}O_3N_4 \cdot ½\ C_6H_6$, M = 407.5, crystal size = 0.30 x 0.11 x 0.06 mm, monoclinic, space group C2/c (I.T. No 15), a = 27.849(4), b = 7.440(1), c = 26.117(3) Å, Z = 8, Dc = 1.237 gcm^{-1}, F(000) = 1736, λ (Cu Kα) = 5.94 cm^{-1}, no correction for absorption, Nicolet P2$_1$ 4-circle diffractometer, 2θ: ω step-scan mode, 3060 reflections measured ($2\theta_{max}$ = 115°) of which 2758 were unique and 1799 were considered observed ($Fo > 4\sigma_{Fo}$). The structure was solved by direct methods and refined by block-cascade least-squares (SHELXTL program package [19]) on a DG Eclipse S/200 computer. The crystals contained half a molecule of disordered benzene solvent in the asymmetric unit. The major position (70%) had a crystallographic two-fold passing through two of the carbon-carbon bonds, while the minor position (30%) had this axis passing through two of the carbon atoms; hence the two fractions of the benzene were staggered with respect to each other. All non-hydrogen atoms (except those of the minor benzene fraction) were refined with anisotropic thermal parameters and fixed at geometrically calculated positions, except for that on N(17) which was refined freely. No hydrogen atoms were placed on the minor benzene component. Final R-factors: $R = \Sigma \mid |Fo| - |Fc| \mid / \Sigma |Fo| = 0.059$, $Rw = \{\Sigma w \mid |Fo| - |Fc| \mid^2 / \Sigma w \mid Fo \mid^2\}^{½} = 0.074$, $w = (\sigma^2_{Fo} + 0.00142\ Fo)$. Maximum residual electron density = 0.16 e $Å^{-3}$.

Figure 1 shows the crystal structure for **6a**; torsional angles N(17)-C(18)-C(20)-C(27) = −7.8(6), N(17)-C(1)-C(8)-C(16) = 18.0(6), C(18)-N(17)-C(1)-N(2) = 131.3(4), C(15)-N(11)-C(12)-O(14) = 2.5(8)°.

Tables of atomic coordinates (including solvent and hydrogen atoms), thermal parameters, bond lengths and bond angles can be obtained as supplementary material or (with structure factor tables) from The Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1 EW, UK.

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