Heterocyclic Synthesis with *N*-Oxides. Preparation of Pyridine *N*-Oxide Substituted Chromones, Chromanones, Coumarins, Quinolones, Dihydroquinolones and Cinnolones

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The synthesis of pyridine *N*-oxide substituted chromones, chromanones, coumarins, quinolines, dihydroquinolines and cinnolines from 1-(2-hydroxyphenyl)-2-(2-pyridinyl)ethanone *N*-oxide, 1-(2-aminophenyl)-2-(2-pyridinyl)ethanone *N*-oxide and 1-[2-(methylamino)phenyl]-2-(2-pyridinyl)ethanone *N*-oxide is described.

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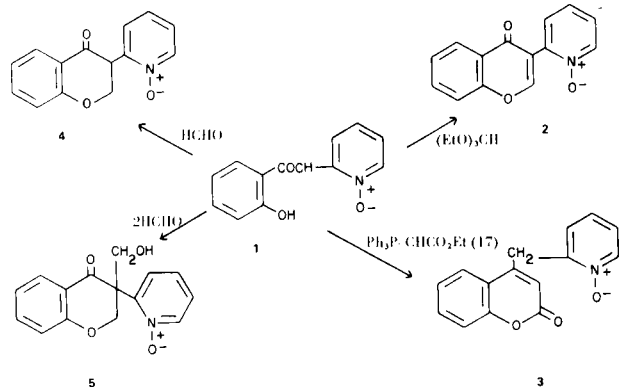
The synthesis of various heterocyclic systems from *o*-substituted-ω-(methylsulfinyl)acetophenones was previously described (1, 2, 3 and 4). As an extension of this work, an investigation of the corresponding *N*-oxides was undertaken. The present study deals with the cyclization reactions of pyridine *N*-oxide intermediates (**1**, **8** and **13**) (5) to give 3-substituted-chromone (**2**), chromanones (**4** and **5**), coumarin (**3**), quinolones (**7** and **15**), dihydroquinolones (**9** and **10**) and cinnolone (**16**), which may possess antiallergy (6) or CNS (7) activity.

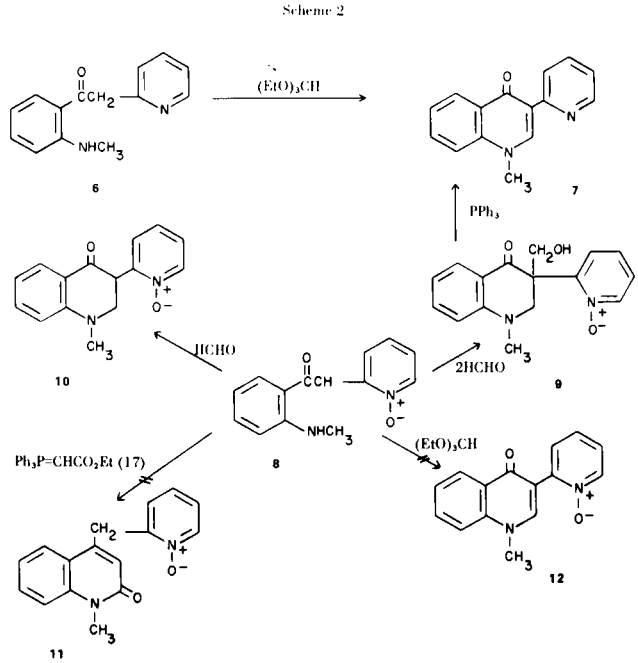
Scheme 1



N-Oxide (**1**) reacted with the various reagents (Scheme 1) in an analogous manner to *o*-hydroxy-ω-(methylsulfinyl)acetophenone. Compound **1** was converted to chromanones (**4** and **5**) with 1 or 2 moles of formaldehyde and gave chromone derivative (**2**) with triethylorthoformate. The reaction of **1** with (carbethoxymethylene)-triphenylphosphorane (**17**) was much slower than the corresponding reaction with *o*-hydroxy-ω-(methylsulfinyl)-acetophenone. This reflects the greater bulk of the pyridine *N*-oxide moiety as compared to the methylsulfinyl group, for the attack of the carbanion on the carbonyl carbon is known to be the slow step (8) in the reaction of carbonyl groups with resonance stabilized ylids.

The reactions of aminoketo *N*-oxide (**8**) are shown in Scheme 2. Compound **8** failed to react with triethyl-

Scheme 2

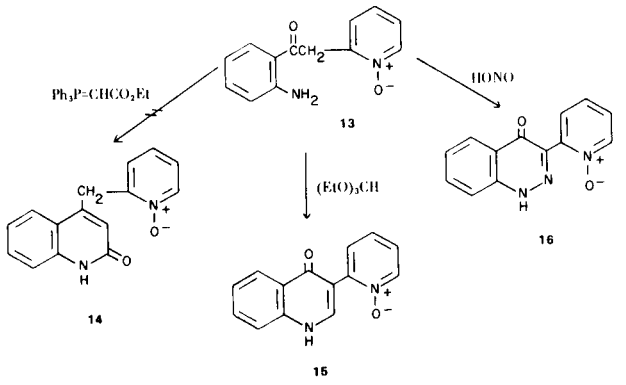


orthoformate to give quinolone (**12**) and with ylid (**17**) to give carbostyril (**11**). The failure to obtain **11** is not unexpected for the carbonyl group of **8** is deactivated, electronically by the *o*-amino group as well as sterically by the pyridine *N*-oxide moiety, towards attack by carbanion (**17**). Compound **8** reacted with 1 mole of formaldehyde to give 2,3-dihydroquinolone (**10**) and with 2 moles to give 2,3-dihydroquinolone (**9**). An attempt to reduce *N*-oxide (**9**) to 2,3-dihydro-3-(hydroxymethyl)-1-methyl-3-(2-pyridinyl)-4(1*H*)quinolinone with triphenylphosphine resulted in the elimination of the elements of methanol giving quinolone (**7**). To confirm the structure, **7** was also prepared by the reaction of aminoketone (**6**) with triethylorthoformate.

Aminoketone (**13**) failed to react with ylid (**17**) but reacted with triethylorthoformate and nitrous acid to give quinolone (**15**) and cinnolone (**16**), respectively.

The broad scope of pyridine *N*-oxide chemistry (*9*) makes the above compounds useful intermediates for further synthetic elaboration. The chemistry of the pyridine *N*-oxide groups in the various heterocycles described above is currently being investigated in this laboratory.

Scheme 3



EXPERIMENTAL

Melting points were measured with a Thomas-Hoover capillary melting point apparatus without correction. Nmr spectra were recorded on a Perkin-Elmer R 12 B spectrometer at 60 MH_Z with TMS as internal standard. Infrared spectra were recorded on a Beckmann IR-18A spectrometer. Ultraviolet spectra were recorded on a Beckmann DK-I spectrometer. Mass spectra were obtained with an AEI MS-902 instrument.

3-(2-Pyridinyl)-4*H*-1-benzopyran-4-one *N*-Oxide (**2**).

A mixture of 1-(2-hydroxyphenyl)-2-(2-pyridinyl)ethanone *N*-oxide (10 g., 0.043 mole), triethylorthoformate (15 ml.), piperidine (5 ml.) and pyridine (60 ml.) was refluxed under nitrogen for 20 hours, cooled, and the product was filtered off. Recrystallization from DMF gave white crystals (4.0 g., 38.4%), m.p. 242-245°; uv (ethanol): λ max (ε) 252 (10,900), 262 (11,000), 290 (9,700), 362 (19,900); ir (Nujol): 1705 (CO), 1260 cm^{-1} (N→O); nmr (DMSO): δ 9.3-7.1 (m, 9, ArH).

Anal. Calcd. for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86. Found: C, 70.25; H, 3.90; N, 6.02.

4-(2-Pyridinylmethyl)-2*H*-1-benzopyran-2-one *N*-Oxide (**3**).

A mixture of 1-(2-hydroxyphenyl)-2-(2-pyridinyl)ethanone *N*-oxide (9.0 g., 0.039 mole) and (carbethoxymethylene)triphenylphosphorane (13.7 g., 0.039 mole) in dioxane (80 ml.) was refluxed under nitrogen for 24 hours. (Carbethoxymethylene)-triphenylphosphorane (6.9 g.) was added and refluxing was continued for a further 16 hours. The mixture was cooled and the product filtered off. Recrystallization from DMF gave white crystals (5.4 g., 54%), m.p. 211-214°; uv (ethanol): λ max (ε) 214 (41,100), 266 (18,000); ir (Nujol): 1725 (CO), 1260 cm^{-1} (N→O); nmr (deuteriochloroform): δ 8.5-7.1 (m, 8, ArH), 6.21 (s, 1, C_3H), 4.49 (s, 2, CH_2).

Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.37; N, 5.53. Found: C, 71.18; H, 4.59; N, 5.57.

2,3-Dihydro-3-(2-pyridinyl)-4*H*-1-benzopyran-4-one *N*-Oxide (**4**).

A mixture of 1-(2-hydroxyphenyl)-2-(2-pyridinyl)ethanone *N*-oxide (17.6 g., 0.076 mole) and 36% aqueous formaldehyde (5.85 g., 0.065 mole) in pyrrolidine (2 ml.) and methanol (200 ml.) was refluxed under nitrogen for 5 hours, cooled, and the product was filtered off. Recrystallization from absolute ethanol gave white crystals (5.4 g., 28%), m.p. 186-187°; uv (ethanol): λ max (ε) 215 (36,300), 256 (15,100), 315 (2,500); ir (Nujol): 1680 (CO), 1260 cm^{-1} (N→O); nmr (deuteriochloroform): δ 8.5-6.9 (m, 8, ArH), 5.18-4.58 (m, 3, C_2H_2 and C_3H).

Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.59; N, 5.80. Found: C, 69.64; H, 4.70; N, 5.84.

2,3-Dihydro-3-(hydroxymethyl)-3-(2-pyridinyl)-4*H*-1-benzopyran-4-one *N*-Oxide (**5**).

A mixture of 1-(2-hydroxyphenyl)-2-(2-pyridinyl)ethanone *N*-oxide (30 g.) and 36% aqueous formaldehyde (90 g.) in pyrrolidine (3 ml.) and methanol (200 ml.) was refluxed under nitrogen for 20 hours, cooled, and the product was filtered off. Recrystallization from absolute ethanol gave white crystals (28.8 g., 81%), m.p. 184-186°; uv (ethanol): λ max (ε) 215 (37,200), 256 (13,500), 319 (3,100); ir (Nujol): 3280 (OH), 1675 (CO), 1233 cm^{-1} (N→O); nmr (deuteriochloroform): δ 8.4-6.8 (m, 8, ArH), 5.23 (d, 1, J = 11 Hz, C_2H), 4.37 (d, 1, J = 11 Hz, C_2H), 4.29 (s, 2, CH_2), 3.35 (b.s., 1, OH, exchanges with deuterium oxide).

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.32; H, 4.94; N, 5.09.

2,3-Dihydro-3-(hydroxymethyl)-1-methyl-3-(2-pyridinyl)-4(1*H*)-quinolinone *N*-Oxide (**9**).

A mixture of 1-[2-(methylamino)phenyl]-2-(2-pyridinyl)-ethanone *N*-oxide (15 g., 0.062 mole), 36% aqueous formaldehyde (41 g., 0.49 mole), pyrrolidine (2 ml.) and methanol (150 ml.) was refluxed under nitrogen for 30 hours, cooled, and the product was filtered off. Recrystallization from ethanol gave green-yellow crystals (8.5 g., 50%), m.p. 198-200°; uv (ethanol): λ max (ε) 214 (28,000), 238 (29,700), 263 (17,000), 385 (4,000); ir (Nujol): 3350 (OH), 1660 (CO), 1230 cm^{-1} (N→O); nmr (deuteriochloroform): δ 8.3-6.5 (m, 8, ArH), 4.64 (d, 1, J = 12 Hz, C_2H), 4.23 (s, 2, CH_2), 3.86 (b.s., 1, OH, exchanges with deuterium oxide), 3.30 (d, 1, J = 12 Hz, C_2H), 2.92 (s, 3, CH_3).

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.58; H, 5.69; N, 9.84.

2,3-Dihydro-1-methyl-3-(2-pyridinyl)-4(1*H*)quinolinone *N*-Oxide (**10**).

A mixture of 1-[2-(methylamino)phenyl]-2-(2-pyridinyl)-ethanone *N*-oxide (16 g., 0.066 mole), 36% aqueous formaldehyde (4.96 g., 0.059 mole), pyrrolidine (4 ml.) and methanol (100 ml.) was refluxed under nitrogen for 50 minutes. The solvents were removed under reduced pressure to give a gum, which crystallized on standing. Recrystallization from 2-propanol gave green-yellow crystals (10.45 g., 62%), m.p. 132-134°; uv (ethanol): λ max (ε) 214 (25,100), 238 (30,800), 262 (18,200), 384 (4,100); ir (Nujol): 1673 (CO), 1234 cm^{-1} (N→O); nmr (deuteriochloroform): δ 8.5-6.6 (m, 8, ArH), 4.92 (q, 1, C_2H), 3.78 (m, 2, C_2H and C_3H), 3.04 (s, 3, CH_3).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.67; H, 5.63; N, 11.02.

1-Methyl-3-(2-pyridinyl)-4(1*H*)quinolinone (**7**) from **9**.

An intimate mixture of 2,3-dihydro-3-(hydroxymethyl)-1-methyl-4(1*H*)quinolinone *N*-oxide (4.0 g.) and triphenylphosphine (3.7 g.) was heated (Woods metal bath) at 240-250° for 40 minutes, cooled and dissolved in chloroform. The chloroform solution was extracted with 1*N* hydrochloric acid (4 x 25 ml.). The product, which crystallized out of the aqueous solution, was filtered, dried and recrystallized from ethanol to give 1-methyl-3-(2-pyridinyl)-4(1*H*)quinolinone hydrochloride (2.46 g., 65%).

A solution of the hydrochloride salt in aqueous ammonium hydroxide was extracted with chloroform. The extracts were dried (sodium sulfate) and evaporated to give the free base. Recrystallization from ethyl acetate gave yellow crystals, m.p. 133-135°; uv (ethanol): λ max (ε) 227 (24,900), 264 (18,000), 329 (17,200); ir (Nujol): 1630 cm^{-1} (CO); nmr (deuteriochloroform): δ 8.9-7.0 (m, 9, ArH), 3.89 (s, 3, CH_3).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 75.97; H, 5.25; N, 11.78.

1-Methyl-3-(2-pyridinyl)-4(1*H*)quinolinone (**7**) from **6**.

A mixture of 1-[2-(methylamino)phenyl]-2-(2-pyridinyl)-ethanone (0.4 g.), triethylorthoformate (1.0 ml.), piperidine (1 ml.) and pyridine (4 ml.) was refluxed under nitrogen for 23 hours. The solvents were removed under reduced pressure to give an oil, which crystallized on standing. Recrystallization from ethyl acetate gave yellow crystals (0.17 g., 46%), m.p. 133-135°. Analytical and spectral data were identical to those described for **7** above.

3-(2-Pyridinyl)-4(1*H*)quinolinone *N*-Oxide (**15**).

A mixture of 1-[2-aminophenyl]-2-(2-pyridinyl)ethanone *N*-oxide (2.0 g.), triethylorthoformate (2.5 ml.), piperidine (1.5 ml.) and pyridine (20 ml.) was refluxed under nitrogen for 20 hours, cooled, and the product was filtered off. Recrystallization from DMF gave white crystals (0.9 g., 43%), m.p. > 300° dec.; uv (ethanol): λ max (ε) 228 (26,700), 263 (16,700), 331 (11,900); ir (Nujol): 3400 (N-H), 1640 (CO), 1200 cm^{-1} (N→O); nmr (TFA): δ 9.0-7.6 (aromatic protons).

Mass spectrum: observed molecular ion 238.0788; calculated for $C_{14}H_{10}N_2O_2$ 238.0742.

3-(2-Pyridinyl)-4(1*H*)cinnolinone *N*-Oxide (**16**).

A mixture of 1-[2-aminophenyl]-2-(2-pyridinyl)ethanone *N*-oxide (2.0 g.), water (40 ml.) and 1*N* hydrochloric acid (10.5 ml.) was cooled to 5° with an ice-salt bath. A cold solution of sodium nitrite (0.726 g.) in water (6 ml.) was slowly added to the mixture maintaining the temperature at 5°. The mixture was allowed to come to 20° and then stirred for 20 minutes. The product was filtered off and washed in succession with water, 2-propanol and ethyl ether. Recrystallization from DMF gave white crystals (1.33 g., 63%), m.p. > 315° dec.; uv (ethanol): λ max (ε) 214 (36,200), 263 (15,000), 338 (13,300), 353 (11,700); ir (Nujol): 1215 cm^{-1} (N→O); nmr (TFA): δ 8.8-7.7 (aromatic protons).

Mass spectrum: observed molecular ion 239.0632; calculated for $C_{13}H_9N_3O_2$ 239.0695.

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