

Reaction of 4-(Benzoylaminomethyl)pyridine 1-Oxides with Indan-1,3-dione in the Presence of Acetic Anhydride

Mercedes GARRIDO,^a Maria L. López RODRÍGUEZ,^{*a} and M. José MORCILLO^b

Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense,^a 28040-Madrid, Spain and Facultad de Ciencias Químicas, Universidad Nacional de Educación a Distancia,^b 28040-Madrid, Spain. Received November 20, 1989

4-(Benzoylaminomethyl)pyridine 1-oxides (1) react with indan-1,3-dione in the presence of acetic anhydride to give 2-(benzoylamino-4-pyridylmethylene)indan-1,3-diones (4) and 4-benzoylaminomethyl-2-(3-hydroxy-1-oxo-2-indenyl)pyridines (5) as enol forms. The reaction mechanism is discussed.

Keywords 4-(benzoylaminomethyl)pyridine 1-oxide; acetic anhydride; indan-1,3-dione; pyridine

In previous papers^{1–7)} we have reported that 4-(benzoylaminomethyl)pyridine 1-oxides (1) react with active methylene compounds such as 4-(benzoylaminomethyl)pyridine,²⁾ *O*-benzoyl-*p*-nitrobenzaldehyde cyanohydrin,³⁾ ethyl cyanoacetate,⁴⁾ phenylbutazone,⁵⁾ barbituric acids⁶⁾ and 1,3-diphenyl-1,3-propanedione⁷⁾ in the presence of acetic anhydride to give *N*-[(α -substituted)-4-pyridylmethyl]benzamides (2) through nucleophilic substitution *via* the intermediate (3)⁸⁾ (Chart 1). As an extension of this work we further investigated the reaction of a series of 4-(benzoylaminomethyl)pyridine 1-oxides (1) with indan-1,3-dione in the presence of acetic anhydride.

Reaction of 4-(4-chlorobenzoylaminomethyl)pyridine 1-oxide⁹⁾ (1a) with indan-1,3-dione in the presence of acetic anhydride afforded 2-(4-chlorobenzoylamino-4-pyridyl-

methylene)indan-1,3-dione (4a) and 4-(4-chlorobenzoylaminomethyl)-2-(3-hydroxy-1-oxo-2-indenyl)pyridine (5a) as the enol form in 25% and 40% yields, respectively. Both compounds were isolated by fractional recrystallization and their structures were established on the basis of elemental analysis and spectral data (Chart 2, Tables I–IV).

Compound 4a, mp 218–220 °C, has the molecular formula C₂₂H₁₃ClN₂O₃. The infrared (IR) spectrum exhibited a broad band at 3200 cm^{–1} and absorptions at 1715, 1690, 1650 cm^{–1}. The proton nuclear magnetic resonance (¹H-NMR, 200 MHz) spectrum in dimethyl sulfoxide-*d*₆ (DMSO-*d*₆)/CF₃COOH showed twelve aromatic protons and indicated the presence of two AA'BB'

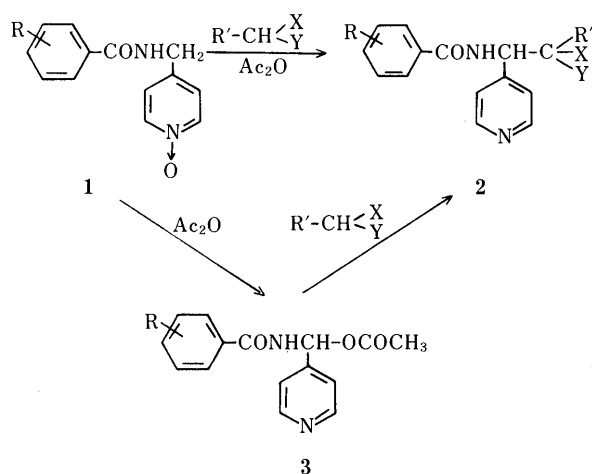


Chart 1

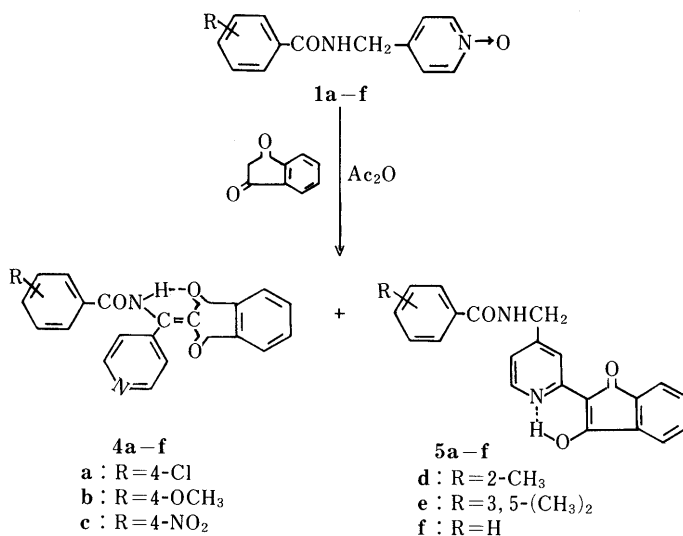


Chart 2

TABLE I. Physical Properties of 4

Compd.	R	Yield (%)	mp (°C) ^{a)}	Formula	Analysis (%)			Found		
					Calcd			C	H	N
4a	4-Cl	25	218–220	C ₂₂ H ₁₃ ClN ₂ O ₃	67.97	3.34	7.20	68.10	3.49	7.11
4b	4-OCH ₃	27	194–196	C ₂₃ H ₁₆ N ₂ O ₄	71.89	4.16	7.29	71.75	4.20	7.37
4c	4-NO ₂	38	208–209	C ₂₂ H ₁₃ N ₃ O ₅	66.16	3.28	10.52	66.00	3.17	10.32
4d	2-CH ₃	21	256–258	C ₂₃ H ₁₆ N ₂ O ₃	75.01	4.34	7.60	75.10	4.40	7.74
4e	3,5-(CH ₃) ₂	32	304–306	C ₂₄ H ₁₈ N ₂ O ₃	75.37	4.74	7.32	75.66	4.85	7.34
4f	H	25	284–285	C ₂₂ H ₁₄ N ₂ O ₃	74.56	3.98	7.90	74.41	4.10	8.20

a) Recrystallization solvent: ethanol.

TABLE II. Physical Properties of 5

Compd.	R	Yield (%)	mp (°C) ^{a)}	Formula	Analysis (%)					
					Calcd			Found		
					C	H	N	C	H	N
5a	4-Cl	40	> 310	C ₂₂ H ₁₅ ClN ₂ O ₃	67.60	3.86	7.17	67.90	4.10	7.19
5b	4-OCH ₃	51	295—296	C ₂₃ H ₁₈ N ₂ O ₄	71.49	4.69	7.25	71.24	4.89	7.46
5c	4-NO ₂	60	277—278	C ₂₂ H ₁₅ N ₃ O ₅	65.83	3.76	10.47	65.67	3.58	10.34
5d	2-CH ₃	46	> 300	C ₂₃ H ₁₈ N ₂ O ₃	74.57	4.89	7.56	74.85	5.20	7.81
5e	3,5-(CH ₃) ₂	58	> 300	C ₂₄ H ₂₀ N ₂ O ₃	74.98	5.24	7.28	74.83	5.48	7.14
5f	H	49	279—280	C ₂₂ H ₁₆ N ₂ O ₃	74.14	4.52	7.86	74.43	4.67	7.84

a) Recrystallization solvent: ethanol.

TABLE III. Spectral Data for 4

Compd.	R	IR ν (KBr) cm^{-1}				$^1\text{H-NMR}$ ($\text{DMSO-}d_6/\text{CF}_3\text{CO}_2\text{H}$) b δ
		ν_{NH} a	ν_{CO}	ν_{amide}		
				I	II	
4a	4-Cl	3200	1715 1690	1650	1570	7.48 (d, 2H, $\text{H}_3, \text{H}_5\text{-py}$, $J=6.0$ Hz), 7.71 (d, 2H, $\text{H}_3, \text{H}_5\text{-ph}$, $J=8.5$ Hz), 7.87 (s, 4H, ind.), 7.99 (d, 2H, $\text{H}_2, \text{H}_6\text{-ph}$, $J=8.5$ Hz), 8.67 (d, 2H, $\text{H}_2, \text{H}_6\text{-py}$, $J=6.0$ Hz)
4b	4- OCH_3	3200	1715 1690	1650	1575	2.65 (s, 3H, OCH_3), 7.47 (d, 2H, $\text{H}_3, \text{H}_5\text{-py}$, $J=5.9$ Hz), 7.71 (d, 2H, $\text{H}_3, \text{H}_5\text{-ph}$, $J=8.6$ Hz), 7.86 (s, 4H, ind.), 7.97 (d, 2H, $\text{H}_2, \text{H}_6\text{-ph}$, $J=8.6$ Hz), 8.66 (d, 2H, $\text{H}_2, \text{H}_6\text{-py}$, $J=5.9$ Hz)
4c	4- NO_2	3300	1715 1700	1650	1565	7.0—8.10 (m, 10H, 4H-ph, 4H-ind, $\text{H}_3, \text{H}_5\text{-py}$), 8.70 (d, 2H, $\text{H}_2, \text{H}_6\text{-py}$, $J=6.0$ Hz)
4d	2- CH_3	3200	1720 1700	1650	1580	2.40 (s, 3H, CH_3), 7.10—7.45 (m, 6H, 4H-ph, $\text{H}_3, \text{H}_5\text{-py}$), 7.60 (s, 4H, ind), 8.40 (d, 2H, $\text{H}_2, \text{H}_6\text{-py}$, $J=6.0$ Hz)
4e	3,5- $(\text{CH}_3)_2$	3300	1720 1700	1650	1580	2.40 (s, 6H, 2CH_3), 7.20—8.0 (m, 7H, 3H-ph, 4H-ind), 8.10 (d, 2H, $\text{H}_3, \text{H}_5\text{-py}$, $J=6.0$ Hz), 8.90 (d, 2H, $\text{H}_2, \text{H}_6\text{-py}$, $J=6.0$ Hz)
4f	H	3200	1715 1700	1650	1575	7.20—8.0 (m, 9H, 5H-ph, 4H-ind), 8.10 (d, 2H, $\text{H}_3, \text{H}_5\text{-py}$, $J=6.0$ Hz), 8.90 (d, 2H, $\text{H}_2, \text{H}_6\text{-py}$, $J=6.0$ Hz)

a) Broad absorption. b) The spectra were taken at 200 MHz (4a, b) or at 60 MHz (4c—f).

TABLE IV. Spectral Data for 5

Compd.	R	IR ν (KBr) cm^{-1}					$^1\text{H-NMR}$ (DMSO- d_6) b δ
		ν_{NH}	ν_{OH}^a	ν_{CO}	ν_{amide}		
					I	II	
5a	4-Cl	3300	3100	1670	1635	1570	4.56 (d, 2H, CH ₂ , $J=5.9$ Hz), 7.07 (d, 1H, H ₅ -py, $J=6.9$ Hz), 7.47—7.54 (m, 5H, 4H-ind, H ₃ -py), 7.58 (d, 2H, H ₃ ,H ₅ -ph, $J=8.5$ Hz), 7.95 (d, 2H, H ₂ ,H ₆ -ph, $J=8.5$ Hz), 8.23 (d, 1H, H ₆ -py, $J=6.9$ Hz), 8.45 (s, 1H, OH), 9.18 (t, 1H, NH, $J=5.9$ Hz)
5b	4-OCH ₃	3300	3100	1670	1640	1570	2.39 (s, 3H, OCH ₃), 4.51 (d, 2H, CH ₂ , $J=5.9$ Hz), 7.08 (d, 1H, H ₅ -py, $J=6.5$ Hz), 7.27—7.56 (m, 9H, 4H-ph, 4H-ind, H ₃ -py), 8.25 (d, 1H, H ₆ -py, $J=6.5$ Hz), 8.49 (s, 1H, OH), 9.01 (t, 1H, NH, $J=5.9$ Hz)
5c	4-NO ₂	3300	3100	1670	1640	1570	4.50 (d, 2H, CH ₂ , $J=6.0$ Hz), 6.90 (d, 1H, H ₅ -py, $J=7.0$ Hz), 7.30—8.0 (m, 9H, 4H-ph, 4H-ind, H ₃ -py), 8.20 (d, 1H, H ₆ -py, $J=7.0$ Hz), 8.30 (s, 1H, OH), 9.2 (t, 1H, NH, $J=6.0$ Hz)
5d	2-CH ₃	3300	3100	1670	1640	1580	2.50 (s, 3H, CH ₃), 4.50 (d, 2H, CH ₂ , $J=6.0$ Hz), 6.90 (d, 1H, H ₅ -py, $J=7.0$ Hz), 7.10—7.5 (m, 9H, 4H-ph, 4H-ind, H ₃ -py), 8.10 (d, 1H, H ₆ -py, $J=7.0$ Hz), 8.30 (s, 1H, OH), 9.0 (t, 1H, NH, $J=6.0$ Hz)
5e	3,5-(CH ₃) ₂	3300	3100	1670	1640	1570	2.33 (s, 6H, 2CH ₃), 4.52 (d, 2H, CH ₂ , $J=5.9$ Hz), 7.05 (d, 1H, H ₅ -py, $J=6.6$ Hz), 7.20—8.28 (m, 8H, 3H-ph, 4H-ind, H ₃ -py), 8.43 (s, 1H, OH), 8.58 (d, 1H, H ₆ -py, $J=6.9$ Hz), 9.12 (t, 1H, NH, $J=5.9$ Hz)
5f	H	3300	3100	1670	1640	1570	4.40 (d, 2H, CH ₂ , $J=6.0$ Hz), 6.90 (d, 1H, H ₅ -py, $J=7.0$ Hz), 7.20—8.10 (m, 10H, 5H-ph, 4H-ind, H ₃ -py), 8.30 (s, 1H, OH), 8.50 (d, 1H, H ₆ -py, $J=7.0$ Hz), 9.0 (t, 1H, NH, $J=6.0$ Hz)

a) Broad absorption. b) The spectra were taken at 200 MHz (5a, b, e) or at 60 MHz (5c, d, f).

systems due to the phenyl and pyridine rings, viz. at δ 7.48 (d, 2H, H₃ and H₅-pyridine, $J=6.0$ Hz), 7.71 (d, 2H, H₃ and H₅-phenyl, $J=8.5$ Hz), 7.99 (d, 2H, H₂ and H₆-phenyl, $J=8.5$ Hz), 8.67 (d, 2H, H₂ and H₆-pyridine, $J=6.0$ Hz) as

well as a singlet at 7.87 (4H) due to the indan-1,3-dione protons. These data led to the formulation of this compounds as 4a, and the IR spectrum indicated that an intramolecular hydrogen bond was present.

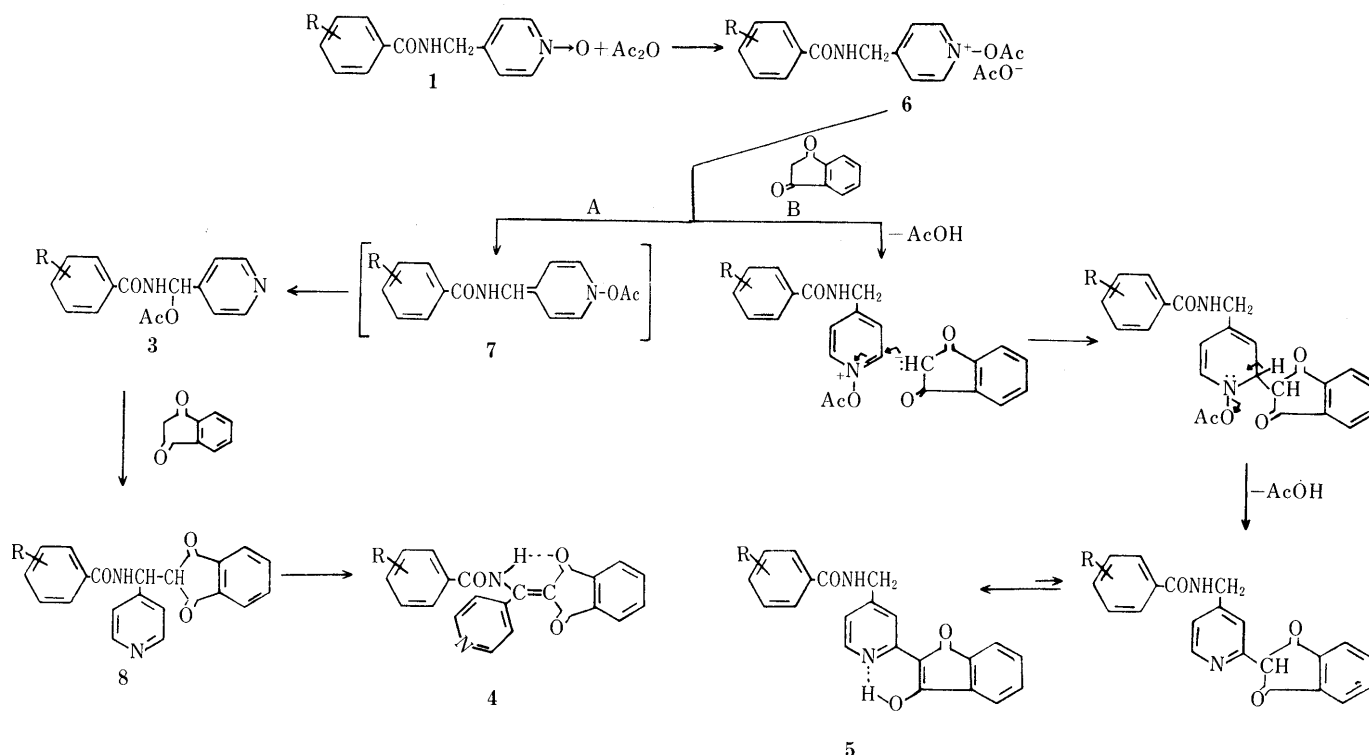


Chart 3

Compound **5a**, mp $>310^{\circ}\text{C}$, has the molecular formula $\text{C}_{22}\text{H}_{15}\text{ClN}_2\text{O}_3$. The IR spectrum displayed a broad absorption in the 3100cm^{-1} region and showed amide group [3300 , 1635 (I) and 1570 (II) cm^{-1}] and carbonyl (1670cm^{-1}) absorptions. The $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 200 MHz) spectrum showed the signals of a methylene moiety (δ : 4.56, $J=5.9\text{ Hz}$), eleven aromatic protons [δ : 7.07 (d, 1H, $J=6.9\text{ Hz}$), 7.47–7.54 (m, 5H), 7.58 (d, 2H, $J=8.5\text{ Hz}$), 7.95 (d, 2H, $J=8.5\text{ Hz}$), 8.23 (d, 1H, $J=6.9\text{ Hz}$)], a singlet at 8.45 (1H) which decreased in intensity in the presence of D_2O as well as a triplet at 9.18 (1H, $J=5.9\text{ Hz}$) exchangeable with D_2O . These data led to the formulation of this compound as **5a** and suggested that it existed as an enol form with an intramolecular hydrogen bond between the enol hydroxyl group and the nitrogen of the pyridine ring.

In order to confirm the generality of this reaction, other 4-(benzoylaminomethyl)pyridine 1-oxides **1b–f** were treated with indan-1,3-dione in the presence of acetic anhydride to give **4** and **5b–f** (Tables I–IV).

The formation of **4** and **5** may occur through the two courses (A) and (B) formulated in Chart 3. The initial step involves acetylation of the *N*-oxide function to form **6** which, in course (A) would form the anhydribase **7** to give the intermediate **3**.⁸⁾ Reaction of **3** with indan-1,3-dione affords **8**, which, by a simple autoxidation process would give rise to **4**. The formation of **5** should be considered to proceed by the addition–elimination mechanism in the usual way as shown in course B.

Experimental

Melting points were measured with a Büchi apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 781 spec-

trophotometer. $^1\text{H-NMR}$ spectra were recorded on Varian T-60A (60 MHz) and Bruker AM (200 MHz) spectrometers using tetramethylsilane (TMS) as an internal standard.

4-(Benzoylaminomethyl)pyridine 1-Oxides (1a–f) These compounds were obtained according to the reported method.⁹⁾

Reaction of 4-(Benzoylaminomethyl)pyridine 1-Oxides (1a–f) with Indan-1,3-dione: General Procedure A suspension of the appropriate 1-oxide **1a–f** (0.01 mol) and indan-1,3-dione (0.01 mol) in acetic anhydride (10 ml) was heated at 100°C for 8 h. The reaction mixture was left overnight at room temperature and the solvent was evaporated off under reduced pressure. The resulting oil was treated with ethanol to give a mixture of compounds **4** and **5**, which were purified by fractional recrystallization from ethanol.

Acknowledgment The authors are grateful to Universidad Complutense, Madrid, and to C.I.C.Y.T. for financial support (Projects N° UCP009/87 and FAR88-0514).

References

- 1) M. F. Braña and M. L. López Rodríguez, *J. Heterocycl. Chem.*, **18**, 869 (1981).
- 2) M. F. Braña, J. M. Castellano, and M. L. López Rodríguez, *J. Heterocycl. Chem.*, **20**, 1723 (1983).
- 3) M. F. Braña, J. Dotor, J. M. Castellano, and M. L. López Rodríguez, *Real Academia de Ciencias Exactas, Físicas y Naturales de Madrid*, **78**, 367 (1984).
- 4) M. F. Braña, M. L. López Rodríguez, C. Rodríguez, and A. Garrido-Pertierra, *J. Heterocycl. Chem.*, **23**, 1019 (1986).
- 5) M. F. Braña, J. M. Castellano, M. C. Redondo, and J. Esplagues, *J. Heterocycl. Chem.*, **24**, 741 (1987).
- 6) M. F. Braña, J. M. Castellano, M. C. Redondo, and M. J. R. Yunta, *J. Heterocycl. Chem.*, **24**, 833 (1987).
- 7) M. F. Braña, M. L. López Rodríguez, P. Fernandez, and A. Garrido-Pertierra, *J. Heterocycl. Chem.*, in press.
- 8) M. F. Braña, J. M. Castellano, R. Donoso, M. L. López Rodríguez, and M. J. R. Yunta, *J. Heterocycl. Chem.*, **25**, 119 (1988).
- 9) M. F. Braña, M. L. López Rodríguez, J. Garrido, and C. M. Roldan, *J. Heterocycl. Chem.*, **18**, 1305 (1981).