Reaction of 4-Acylaminomethylpyridine *N*-Oxides with Phenylbutazone in the Presence of Acetic Anhydride

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Reaction of 4-acylaminomethylpyridine *N*-oxides with phenylbutazone in the presence of acetic anhydride is described. In the pharmacological screening one compound shows an interesting anticonvulsant activity.

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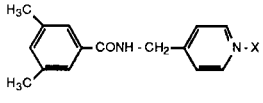
In a previous paper [1], we reported the synthesis and pharmacological activity of *N*-(4-pyridylmethyl)-3,5-dimethylbenzamide (Picobenzide) **1**. This compound, whose pharmacological spectrum is a partial analogue of neuroleptics of the phenothiazine type, exhibits further anti-inflammatory activity.

On the other hand, we have found that the reaction of picobenzide *N*-oxide **2** (the main metabolite of **1** [2]) with compounds which have acidic protons in the presence of acetic anhydride is a useful route to functionalize the methylene group. The reaction takes place even with active methylene compounds, to form, a C-C bond in different yields [3-7].



1, X = –

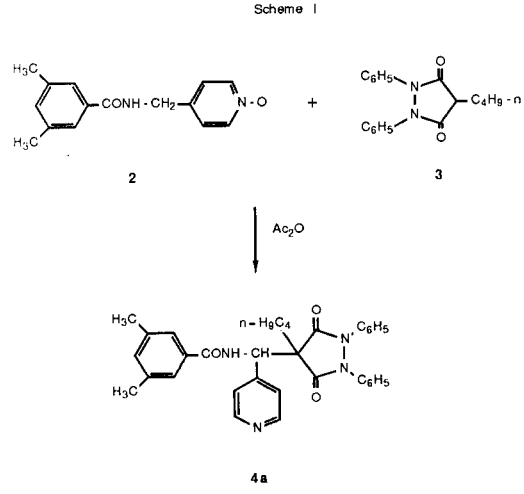
2, X = O

Figure 1

In the present paper, we report the reactivity of **2** with phenylbutazone **3** in the presence of acetic anhydride. We considered that this study could be interesting in order to know the behavior of **3** in this reaction, because **3** contains an activated hydrogen, (p*K*a = 4.5 [8]) and, on the other hand, the introduction of a phenylbutazone molecule in **1**, could increase its anti-inflammatory activity and even obtain a greater selectivity of action. Although it has been observed [9] that when the acidic proton of the phenylbutazone is replaced, there is no activity at all, there are some anti-inflammatory drugs which do not have this requirement like Pipebuzone [10] and Suxibuzone [11].

In the reaction of *N*-(4-pyridylmethyl)-3,5-dimethylbenzamide *N*-oxide **2** with phenylbutazone in the presence of acetic anhydride and dimethylformamide as solvent at 80° compound **4a** was obtained in good yield, mp 164-166°.

Scheme I

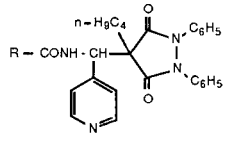


The structure of **4a** was established according to spectral data, together with quantitative elemental analysis. The infrared (ir) spectrum showed an absorption band for the amino group at 3400 cm^{-1}, two C=O stretching bands at 1740 and 1700 cm^{-1} corresponding to the carbonyl groups attached to a pyrazole ring and at 1670 cm^{-1} a band due to the C=O of the amide group. The nmr spectrum showed the following signals: at δ ppm 0.9 a deformed singlet corresponding to the methyl group of *n*-butyl, at 1.2-1.8 a broad multiplet owing to the 4H of two methylene groups, at 2.2-2.5 a multiplet corresponding to another methylene group, at 2.5 a singlet which can be attributed to the two methyl groups attached to a phenyl ring, at 5.8 a doublet corresponding to the CH, between 6.8 and 7.6, a multiplet due to the phenyl hydrogens and two H-β-pyridine, at 8.3 a doublet corresponding to the amino group, and 8.5 a doublet of two H-α-pyridine. The elemental analysis corresponds to the molecular formula $C_{34}H_{34}N_4O_3$.

In order to extend this reaction, other *N*-oxides were treated under the same conditions, to give the expected compounds (Table I).

Table I

4-Butyl-4-[(acylamino)(4-pyridyl)]methyl-1,2-diphenyl-3,5-pyrazolidinedione **4a-g**



4

Figure II

No.	R	mp °C	Solvent of Crystallization	Yield %	Formula
4a	3,5-$(CH_3)_2$-C_6H_3	164-166	methanol-water	75	$C_{34}H_{34}N_4O_3$
4b	4-CH_3-C_6H_4	183-185	methanol-water	61	$C_{33}H_{32}N_4O_3$
4c	2-CH_3-C_6H_4	138-140	cyclohexane	50	$C_{33}H_{32}N_4O_3$
4d	4-NO_2-C_6H_4	110-111	methanol-water	53	$C_{32}H_{29}N_5O_5$
4e	4-CH_3-O-C_6H_4	83-85	cyclohexane	62	$C_{33}H_{32}N_4O_4$
4f	2-Cl-C_6H_4	120-122	cyclohexane	55	$C_{32}H_{29}ClN_4O_3$
4g	CH_3	171-172	cyclohexane	66	$C_{27}H_{28}N_4O_3$

Biological Results.

In an initial screening, all of these compounds showed a mild acute toxicity (LD_{50} greater than 1 g/Kg ICR Swiss mice). They did not modify either histamine, acetylcholine, norepinephrine and serotonine effects on isolated organs nor the responses to experimentally-induced gastric ulcer. The assessment of analgesic effects yielded activity only for products **4a** and **4b** in the hot plate test. Compound **4g** showed activity in the ovoalbumin and carrageenan tests, and anticonvulsant activity in strychnine and cardiazole induced seizures in the mouse, while the rest of the compounds did not show anticonvulsant activity.

These results seem to point out that the aliphatic nature of the R-group in the formula **4** favours anti-inflammatory action, as so as an interesting depressant effects on central nervous system.

EXPERIMENTAL

The melting points were obtained on a Büchi apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer model 257. The nmr spectra were determined with a Varian T-60A spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. The elemental analysis were performed by Centro Nacional de Química Orgánica, Madrid.

N-(4-Pyridylmethyl)amides.

These compounds have been obtained following the method reported in the literature [12].

N-(4-Pyridylmethyl)amide *N*-Oxides.

These compounds have been prepared according to the method reported in the literature [13].

General Procedure for the Reaction of *N*-Oxides with Phenylbutazone.

A mixture of 0.01 mole of the corresponding *N*-(4-pyridylmethyl)amino *N*-oxide, 0.01 mole of phenylbutazone, 5 ml of acetic anhydride and 5 ml of dimethylformamide was heated at 80° for 3 hours. The reaction mixture was kept overnight at room temperature, and was then poured into 50 ml of water. The solution was treated with chloroform twice, the organic extracts were washed with 10% sodium hydroxide and two portions of water, dried over anhydrous magnesium sulphate and evaporated. The residue was recrystallized.

4-Butyl-4-[(3,5-dimethylbenzoylamino)(4-pyridyl)methyl]-1,2-diphenyl-3,5-pyrazolidinedione (**4a**).

This compound was obtained in a yield of 75%, mp 164-166° (methanol-water); ir (potassium bromide): ν 3400 (NH), 1740, 1700, 1670 (C=O), 1600 (Ar) cm^{-1}; nmr (deuteriochloroform): δ 0.9 (t, 3H, CH_3), 1.2-1.8 (m, 4H, CH_2-CH_2), 2.2-2.5 (m, 2H, CH_2), 2.5 (s, 6H, 2CH_3-Ph), 5.8 (d, 1H, CH), 6.8-7.6 (m, 15H, 13H-Ph and H_3,H_5-Py), 8.3 (d, 1H, NH), 8.5 (d, 2H, H_2 and H_6-Py) ppm.

Anal. Calcd. for $C_{34}H_{34}N_4O_3$: C, 74.70; H, 6.26; N, 10.24. Found: C, 74.38; H, 6.40; N, 10.28.

4-Butyl-4-[(4-methylbenzoylamino)(4-pyridyl)methyl]-1,2-diphenyl-3,5-pyrazolidinedione (**4b**).

This compound was obtained in a yield of 61%, mp 183-185° (methanol-water); ir (potassium bromide): δ 3420 (NH), 1740, 1700, 1665 (C=O), 1610, 1600 (Ar) cm^{-1}; nmr (deuteriochloroform): δ 0.7-1.1 (m, 3H, CH_3), 1.2-1.6 (m, 4H, CH_2-CH_2), 2.2-2.4 (m, 2H, CH_2), 2.4 (s, 3H, CH_3-Ph), 5.8 (d, 1H, CH), 6.7-7.4 (m, 14H, 10H-Ph, H_3,H_5-Ph and H_3,H_5-Py), 7.8 (m, 2H, H_2 and H_6-Py) ppm.

Anal. Calcd. for $C_{33}H_{32}N_4O_3$: C, 74.41; H, 6.05; N, 10.51. Found: C, 74.38; H, 6.40; N, 10.28.

4-Butyl-4-[(2-methylbenzoylamino)(4-pyridyl)methyl]-1,2-diphenyl-3,5-pyrazolidinedione (**4c**).

This compound was obtained in a yield of 50%, mp 138-140°; (cyclo-

hexane); ir (potassium bromide): ν 3400, 3280 (NH), 1750, 1710, 1650 (C=O), 1600 (Ar) cm^{-1}; nmr (deuteriochloroform): δ 0.8-1.1 (m, 3H, CH_3), 1.1-1.6 (m, 4H, CH_2-CH_2), 2.2-2.4 (m, 2H, CH_2), 2.5 (s, 3H, CH_3-Ph), 5.8 (d, 1H, CH), 6.7-7.4 (m, 16H, 14H-Ph and H_3,H_5-Py), 7.9 (m, 1H, NH), 8.5 (m, 2H, H_2 and H_6-Py) ppm.

Anal. Calcd. for $C_{33}H_{32}N_4O_3$: C, 74.41; H, 6.05; N, 10.51. Found: C, 74.63; H, 6.30; N, 10.33.

4-Butyl-4-[(4-nitrobenzoylamino)(4-pyridyl)methyl]-1,2-diphenyl-3,5-pyrazolidinedione (**4d**).

This compound was obtained in a yield of 53%, mp 110-111° (methanol-water); ir (potassium bromide): ν 3380 (NH), 1750, 1700, 1670 (C=O), 1600 (Ar) 1525, 1340 (C-NO_2) cm^{-1}; nmr (deuteriochloroform): δ 0.8-1.2 (m, 3H, CH_3), 1.2-1.7 (m, 4H, CH_2-CH_2), 2.2-2.5 (m, 2H, CH_2), 5.8 (d, 1H, CH), 6.8-7.4 (m, 12H, 10H-Ph and H_3,H_5-Py), 8.0-8.7 (m, 7H, 4H-Ph, H_2,H_6-Py and NH) ppm.

Anal. Calc.d for $C_{32}H_{29}N_5O_5$: C, 68.19; H, 5.18; N, 12.42. Found: C, 68.23; H, 5.24; N, 12.65.

4-Butyl-4-[(4-methoxybenzoylamino)(4-pyridyl)methyl]-1,2-diphenyl-3,5-pyrazolidinedione (**4e**).

This compound was obtained in a yield of 62%, mp 83-85° (cyclohexane); ir (potassium bromide): ν 3400 (NH), 1750, 1705, 1665 (C=O), 1610 (Ar), 1255 (C-O) cm^{-1}; nmr (deuteriochloroform): δ 0.7-1.0 (m, 3H, CH_3), 1.1-1.5 (m, 4H, CH_2-CH_2), 2.0-2.4 (m, 2H, CH_2), 3.8 (s, 3H, CH_3O), 5.7 (d, 1H, CH), 6.7-7.3 (m, 14H, 10H-Ph, H_3,H_5-Ph and H_3,H_5-Py), 7.8 (m, 2H, H_2 and H_6-Ph), 8.4 (m, 2H, H_2 and H_6-Py) ppm.

Anal. Calcd. for $C_{33}H_{32}N_4O_4$: C, 72.24; H, 5.87; N, 10.21. Found: C, 72.55; H, 6.15; N, 10.03.

4-Butyl-4-[(2-chlorobenzoylamino)(4-pyridyl)methyl]-1,2-diphenyl-3,5-pyrazolidinedione (**4f**).

This compound was obtained in a yield of 55%; mp 120-122°C (cyclohexane); ir (potassium bromide): ν 3380, 3240 (NH), 1750, 1710, 1660 (C=O), 1600 (Ar) cm^{-1}; nmr (deuteriochloroform): δ 0.6-1.0 (m, 3H, CH_3), 1.1-1.6 (m, 4H, CH_2-CH_2), 2.0-2.4 (m, 2H, CH_2), 5.8 (d, 1H, CH), 6.4-7.4 (m, 16H, 14H-Ph and H_3, H_5-Py), 8.4 (m, 2H, H_2 and H_6-Py) ppm.

Anal. Calcd. for $C_{32}H_{29}ClN_4O_3$: C, 69.49; H, 5.28; N, 10.13; Cl, 6.41. Found: C, 69.64; H, 5.50; N, 10.12; Cl, 6.09.

4-Butyl-4-[(acetylamino)(4-pyridyl)methyl]-1,2-diphenyl-3,5-pyrazolidinedione (**4g**).

This compound was obtained in a yield of 66%; mp 171-172° (cyclohexane); ir (potassium bromide): ν 3300 (NH), 1750, 1710, 1660 (C=O), 1600 (Ar) cm^{-1}; nmr (deuteriochloroform): δ 0.6-1.0 (m, 3H, CH_3), 1.0-1.6 (m, 4H, CH_2-CH_2), 1.8-2.4 (m, 2H, CH_2), 2.0 (s, 3H, CH_3-CO), 5.5 (d, 1H, CH), 6.6-7.4 (m, 12H, 10H-Ph and H_3,H_5-Py), 8.4 (m, 2H, H_2 and H_6-Py) ppm.

Anal. Calcd. for $C_{27}H_{28}N_4O_3$: C, 71.03; H, 6.18; N, 12.27. Found: C, 71.01; H, 6.46; N, 12.49.

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