Reaction of 4-Acylaminomethylpyridine *N*-Oxides with 5-Monosubstituted Barbituric Acids in Presence of Acetic Anhydride

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The 5-alkyl-5-[(3,5-dimethylbenzoylamino)(4-pyridyl)methyl]barbituric acids are obtained in the title reactions, but they fail when barbituric or 5-phenylbarbituric acids are used. These results are explained by the pK_a values of barbituric acids.

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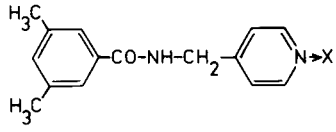
Picobenzide **1**, is a CNS depressant with pharmacological properties partly similar to those of phenothiazine type neuroleptics. As part of a research program currently underway in our laboratories on the synthesis of new compounds which introduce new pharmacofores in the molecule, keeping the fundamental structure of 4-acylaminomethylpyridine, we found interesting the use of barbituric acids because **1** greatly increases the hypnosis time of this type of drugs [1].



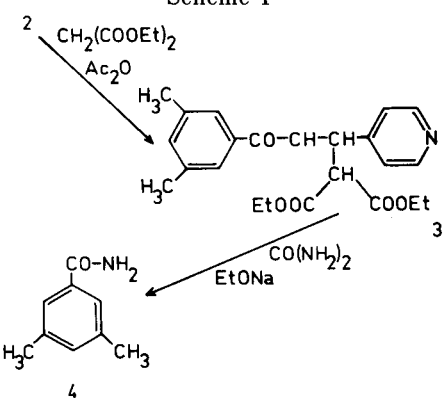
1: X = –
2: X = O

Figure 1

In previous publications [2-6] we have reported that 4-acylaminomethylpyridine *N*-oxides react with compounds containing active hydrogen atoms bound to heteroatom or carbon, being the second case a good method for C-C bonds formation. In all cases studied by our team, introduction of new group occurs at methylene group in position 4 of pyridine ring.

Even though the introduction of a barbituric group have been previously attempted by our team, *via* malonic ester **3** (Scheme 1) [6], condensation with urea always afforded 3,5-dimethylbenzamide **4** as the only product. This is a general result as 4-acylaminomethylpyridines undergo a Nitrogen-4-pyridylmethyl bond-breaking in strong basic medium [6].

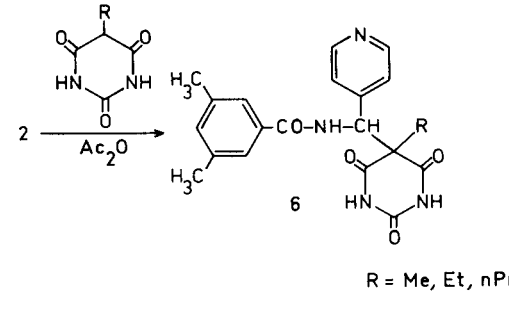
Scheme 1



When reaction of **2** with barbituric acid is carried out, expected product was not obtained but 5-acetylderivative. However, using 5-methylbarbituric acid a crystalline product was obtained with a quantitative elementary analysis corresponding to a $C_{20}H_{20}N_4O_4$ formula. The 5-methyl-5-[(3,5-dimethylbenzoylamino)(4-pyridyl)methyl]barbituric acid structure was assigned to this product as its ir spectrum showed absorption bands at 3400 cm^{-1} for NH group, at 1760 and 1720 cm^{-1} for CO of the barbituric acid moiety and at 1650 cm^{-1} for the amide moiety.

Likewise, the nmr spectrum showed peaks at δ 2.0 a singlet corresponding to a methyl group bound to barbituric acid, at 2.3 a singlet corresponding to two methyl groups bound to phenyl, at 6.2 a doublet corresponding to a CH group bound to pyridine, at 7.1-7.3 a multiplet corresponding to *ortho* and *para*-phenyl hydrogens, at 8.1 and 8.6 two doublets corresponding to the AA'BB' system of 4-substituted pyridine, and at 8.8 a multiplet corresponding to a NH group.

Scheme 2

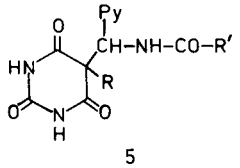


R = Me, Et, nPr

Compounds shown in Table 1 have been obtained in order to establish the generality of this reaction, using different amides and barbituric acids.

In several attempts we have always found that whereas using 5-methyl, 5-ethyl and 5-(*n*-propyl)barbituric acids, expected condensation products **6** are obtained in good yield, when barbituric or 5-phenylbarbituric acids are used there is no reaction of this type.

Table 1



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Compound	R	R'	Rto. %	Mp °C	Crystallization Solvent
5a	Me	3,5-$(CH_3)_2$-C_6H_3	80	246	A
5b	Me	2-(CH_3)-C_6H_4	41	246-248	A
5c	Me	4-(NO_2)-C_6H_4	30	243-245	A
5d	Me	C_6H_5	34	245-247	A
5e	Me	OEt	46	218	B
5f	Et	3,5-$(CH_3)_2$-C_6H_3	77	239-241	A
5g	Et	$(CH_3\text{-}CH_2)_2CH$	81	221	C
5h	Et	2-(CH_3)-C_6H_4	55	237-239	A
5i	*n*-Pr	OEt	57	220-222	D
5j	*n*-Pr	4-(NO_2)-C_6H_4	65	250-255	A
5k	*n*-Pr	3,5-$(CH_3)_2$-C_6H_3	76	245-247	A
5l	*n*-Pr	4-(CH_3)-C_6H_4	75	250	A
5m	*n*-Pr	2-(CH_3)-C_6H_4	75	241-243	A
5n	*n*-Pr	$(CH_3\text{-}CH_2)_2CH$	50	222-224	E
5o	*n*-Pr	4-(CH_3O)-C_6H_4	56	238-240	A

A = Dimethylformamide-water, B = Ethyl acetate-petroleum ether, C = Ethanol, D = Ethyl acetate, E = Methanol-water.

In the reaction with 5-phenylbarbituric acid, the only obtained product is *N,N'*-di(3,5-dimethylbenzoyl)-1,2-di(4-pyridyl)ethylenediamine **7**. This result can be explained by the fact that even though the acidity of the compound is high (pK_a = 2.54) [7] and so, the anion is easily formed, it has so little reactivity that dimerization reaction

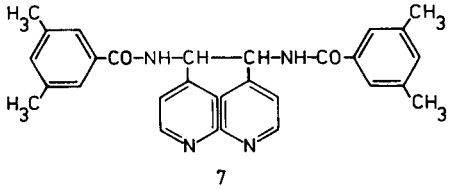

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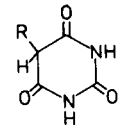
Figure 2

of **2** prevails [8]. On the other hand, barbituric acid, less acidic than the others (pK_a = 4.02) [7], forms the carbanion with difficulty and so the reaction with *N*-oxide **2** is not favoured. However, one of the barbituric acid enolic forms, the one involving methylene hydrogens, is able to form the 5-acetyl derivative by nucleophilic attack to acetic anhydride, according to a mechanism similar to the one proposed by Vul'fson *et al.* [9].

As the acidity of the other three barbituric acids lies between those two cited values (see Table 2), compounds **6** are formed in good yield (76-80%) in all cases.

Table 2

Acidity of 5-Alkylbarbituric Acids



R	p*K*a	Ref
H	4.02	[7]
Me	3.39	[7]
Et	3.69	[7]
n-Pr	3.43	[10]
Ph	2.54	[7]

EXPERIMENTAL

Melting points were determined in open capillary on a Buchi SMP-20 and are uncorrected. The ir spectra were performed on a Perkin Elmer Model 257. Reported values are the more intense or characteristic peaks. The pmr spectra were registered on a Varian Model T-60 A spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. The elemental analysis were performed by Centro Nacional de Química Orgánica, Madrid.

Barbituric acid is commercial. All the 5-alkylbarbituric acids were prepared by the usual method [11].

Reaction of *N*-(1-Oxido-4-pyridylmethyl)amides with 5-Alkylbarbituric Acids in Presence of Acetic Anhydride. General procedure.

A solution of 0.01 mole of *N*-(1-oxide-4-pyridylmethyl) amide and 0.01 mole of 5-alkylbarbituric acid in 5 ml of acetic anhydride is placed in a round bottomed flask and heated at 80° during 3 hours. After standing overnight at room temperature, the solid is filtered, washed with ethyl acetate and purified by crystallization in the adecuate solvent.

5-Methyl-5-[(3,5-dimethylbenzoylamino)(4-pyridyl)methyl]barbituric Acid (**5a**).

This compound was obtained as white crystals (dimethylformamide-water), mp 246°; ir (potassium bromide): ν 3400 (NH), 1760, 1720, 1650 (CO), 1600 (Ar) cm^{-1}; pmr (trifluoracetic acid): δ 2.0 (s, 3H, CH_3), 2.3 (s, 6H, $2CH_3$-Ph), 6.2 (d, 1H, CH), 7.1-7.3 (m, 3H, 3H-Ph), 8.1 (d, 2H, H_3 and H_5-pyridine), 8.6 (d, 2H, H_2 and H_6-pyridine), 8.8 (m, 1H, NH) ppm.

Anal. Calcd. for $C_{20}H_{20}N_4O_4$: C, 63.14; H, 5.29; N, 14.78. Found: C, 62.72; H, 5.45; N, 14.57.

5-Methyl-5-[(2-methylbenzoylamino)(4-pyridyl)methyl]barbituric Acid (**5b**).

This compound was obtained as white crystals (dimethylformamide-water), mp 246-248°; ir (potassium bromide): ν 3350, 3200, 3100 (NH), 1740, 1715, 1680 (CO), 1605 (Ar) cm^{-1}; pmr (trifluoracetic acid): δ 2.0 (s, 3H, CH_3), 2.3 (s, 3H, CH_3-Ph), 6.2 (d, 1H, CH), 7.2 (m, 4H, 4H-Ph), 8.0 (d, 2H, H_3 and H_5-pyridine), 8.9 (d, 2H, H_2 and H_6-pyridine) ppm.

Anal. Calcd. for $C_{19}H_{18}N_4O_4$: C, 62.28; H, 4.95; N, 15.29. Found: C, 61.85; H, 5.00; N, 15.32.

5-Methyl-5-[(4-nitrobenzoylamino)(4-pyridyl)methyl]barbituric Acid (**5c**).

This compound was obtained as yellowish crystals (dimethylformamide-water), mp 243-245°; ir (potassium bromide): ν 3400, 3220, 3100 (NH), 1720, 1690 (CO), 1605 (Ar), 1525 (NO_2) cm^{-1}; pmr (trifluoracetic acid): δ 2.2 (s, 3H, CH_3), 6.4 (d, 1H, CH), 8.2 (m, 6H, 4H-Ph and H_3 and H_5-

pyridine), 8.8 (m, 2H, H_2 and H_6-pyridine) ppm.

Anal. Calcd. for $C_{16}H_{15}N_5O_6$: C, 54.41, H, 3.80; N, 17.62. Found: C, 54.69; H, 3.85; N, 17.47.

5-Methyl-5-[(benzoylamino)(4-pyridyl)methyl]barbituric Acid (**5d**).

This compound was obtained as white crystals (dimethylformamide-water), mp 245-247°; ir (potassium bromide): ν 3360, 3200, 3100 (NH), 1720, 1690, (CO), 1600 (Ar) cm^{-1}; pmr (trifluoracetic acid): δ 2.2 (s, 3H, CH_3), 6.5 (d, 1H, CH), 7.8 (m, 5H, 5H-Ph), 8.3 (d, 2H, H_3 and H_5-pyridine), 8.9 (d, 2H, H_2 and H_6-pyridine) ppm.

Anal. Calcd. for $C_{16}H_{16}N_4O_4$: C, 61.35; H, 4.57; N, 15.90. Found: C, 61.44; H, 4.61; N, 15.91.

5-Methyl-5-[(carbethoxyamino)(4-pyridyl)methyl]barbituric Acid (**5e**).

This compound was obtained as white crystals (ethyl acetate-petroleum ether), mp 218°; ir (potassium bromide): ν 3500, 3250 (NH), 1730 (CO), 1600 (Ar) cm^{-1}; pmr (trifluoroacetic acid): δ 1.3 (t, 3H, CH_3-CH_2-), 2.1 (s, 3H, CH_3), 4.4 (c, 2H, CH_2-O), 6.2 (d, 1H, CH), 8.4 (d, 2H, H_3 and H_5-pyridine), 9.0 (d, 2H, H_2 and H_6-pyridine) ppm.

Anal. Calcd. for $C_{14}H_{16}N_4O_5$: C, 52.49; H, 5.03; N, 17.49. Found: C, 52.74; H, 5.23; N, 17.50.

5-Ethyl-5-[(3,5-dimethylbenzoylamino)(4-pyridyl)methyl]barbituric Acid (**5f**).

This compound was obtained as white crystals (dimethylformamide-water), mp 239-241°; ir (potassium bromide): ν 3400, 3200, 3130, 3080 (NH), 1760, 1710, 1685, 1650 (CO), 1600 (Ar) cm^{-1}; pmr (trifluoracetic acid): δ 1.0 (t, 3H, CH_3-CH_2-), 2.3 (m, 8H, $2CH_3$-Ph and CH_3-CH_2-), 6.1 (d, 1H, CH), 7.1 (s, 3H, 3H-Ph), 8.0 (d, 2H, H_3 and H_5-pyridine), 8.5 (d, 2H, H_2 and H_6-pyridine) ppm.

Anal. Calcd. for $C_{21}H_{22}N_4O_4$: C, 63.94; H, 5.62; N, 14.21. Found: C, 63.77; H, 5.81; N, 14.51.

5-Ethyl-5-[(2,2-di-*n*-propylacetylamino)(4-pyridyl)methyl]barbituric Acid (**5g**).

This compound was obtained as white crystals (ethanol), mp 221°; ir (potassium bromide): ν 3400, 3200 (NH), 1750, 1710, 1690 (CO), 1600 (Ar) cm^{-1}; pmr (trifluoracetic acid): δ 0.6-2 (m, 17H, $2(CH_3$-CH_2-$CH_2)$ and CH_3-), 2.2-2.8 (m, 3H, CH_2 and CH-CO), 6.3 (d, 1H, CH), 8.3 (d, 2H, H_3 and H_5-pyridine), 8.6 (d, 1H, NH), 9.0 (d, 2H, H_2 and H_6-pyridine) ppm.

Anal. Calcd. for $C_{20}H_{28}N_4O_4$: C, 61.83; H, 7.26; N, 14.42. Found: C, 61.81; H, 6.97; N, 14.31.

5-Ethyl-5-[(2-methylbenzoylamino)(4-pyridyl)methyl]barbituric Acid (**5h**).

This compound was obtained as white crystals (dimethylformamide-water), mp 237-239°; ir (potassium bromide): ν 3400, 3980 (NH), 1750, 1710, 1680 (CO), 1600 (Ar) cm^{-1}; pmr (trifluoracetic acid): δ 1.3 (t, 3H, CH_3), 2.5 (s broad, 5H, CH_3-Ph and CH_2), 6.4 (d, 1H, CH), 7.4 (m, 4H, 4H-Ph), 8.2 (d, 2H, H_3 and H_5-pyridine), 8.6 (m, 1H, NH), 8.9 (d, 2H, H_2 and H_6-pyridine) ppm.

Anal. Calcd. for $C_{20}H_{20}N_4O_4$: C, 63.14; H, 5.29; N, 14.78. Found: C, 63.17; H, 5.43; N, 14.47.

5-Propyl-5-[(carbethoxyamino)(4-pyridyl)methyl]barbituric Acid (**5i**).

This compound was obtained as white crystals (ethyl acetate), mp 220-222°; ir (potassium bromide): ν 3400, 3220 (NH), 1710, 1690 (CO), 1600 (Ar) cm^{-1}; pmr (trifluoracetic acid): δ 0.9-1.6 (m, 8H, CH_3-CH_2 and CH_3), 2.0-2.6 (m, 2H, -CH_2-CH_2-), 4.3 (c, 2H, CH_2-O), 6.0 (d, 1H, CH), 7.3 (m, 1H, NH), 8.2 (d, 2H, H_3 and H_5-pyridine), 8.9 (d, 2H, H_2 and H_6-pyridine) ppm.

Anal. Calcd. for $C_{16}H_{20}N_4O_5$: C, 55.16; H, 5.78; N, 16.08. Found: C, 54.99; H, 5.90; N, 15.78.

5-Propyl-5-[(4-nitrobenzoylamino)(4-pyridyl)methyl]barbituric Acid (**5j**).

This compound was obtained as yellowish crystals (dimethylformamide-water), mp 250-252°; ir (potassium bromide): ν 3380, 3250 (NH), 1740, 1690 (CO), 1605 (Ar) cm^{-1}; pmr (trifluoracetic acid): δ 0.8-2.0 (m, 5H, CH_3-CH_2), 2.6 (m, 2H, CH_2), 6.4 (d, 1H, CH), 8.2 (m, 6H, 4H-Ph and H_3 and H_5-pyridine), 8.9 (d, 2H, H_2 and H_6-pyridine), 9.3 (m, 1H, NH) ppm.

Anal. Calcd. for $C_{20}H_{19}N_5O_6$: C, 56.46; H, 4.50; N, 16.46. Found: C, 56.34; H, 4.53; N, 16.46.

5-Propyl-5-[(3,5-dimethylbenzoylamino)(4-pyridyl)methyl]barbituric Acid (**5k**).

This compound was obtained as white crystals (dimethylformamide-water), mp 245-247°; ir (potassium bromide): ν 3410, 3240 (NH), 1740, 1690 (CO), 1600 (Ar) cm^{-1}; pmr (trifluoracetic acid): δ 1.0 (m, 3H, CH_3-CH_2-), 2.4 (m, 10H, $2CH_3$-Ph and 2-CH_2-), 6.2 (d, 1H, CH), 7.2 (m, 3H, 3H-Ph), 8.0 (d, 2H, H_3 and H_5-pyridine), 8.6 (d, 2H, H_2 and H_6-pyridine), 8.8 (s, 1H, NH) ppm.

Anal. Calcd. for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.71. Found: C, 64.43; H, 5.90; N, 13.41.

5-Propyl-5-[(4-methylbenzoylamino)(4-pyridyl)methyl]barbituric Acid (**5l**).

This compound was obtained as white crystals (dimethylformamide-water), mp 250°; ir (potassium bromide): ν 3400, 3250 (NH), 1740, 1690 (CO), 1600 (Ar) cm^{-1}; pmr (trifluoracetic acid): δ 0.8-2.0 (m, 5H, CH_3-CH_2-), 2.6 (s broad, 5H, CH_3-Ph and -CH_2-), 6.4 (d, 1H, CH), 7.6 (c, 4H, H-Ph), 8.2 (d, 2H, H_3 and H_5-pyridine), 8.8 (d, 2H, H_2 and H_6-pyridine) ppm.

Anal. Calcd. for $C_{21}H_{22}N_4O_4$: C, 63.94; H, 5.62; N, 14.20. Found: C, 64.12; H, 5.59; N, 14.08.

5-Propyl-5-[(2-methylbenzoylamino)(4-pyridyl)methyl]barbituric Acid (**5m**).

This compound was obtained as white crystals (dimethylformamide-water), mp 241-243°; ir (potassium bromide): ν 3400, 3220 (NH), 1740, 1720, 1680 (CO), 1600 (Ar) cm^{-1}; pmr (trifluoracetic acid): δ 0.7-1.8 (m, 5H, CH_3-CH_2-), 2.4 (m, 5H, CH_3-Ph and -CH_2-), 6.2 (d, 1H, CH), 7.2 (s, 4H, 4H-Ph), 8.0 (d, 2H, H_3 and H_5-pyridine), 8.4 (m, 1H, NH), 8.6 (d, 2H, H_2 and H_6-pyridine) ppm.

Anal. Calcd. for $C_{21}H_{22}N_4O_4$: C, 63.94, H, 5.62; N, 14.20. Found: C, 63.95; H, 5.65; N, 14.23.

5-Propyl-5-[(2,2-di-*n*-propylacetylamino)(4-pyridyl)methyl]barbituric Acid (**5n**).

This compound was obtained as white crystals (methanol-water), mp 222-224°; ir (potassium bromide): ν 3200 (NH), 1750, 1700, 1650 (CO), 1600 (Ar) cm^{-1}; pmr (trifluoracetic acid): δ 0.6-2.0 (m, 19H, $2CH_3$-CH_2-CH_2- and CH_3-CH_2-), 2.2-2.9 (m, 3H, CH_2 and CH), 6.4 (d, 1H, CH), 8.4 (d, 2H, H_3 and H_5-pyridine), 8.7 (m, 1H, NH), 9.0 (d, 2H, H_2 and H_6-pyridine) ppm.

Anal. Calcd. for $C_{21}H_{30}N_4O_4$: C, 62.66; H, 7.51; N, 13.91. Found: C, 62.72; H, 7.25; N, 13.79.

5-Propyl-5-[(4-methoxybenzoylamino)(4-pyridyl)methyl]barbituric Acid (**5o**).

This compound was obtained as white crystals (dimethylformamide-water), mp 238-240°; ir (potassium bromide): ν 3420, 3240 (NH), 1750, 1710, 1650 (CO), 1600 (Ar), 1250 (O-C) cm^{-1}; pmr (trifluoracetic acid): δ 0.7-1.6 (m, 5H, CH_3-CH_2-), 2.4 (m, 2H, -CH_2-), 4.0 (s, 3H, CH_3O-), 6.4 (d, 1H, CH), 7.2 (m, 2H, H_3 and H_5-phenyl), 8.0 (m, 2H, H_2 and H_6-phenyl), 8.3 (m, 2H, H_3 and H_5-pyridine), 9.0 (m, 2H, H_2 and H_6-pyridine) ppm.

Anal. Calcd. for $C_{21}H_{22}N_4O_5$: C, 61.45; H, 5.40; N, 13.65. Found: C, 61.54; H, 5.53; N, 13.69.

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