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

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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 acids[6] and 1,3-diphenyl-1,3-propanedione[7] 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-oxide[9] (**1a**) with indan-1,3-dione in the presence of acetic anhydride afforded 2-(4-chlorobenzoylamino-4-pyridylmethylene)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 $C_{22}H_{13}ClN_2O_3$. 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 (^{1}H-NMR, 200 MHz) spectrum in dimethyl sulfoxide-d_6 (DMSO-d_6)/CF_3COOH showed twelve aromatic protons and indicated the presence of two AA′BB′

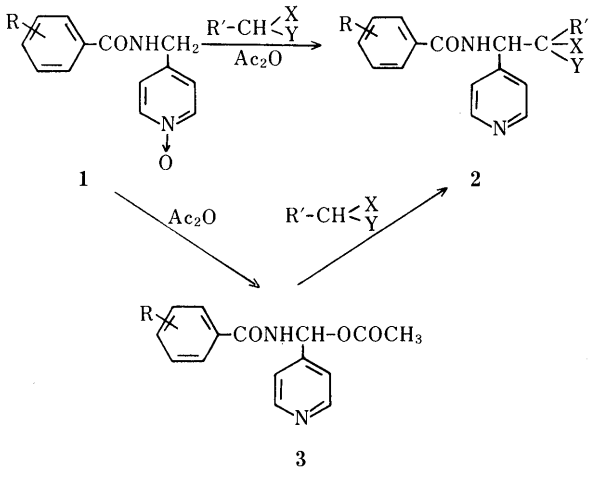

Chart 1

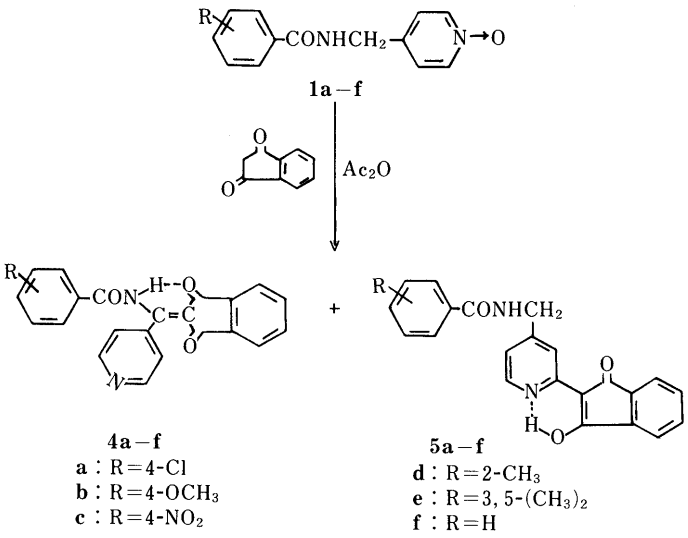

Chart 2

TABLE I. Physical Properties of **4**

Compd.	R	Yield (%)	mp (°C)[a]	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
4a	4-Cl	25	218—220	$C_{22}H_{13}ClN_2O_3$	67.97	3.34	7.20	68.10	3.49	7.11
4b	4-OCH_3	27	194—196	$C_{23}H_{16}N_2O_4$	71.89	4.16	7.29	71.75	4.20	7.37
4c	4-NO_2	38	208—209	$C_{22}H_{13}N_3O_5$	66.16	3.28	10.52	66.00	3.17	10.32
4d	2-CH_3	21	256—258	$C_{23}H_{16}N_2O_3$	75.01	4.34	7.60	75.10	4.40	7.74
4e	3,5-$(CH_3)_2$	32	304—306	$C_{24}H_{18}N_2O_3$	75.37	4.74	7.32	75.66	4.85	7.34
4f	H	25	284—285	$C_{22}H_{14}N_2O_3$	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 C	Calcd H	Calcd N	Found C	Found H	Found N
5a	4-Cl	40	>310	$C_{22}H_{15}ClN_2O_3$	67.60	3.86	7.17	67.90	4.10	7.19
5b	4-OCH_3	51	295—296	$C_{23}H_{18}N_2O_4$	71.49	4.69	7.25	71.24	4.89	7.46
5c	4-NO_2	60	277—278	$C_{22}H_{15}N_3O_5$	65.83	3.76	10.47	65.67	3.58	10.34
5d	2-CH_3	46	>300	$C_{23}H_{18}N_2O_3$	74.57	4.89	7.56	74.85	5.20	7.81
5e	3,5-$(CH_3)_2$	58	>300	$C_{24}H_{20}N_2O_3$	74.98	5.24	7.28	74.83	5.48	7.14
5f	H	49	279—280	$C_{22}H_{16}N_2O_3$	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} ν_{NH}[a]	ν_{CO}	ν_{amide} I	ν_{amide} II	^{1}H-NMR (DMSO-d_6/CF_3CO_2H)[b] δ
4a	4-Cl	3200	1715 1690	1650	1570	7.48 (d, 2H, H_3,H_5-py, J=6.0 Hz), 7.71 (d, 2H, H_3,H_5-ph, J=8.5 Hz), 7.87 (s, 4H, ind.), 7.99 (d, 2H, H_2,H_6-ph, J=8.5 Hz), 8.67 (d, 2H, H_2,H_6-py, J=6.0 Hz)
4b	4-OCH_3	3200	1715 1690	1650	1575	2.65 (s, 3H, OCH_3), 7.47 (d, 2H, H_3,H_5-py, J=5.9 Hz), 7.71 (d, 2H, H_3,H_5-ph, J=8.6 Hz), 7.86 (s, 4H, ind.), 7.97 (d, 2H, H_2,H_6-ph, J=8.6 Hz), 8.66 (d, 2H, H_2,H_6-py, J=5.9 Hz)
4c	4-NO_2	3300	1715 1700	1650	1565	7.0—8.10 (m, 10H, 4H-ph, 4H-ind, H_3,H_5-py), 8.70 (d, 2H, H_2,H_6-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, H_3,H_5-py), 7.60 (s, 4H, ind), 8.40 (d, 2H, H_2,H_6-py, J=6.0 Hz)
4e	3,5-$(CH_3)_2$	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, H_3,H_5-py, J=6.0 Hz), 8.90 (d, 2H, H_2,H_6-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, H_3,H_5-py, J=6.0 Hz), 8.90 (d, 2H, H_2,H_6-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} ν_{NH}	ν_{OH}[a]	ν_{CO}	ν_{amide} I	ν_{amide} II	^{1}H-NMR (DMSO-d_6)[b] δ
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, H_3 and H_5-pyridine, J=6.0 Hz), 7.71 (d, 2H, H_3 and H_5-phenyl, J=8.5 Hz), 7.99 (d, 2H, H_2 and H_6-phenyl, J=8.5 Hz), 8.67 (d, 2H, H_2 and H_6-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.

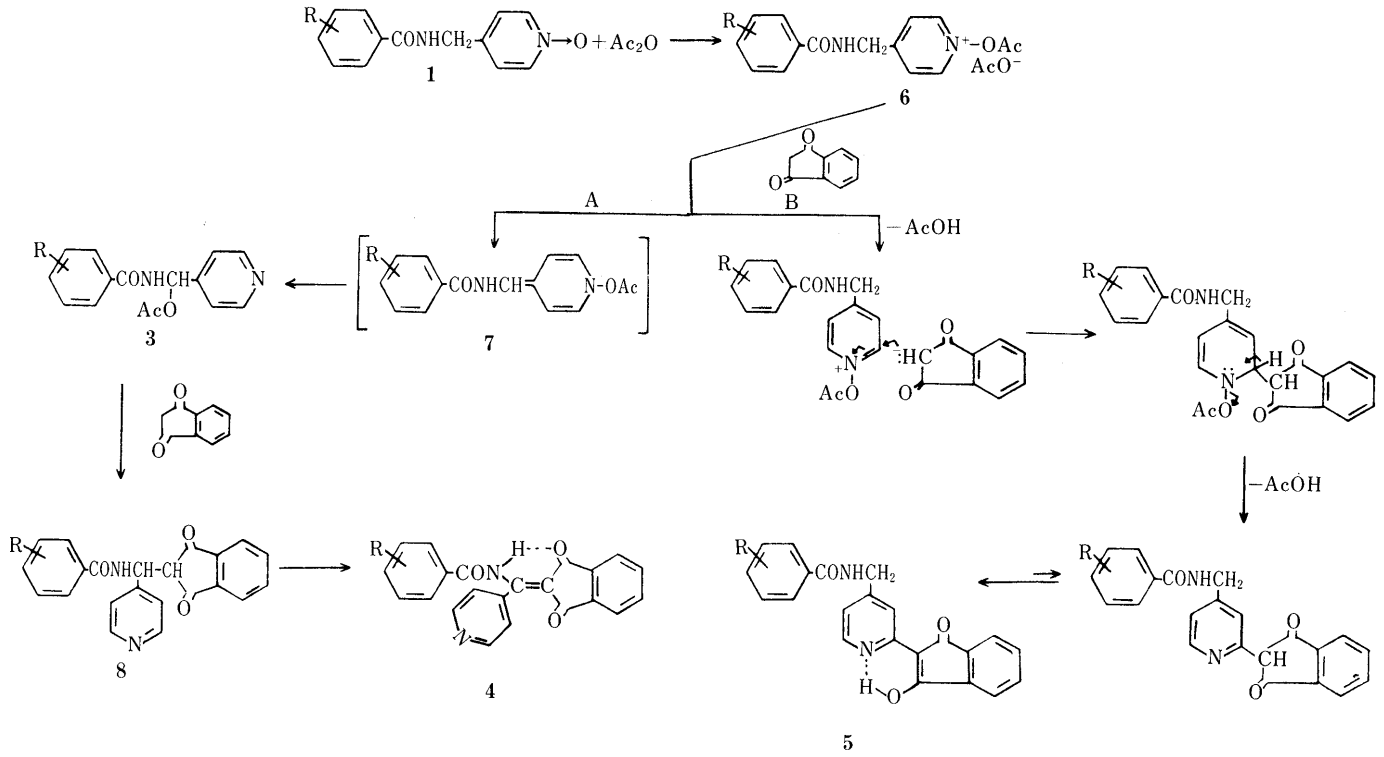

Chart 3

Compound **5a**, mp >310 °C, has the molecular formula $C_{22}H_{15}ClN_2O_3$. The IR spectrum displayed a broad absorption in the 3100 cm^{-1} region and showed amide group [3300, 1635 (I) and 1570 (II) cm^{-1}] and carbonyl (1670 cm^{-1}) absorptions. The ^{1}H-NMR (DMSO-d_6, 200 MHz) spectrum showed the signals of a methylene moiety (δ: 4.56, J=5.9 Hz), eleven aromatic protons [δ: 7.07 (d, 1H, J=6.9 Hz), 7.47—7.54 (m, 5H), 7.58 (d, 2H, J=8.5 Hz), 7.95 (d, 2H, J=8.5 Hz), 8.23 (d, 1H, J=6.9 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 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 anhydrobase **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 spectrophotometer. ^{1}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.

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