The Synthesis of Pyridine Derivatives from 3-Formylchromone

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3-Formylchromone (**1**) reacts with active methylene derivatives to yield condensation products **2a-d**, **10**, **11** and **12**. Treatment of **2a-d** with ammonia or methylamine gives pyridines **3-6**. Alternatively, reaction of **1** with enamine derivatives yields pyrido compounds **15**, **17**, **19**, **21**, **23** and **28** in one step. Factors determining the formation and regiospecificity of the pyridine ring forming reactions are also discussed.

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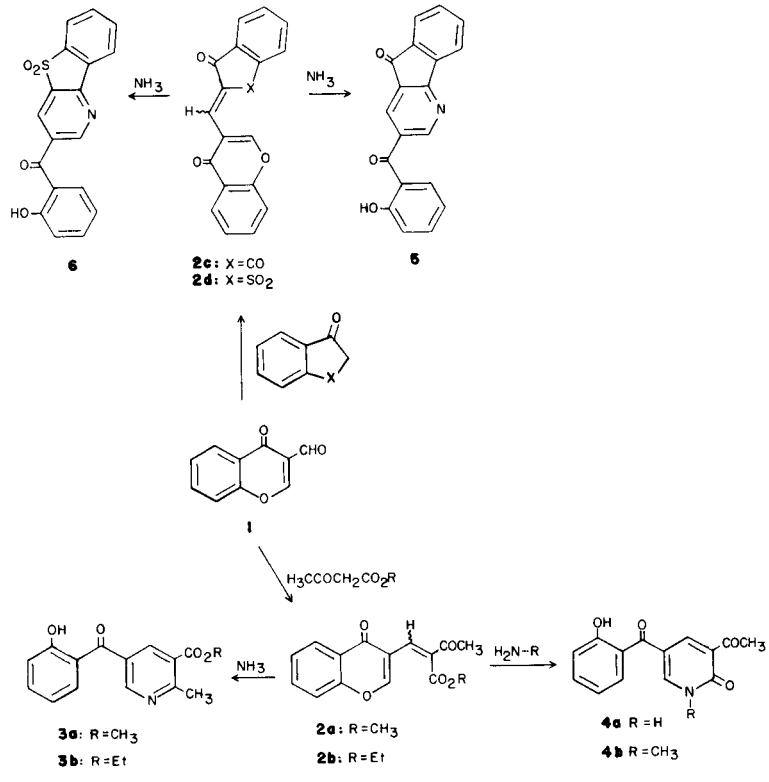
Since becoming readily available (1), 3-formylchromone (**1**) has been used to prepare a variety of heterocyclic systems (2). As a susbtrate, **1** contains three potential sites of nucleophilic attack: C-2, C-4 and the 3-formyl group. Condensation of a suitable reactant at two of these sites leads to formation of a new ring system. In this report we describe the preparation of a number of pyridine and pyrido derivatives starting from **1**.

Two methods were used to prepare the pyridine containing products. As summarized in Scheme 1, one method involves condensation of **1** with active methylene derivatives followed by reaction of this intermediate product with ammonia to give pyridine compounds **3-6**. The reaction proceeds as outlined in Scheme 2. Initially, an active methylene derivative condenses with the 3-formyl group of **1** to yield **2**. Subsequent reaction of **2** with ammonia leads *via* imine **7b** or enamide **7c** to formation of the pyridine product **8**.

Particular examples of this method are outlined in Scheme 1. The details of the condensation reaction are summarized in Table 1. These reactions were carried out in pyridine or with sodium acetate in acetic anhydride and the condensation products were obtained in 37-92% yield. The details of the pyridine forming step are listed in Table 2. These reactions were carried out in aqueous alcoholic ammonia or methylamine and the products were isolated in 32-89% yield. Structural assignments were based on nmr, ir and mass spectral data (see discussion below).

For condensation products **2a** and **2b**, treatment with ammonia gave the expected pyridines **3a** and **3b** as well as minor amounts of the pyridone **4a**. However, reaction of **2b** with methylamine gave only pyridone **4b** which arises



Scheme 1. Pyridine derivatives from **1** by reaction with active methylene derivatives.

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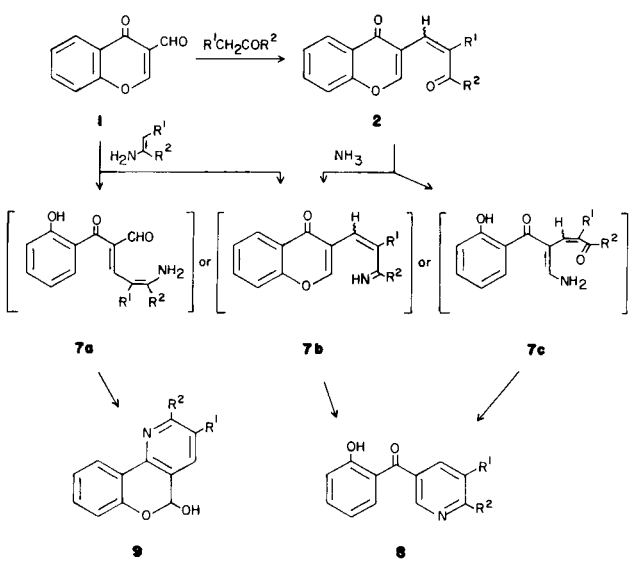
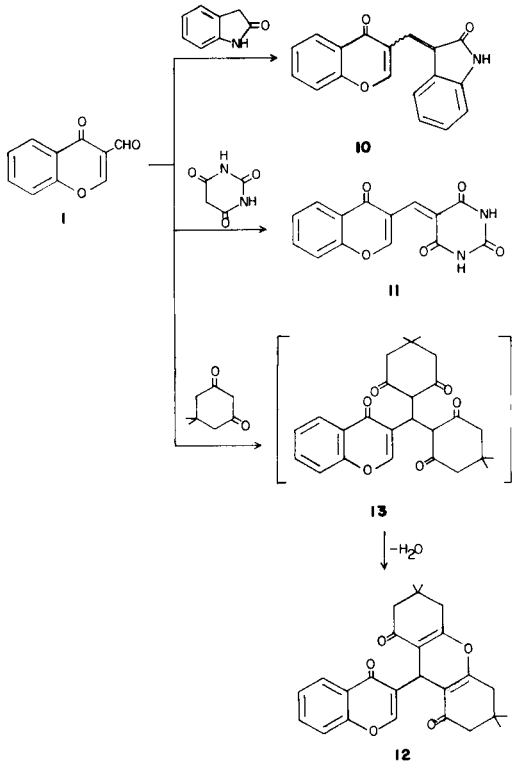
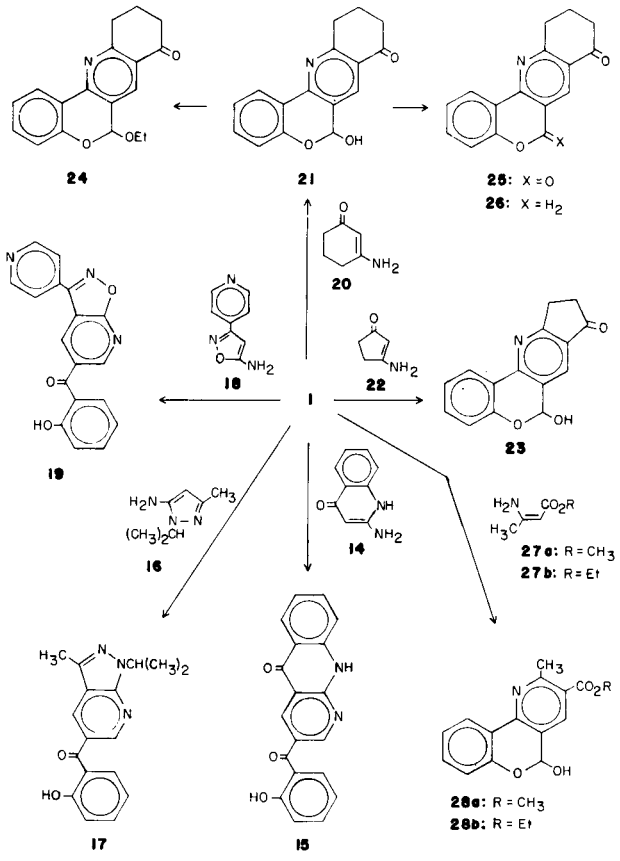


Scheme 2. Possible mechanism for formation of pyridine derivatives from **1**.



Scheme 3. Condensation products of **1** with active methylene derivatives that did not cyclize with ammonia.

from cyclization at the ester rather than at the ketone group (4). Since the product of attack of methylamine at the ketone carbonyl would yield a methyl pyridinium salt, pyridone **4b** represents the more stable and irreversibly



Scheme 4. Pyridine derivatives from **1** by reaction with enamine derivatives.

formed product, probably arising *via* an enamide intermediate analogous to **7c**.

Pyridine **3a**, prepared by condensation of **1** with methyl acetoacetate followed by treatment of this product with ammonia, is isomeric to pyridine **28a**, which was reported to form in the reaction of **1** with methyl 3-aminocrotonate (5). Each of these reactions as well as the reactions leading to the corresponding ethyl ester analogs **3b** and **28b** were carried out and scrutinized for the presence of the other pyridine isomer in each reaction mixture. For each pair of reactions, no other pyridine isomer was detected in either reaction mixture by analytial thin layer chromatography using 9:1 chloroform-methanol or chloroform (two elutions) and by proton nmr. Thus it is possible to prepare either pyridine isomer from **1** by proper selection of reagent and reaction conditions. Also, having the two possible pyridine isomers on hand provides additional support for the assignment of the structures of **3-6**.

Several condensation products of **1** with active methylene derivatives failed to cyclize in the presence of ammonia under our reaction conditions. Condensation of **1** with oxindole, barbituric acid and dimedone gave adducts **10, 11** and **12** respectively (Scheme 3). Treatment

Table 1

Condensation Products of **1** with Active Methylene Derivatives

Reactant	Reaction Conditions Conditions	Condensation Product	Yield (%)	M.p. (°C)
$H_3CCOCH_2CO_2CH_3$	sodium acetate-acetic anhydride	**2a**	37	147-149
$H_3CCOCH_2CO_2C_2H_5$	pyridine	**2b**	49	123-125 (a)
indan-1,3-dione	pyridine	**2c**	92	272-274
3-oxo-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide	pyridine	**2d**	62	242-243
oxindole	pyridine	**10**	64	249-250
barbituric acid	pyridine	**11**	94	290-292-
dimedone	pyridine	**12**	73	287-288

(a) Lit. (2a) m.p. 120-122°.

Table 2

Pyridine Derivatives by Reaction of **2a-d** with Ammonia or Methylamine

Reactant	Pyridine Product	Yield (%)	M.p. (°C)
2a	**3a**	32	79-81
	4a	11	182-185
2b	**3b**	52	66-67
	4a	6	182-185
2b	**4b**	35	157-158
2c	**5**	81	178-179
2d	**6**	89	218-220

of each of these products with ammonia resulted in recovery of starting material. In contrast to the ketone carbonyls described above, it appears that the amide carbonyls of **10** and **11** as well as the vinylogous ester carbonyl of **12** are not sufficiently electrophilic to react with ammonia. Compound **13**, a 2:1 adduct of dimdeone with **1**, has been reported to be formed in aqueous ethanol under piperidine catalysis (6). Under our conditions, reaction in pyridine followed by recrystallization from ethanol containing hydrochloric acid, concomitant dehydration of **13** occurred to yield the observed product **12**. Similar dehydration products of dimedone and aromatic or α,β-unsaturated aldehydes have been reported earlier (7).

Another method for the preparation of pyridine compounds from **1** was also explored. As shown in Scheme 4, reaction of **1** with enamine derivatives **14, 16, 18, 20, 22** and **27** led in one step to the fused pyridine derivatives **15, 17, 19, 21, 23** and **28** respectively. The reaction details are summarized in Table 3. The reactions were carried out in pyridine or glacial acetic acid and the products were isolated in 46-82% yield. The mechanism probably follows a course similar to that previously described in Scheme 2 for the two step procedure. In this case, *C*-condensation of an enamine at the 3-formyl group of **1** gives **7b**. Alternatively, attack of the enamine at the C-2 position of **1** yields **7a**. Under the reaction conditions, intermediates **7a** and **7b** then cyclize to the pyridine derivatives **9** or **8**. The structures are supported by nmr, ir and mass spectral data.

Considering the compounds prepared by both methods, the nmr spectra show the presence of the C*H*OH hydrogen of **21, 23** and **28a,b** at δ 6.52-6.57 but its absence in the spectra of the other pyridine derivatives. In addition, **3-6, 15, 17** and **19** clearly exhibit two meta coupled aromatic protons on a pyridine ring whereas **21, 23** and **28a,b** have only singlets for the lone pyridine proton ranging from δ 8.02-8.19. Also for **3-6, 15, 17** and **19**, the ir spectra have typical apsorptions for the salicylyl group at 3050-3300, 1630-1640 and 1590-1600 cm^{-1}. In the mass spectrum, a

Table 3

Pyridines from **1** and Enamine Derivatives

Reactant	Reaction Conditions	Pyridine Product	Yield (%)	M.p. (°C) or B.p. (°C) (mm)
14	acetic acid	**15**	65	314 dec.
16	acetic acid	**17**	46	160-162 (0.010)
18	acetic acid	**19**	74	197-198
20	pyridine	**21**	82	218-221
22	pyridine	**23**	59	230 dec.
27a	DMF (5)	**28a**	32	231-233
27b	DMF (5)	**28b**	42	200-203

peak at 121 for the salicylyl cation was evident for **3-6, 15, 17** and **19**.

For pyridines **15, 17** and **19**, even if the orientation of attack of nucleophiles **14, 16** and **18** respectively on **1** took place in the reverse manner, the product obtained would be the same due to the "chemical symmetry" of the 3-formyl group and C-2 of **1**. Pyridines **15, 17** and **19** result from amine attack at C-2 of **1** whereas pyridines **21** and **23** as well as the reported pyridine **28a**, which was prepared by the literature method along with **28b** (5), were formed by amine attack at C-4 of **1**. It is apparent that the relative basicity of the amino group in the intermediate condensation product plays a key role in determining the regioselectivity of the pyridine forming step.

The structure of **21** was further supported by ketalization to ethoxy analog **24**, by oxidation to lactone **25**, and by reduction to ether **26**.

In summary, we have found that a variety of pyridine derivatives are readily accessible starting with 3-formylchromone (**1**). Reaction of **1** with an active methylene derivative and then ammonia or with an enamine derivative leads to substituted or fused pyridines that would not be readily available by other means.

EXPERIMENTAL

Melting points were taken on a Büchi melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 157 spectrophotometer. Proton nmr spectra were determined on a Varian HA 100 or T 60. Chemical shifts are in δ units (in parts per million relative to tetramethylsilane as internal standard). Splitting patterns are designated s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Coupling constants are given in hertz. Column chromatography was performed on Merck silica gel 60, mesh size 70-238. Mass spectra were taken on a Varian CH-7 mass spectrometer.

2-Acetyl-3-(3-chromonyl)acrylic Acid Methyl Ester (**2a**) (2a).

3-Formylchromone (**1**) (17.4 g., 100 mmoles), sodium acetate (8.2 g., 100 mmoles), acetoacetic acid methyl ester (11.6 g., 100 mmoles) and 50 ml. of acetic anhydride were stirred for 2 hours at 100°. The dark solution was poured onto 300 ml. of ice-water and stirred for another 15 minutes. The precipitate was filtered, washed with water, dissolved in methylene chloride, dried (sodium sulfate) and filtered through silica gel using methylene chloride as eluent. Crystallization from methylene chloride-ether-petroleum ether gave yellow crystals (**2a**) (10.1 g., 37%), m.p. 147-149°; nmr (deuteriochloroform): 8.30 (1H, s), 8.20 (1H, dd, J = 8, 2); 7.28-7.8 (4H, m), 3.87 (3H, s), 2.49 (3H, s); ir (dichloromethane): 3030, 2950, 1725, 1700, 1660, 1620, 1575, 1470, 1235, 1220 cm^{-1}.

Anal. Calcd. for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.17; H, 4.44.

2-Acetyl-3-(3-chromonyl)acrylic acid Ethyl Ester (**2b**).

A solution of **1** (35.0 g., 201 mmoles) and ethyl acetoacetate (37.0 g., 284 mmoles) in 200 ml. of pyridine was refluxed for 4 hours. The solvent was rotary evaporated and the residue was slurried with toluene and again rotary evaporated. Recrystallization from benzene-petroleum ether gave yellow crystals (**2b**) (28.2 g., 49%), m.p. 123-125° (2a); nmr (deuteriochloroform): 8.30 (1H, s), 8.22 (1H, dd, J = 8), 7.22-7.80 (4H, m), 4.31 (2H, q, J = 8), 1.50 (3H, s), 1.39 (3H, t, J = 8); ir (dichloromethane): 1700, 1660, 1620 cm^{-1}; ms: m/e 286 (M^+), 243 (M^+ -$COCH_3$).

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.20; H, 4.93. Found: C, 66.92; H, 4.94.

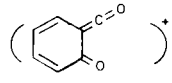
2-(4-Oxo-4*H*-benzopyran-3-ylmethylene)indan-1,3-dione (**2c**).

A solution of **1** (15.0 g., 86.1 mmoles) and indan-1,3-dione (12.6 g., 86.1 mmoles), in 125 ml. of pyridine was stirred at room temperature for 3 hours. The precipitate was collected by filtration and washed with ethanol and then ether. Recrystallization from DMF gave yellow crystals (**2c**) (24.0 g., 92%), m.p. 272-274°; nmr (trifluoroacetic acid): 10.28 (1H, s), 8.52 (1H, s), 7.58-8.48 (8H, m); ir (nujol): 1690, 1660, 1620 cm^{-1}; ms: m/e 302 (M^+), 246.

Anal. Calcd. for $C_{19}H_{10}O_4$: C, 75.50; H, 3.34. Found: C, 75.39; H, 3.35.

2-(4-Oxo-4*H*-benzopyran-3-ylmethylene)-3-oxo-2,3-dihydrobenzo[*b*]thiophene 1,1-Dioxide (**2d**).

To a solution of 3-oxo-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide (8) (2.00 g., 11.0 mmoles) in 10 ml. of pyridine was added 3-formylchromone (**1**) (2.00 g., 11.5 mmoles). The reaction was stirred 6 hours at room temperature. The product was collected by filtration and washed with ethanol followed by ether to give red crystals (**2d**) (2.30 g., 61.8%), m.p. 242-243°; nmr (trifluoroacetic acid): 9.57 (1H, s), 8.72 (1H, s), 7.60-8.60 (8H, m); ir (nujol): 1710, 1670, 1620 cm^{-1}; ms: m/e 274 (M^+ -SO_2), 246, 120



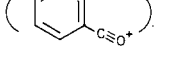
Anal. Calcd. for $C_{18}H_{10}O_5S$: C, 63.90; H, 2.98; S, 9.48. Found: C, 63.91; H, 2.95; S, 9.51.

2-Methyl-5-(2-hydroxybenzoyl)nicotinic Acid Methyl Ester (**3a**) and 3-Acetyl-5-(2-hydroxybenzoyl)-2-pyridone (**4a**).

To the above ester (**2a**) (5.7 g., 21 mmoles) dissolved in 100 ml. of methanol was added 25 ml. of concentrated aqueous ammonia and 200 ml. of water. The reaction was refluxed for 30 minutes and the methanol removed by means of a rotary evaporator. The aqueous portion was extracted by 2 × 100 ml. of chloroform. The combined organic layers were washed with 2 × 100 ml. of water, dried (sodium sulfate) and rotary evaporated to give a reddish oil (4.6 g.). Silica gel column chromatography using ether as eluent gave the ester (**3a**) as yellow crystals (1.8 g., 32%), m.p. 79-81°; nmr (deuteriochloroform): 11.68 (1H, s), 8.88 (1H, d, J = 3), 8.49 (1H, d, J = 3), 7.47-7.64 (2H, m), 6.83-7.13 (2H, m), 3.96 (3H, s), 2.95 (3H, s); ir (dichloromethane): 3010, 2950, 1730, 1630, 1590, 1235, 1085 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.83; N, 5.16. Found: C, 66.36; H, 4.81; N, 5.09.

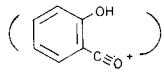
Further elution with ether also gave after crystallisation from acetone-ether (0.60 g. (11%) 3-acetyl-5-(2-hydroxybenzoyl)-2-pyridone (**4a**), yellow crystals, m.p. 182-185°; nmr (DMSO-d_6): 10-13 (2H, s, broad OH and NH), 8.32 (1H, d, J = 3), 8.02 (1H, d, J = 3), 7.28-7.50 (2H, m), 6.85-7.02 (2H, m), 2.57 (3H, s); ir (nujol): 3130-2330 (broad), 1680, 1630, 1220, 752 cm^{-1}; ms: m/e 257 (M^+), 121



Anal. Calcd. for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44. Found: C, 65.12; H, 4.25; N, 5.31.

2-Methyl-5-(2-hydroxybenzoyl)nicotinic Acid Ethyl Ester (**3b**) and 3-Acetyl-5-(2-hydroxybenzoyl)-2-pyridone (**4a**).

A mixture of **2b** (14.31 g., 50.0 mmoles) in 200 ml. of ethanol, 50 ml. of concentrated aqueous ammonia and 400 ml. of water was refluxed for 40 minutes. The ethanol was removed by rotary evaporation and the product was extracted with 3 × 100 ml. of chloroform. The combined organic portions were washed with water, dried (sodium sulfate) and rotary evaporated. Silica gel column chromatography using ether as eluent gave the ester (**3b**) as yellow crystals (7.4 g., 52%), m.p. 66-67°; nmr (deuteriochloroform): 11.74 (1H, s), 8.91 (1H, d, J = 2), 8.51 (1H, d, J = 2), 7.45-7.65 (2H, m), 6.80-7.20 (2H, m), 4.42 (2H, q, J = 7), 2.96 (3H, s),1.46 (3H, t, J = 7); ir (dichloromethane): 3010, 1725, 1590, 1080 cm^{-1}; ms: m/e 285 (M^+), 121



Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.14; H, 5.22; N, 4.80.

Further elution with ether also gave after crystallisation from acetone-ether 0.80 g. (6.2%) 3-acetyl-5-(2-hydroxybenzoyl)-2-pyridone **4a**, yellow crystals, m.p. 182-185°, identical to the minor product isolated from **2a**.

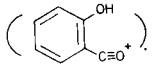
N-Methyl-3-acetyl-5-(2-hydroxybenzoyl)-2-pyridone (**4**).

A suspension of **2b** (9.00 g., 31.4 mmoles) in 40 ml. of 35% aqueous methylamine and 50 ml. of water was stirred for 1 hour at room temperature. The solution was neutralized with 2*N* hydrochloric acid. The cloudy solution was clarified by filtration and the filtrate was acidified with 2*N* hydrochloric acid to *p*H 5. The product (**4**) was collected by filtration. Recrystallization from methylene chloride-ether gave 3.00 g. (32%), m.p. 157-158° nmr (DMSO-d_6): 10.25 (1H, s, OH), 8.67 (1H, d, J = 3), 8.27 (1H, d, J = 3), 7.30-7.56 (2H, m), 6.85-7.09 (2H, m), 3.62 (3H, s), 2.60 (3H, s); ir (dichloromethane): 3100, 1690, 1680, 1640, 1600 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}NO_4$:C, 66.42; H, 4.83; N, 5.16. Found: C, 66.23; H, 4.74; N, 5.33.

3-(2-Hydroxybenzoyl)-5-oxoindano[3,2-*b*]pyridine (**5**).

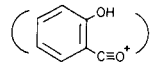
A suspension of **2c** (10.0 g., 33.1 mmoles) in 55 ml. of concentrated aqueous ammonia and 110 ml. of water was refluxed for 1 hour. The reaction was cooled to room temperature. The product was collected by filtration and washed with ethanol and hexane. Recrystallization from chloroform-ethanol gave yellow crystals (**5**) (8.10 g., 81%), m.p. 178-179°; nmr (deuteriochloroform): 11.70 (1H, s), 8.90 (1H, d, J = 2), 8.15 (1H, d, J = 2), 6.80-8.00 (8H, m); ir (dichloromethane): 1730, 1630, 1620, 1600 cm^{-1}; ms: m/e 301 (M^+), 272 (M^+-CO), 121



Anal. Calcd. for $C_{19}H_{11}NO_3$: C, 75.74; H, 3.68; N, 4.65. Found: C, 75.59; H, 3.84; N, 4.59.

3-(2-Hydroxybenzoyl)-5-dioxo[1]benzothieno[3,2-*b*]pyridine (**6**).

A suspension of **2d** (9.00 g., 26.6 mmoles) in 50 ml. of aqueous ammonia and 100 ml. of water was stirred at 80° for 5 minutes. During this time the reaction became homogeneous and then a yellow precipitate formed. The reaction was cooled to room temperature. The product was collected by filtration, washed with water, ethanol, and finally with hexane to give **6** (8.0 g., 89%), m.p. 218-220°; nmr (DMSO-d_6): 6.98 (1H, d, J = 1), 7.04 (1H, d, J = 8), 7.42-7.67 (2H, m), 7.75-8.05 (2H, m), 8.10-8.35 (2H, m), 8.66 (1H, d, J = 2), 9.12 (1H, d, J = 2), 10.55 (1H, m, OH); ir (nujol): 3050, 1630, 1590 cm^{-1}; ms: m/e 337 (M^+), 273 (M^+-SO_2), 121



Anal. Calcd. for $C_{18}H_{11}NO_4S$: C, 64.09; H, 3.29; N, 4.15. Found: C, 63.78; H, 3.26; N, 4.17.

3-(4-Oxo-4*H*-benzopyran-3-ylmethylene)oxindole (**10**).

To oxindole (14.0 g., 105 mmoles) in 150 ml. of pyridine was added **1** (17.4 g., 100 mmoles). The reaction was stirred for 3 hours at room temperature. The precipitate was collected by filtration and washed with ether. Recrystallization from DMF gave the yellow crystalline product (**10**) (18.5 g., 64%), m.p. 249-250°; nmr (DMSO-d_6): 10.61-10.90 (1H, b, NH), 10.02 (1H, s), 6.67-8.23 (9H, m); ir (nujol): 1700, 1670, 1640, 1620 cm^{-1}; ms: m/e 289 (M^+), 261 (M^+-CO).

Anal. Calcd. for $C_{18}H_{11}NO_3$: C, 74.74; H, 3.83; N, 4.84. Found: C, 74.54; H, 3.84; N, 4.91.

5-(4-Oxo-4*H*-benzopyran-3-ylmethylene)barbituric Acid (**11**).

To barbituric acid (11.7 g., 117 mmoles) in 250 ml. of refluxing pyridine was added **1** (15.6 g., 89.6 mmoles) in 50 ml. of pyridine over 10 minutes. After 10 minutes more the reaction was cooled to room temperature. The product was collected by filtration and washed with ether. Recrystallization from DMF-methanol-ether gave yellow crystals (**11**) (24.0 g., 94%), m.p. 290-292°; nmr (DMSO-d_6): 10.94-11.32 (2H, b, exchangeable with deuterium oxide), 9.43 (1H, s), 7.52-8.46 (5H, m); ir (nujol): 1760, 1700, 1670 cm^{-1}.

Anal. Calcd. for $C_{14}H_8N_2O_5$: C, 59.16; H, 2.84; N, 9.86. Found: C, 58.94; H, 2.84; N, 9.79.

3-(3,3,6,6-Tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthen-9-yl)-chromone (**12**).

To 3-formylchromone (**1**) (10 g., 57 mmoles) and dimedone (16 g., 114 mmoles) was added 75 ml. of pyridine under stirring. After 5 minutes the reaction became a homogeneous red solution. After 15 minutes the reaction was rotary evaporated, acidified with 2*N* hydrochloric acid (*p*H 3) and extracted with 3 × 150 ml. of methylene chloride. The combined organic portions were dried (sodium sulfate) and concentrated to 70-80 ml. Addition of 200 ml. of ether precipitated white crystals (19.5 g.), m.p. 280-282°. Crystallization from 330 ml. of ethanol containing 5 ml. of concentrated hydrochloric acid gave after drying *in vacuo* at 100°, colorless crystals (**12**) (71.4 g., 73%), m.p. 287-288°; nmr (trifluoroacetic acid): 8.35 (1H, s), 7.97 (1H, dd, J = 8, 2), 7.13-7.67 (3H, m), 4.54 (1H, s), 2.37 (4H, s), 2.13 (4H, s), 0.81 (6H, s), 0.70 (6H, s); ir (dichloromethane): 2970, 2900, 1650, 1620, 1475, 1375, 1360, 1175 cm^{-1}.

Anal. Calcd. for $C_{26}H_{26}O_5$: C, 74.62; H, 6.26. Found: C, 74.62; H, 6.29.

3-(2-Hydroxybenzoyl)-5-oxo-5*H*,10*H*-benzo[1,8-*b*]naphthyridine (**15**).

3-Formylchromone (**1**) (5.2 g., 30 mmoles), 2-amino-4-hydroxyquinoline (**14**) (9) (4.8 g., 30 mmoles) and 150 ml. of glacial acetic acid were heated under reflux for 2 hours. The precipitate formed upon cooling to room temperature was collected by filtration and crystallized from dimethylformamide to give a crystalline product (**15**) (6.2 g., 65%), m.p. 315° dec.; nmr (DMSO-d_6): 12.52 (1H, s, broad), 10.4 (1H, s, broad), 9.09 (1H, d, J = 3), 8.78 (1H, d, J = 3), 8.22 (1H, dd, J = 8, 1), 6.96-7.9 (7H, m); ir (nujol): 3220, 3120, 1630, 1590, 785, 764 cm^{-1}.

Anal. Calcd. for $C_{19}H_{12}N_2O_3$: C, 72.15; H, 3.83; N, 8.86. Found: C, 71.9; H, 3.8; N, 9.0.

1-Isopropyl-3-methyl-5-(2-hydroxybenzoyl)-1*H*-pyrazolo[3,4-*b*]pyridine (**17**).

To a mixture of 3-formylchromone (**1**) (5.8 g., 33.4 mmoles) and 1-isopropyl-3-methyl-5-aminopyrazole (**16**) (10) (4.65 g., 33.5 mmoles) was added 250 ml. of glacial acetic acid. The reaction was refluxed for 4 hours, rotary evaporated, treated with 100 ml. of pentane and allowed to stand for 24 hours at room temperature. The insoluble portion was filtered and the filtrate was evaporated to dryness. The residue was distilled to give an oil (**17**) (4.5 g., 46%), b.p. 160-162° (0.01 mm); nmr (deuteriochloroform): 11.82 (1H, s), 8.85 (1H, d, J = 2), 8.36 (1H, d, J = 2), 7.64 (1H, dd, J = 8, 1), 7.55 (1H, dt, J = 1, 8), 7.12 (1H, dd, J = 8, 1), 6.93 (1H, dt, J = 1, 8), 5.31 (1H, heptet, J = 7), 2.62 (3H, s), 1.62 (6H, d, J = 7); ir (dichloromethane): 3200, 2890, 1640, 1600 cm^{-1}; ms: m/e 295 (M^+), 280, 121.

Anal. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.1; H, 5.9; N, 14.4.

3-(4-Pyridyl)-5-(2-hydroxybenzoyl)isoxazolo[5,4-*b*]pyridine (**19**).

3-Formylchromone (**1**) (5.8 g., 33.4 mmoles) and 3-(4-pyridyl)-5-isoxazoleamine (**18**) (11) (4.85 g., 30 mmoles) were suspended in 50 ml. of acetic acid. The mixture was then stirred under reflux for 4 hours. The gold-brown solution that formed was evaporated to dryness by means of a rotary evaporator. The residue was slurried in 30 ml. of ethanol and

filtered to give a crystalline product, m.p. 194°. Crystallization from chloroform-ether afforded yellow crystals (**19**) (7.1 g., 74%), m.p. 197-198°; nmr (DMSO-d_6): 10.68 (1H, s), 8.99 (2H, s), 8.85 (2H, d, J = 6), 8.06 (2H, dd, J = 6, 2), 7.42-7.63 (2H, m), 7.04 (1H, d, J = 8), 6.99 (1H, dt, J = 1,8); ir (nujol): 3050, 1630, 1600, 730 cm^{-1}.

Anal. Calcd. for $C_{18}H_{11}N_3O_3$: C, 68.14; H, 3.50; N, 13.24. Found: C, 67.80; H, 3.54; N, 13.21.

4-Oxo-1,2,3,4-tetrahydro-6-hydroxy[1]benzopyrano[4,3-*b*]quinoline (**21**).

3-Formylchromone (**1**) (17.4 g. 100 mmoles), 3-amino-2-cyclohexen-1-one (**20**) (12) (11.1 g., 100 mmoles) and 166 ml. of pyridine were heated under reflux for 5 hours. The resulting red solution was evaporated to dryness. The red crystalline residue was slurried in 100 ml. of methanol, filtered, and washed with a small quantity of cold methanol to give a pink crystalline product (**21**) (21.9 g., 82%), m.p. 218-221°; nmr (DMSO-d_6): 8.28 (1H, dd, J = 8, 2), 8.16 (1H, s, pyridine), 7.65 (1H, d, J = 5, OH), 7.45 (1H, dt, J = 2, 8), 7.14 (1H, dt, J = 2, 8), 7.05 (1H, dd, J = 8, 2), 6.52 (1H, d, C*H*OH), 3.14 (2H, t, J = 6, CH_2), 2.68 (2H, t, J = 6, CH_2), 2.13 (2H, m, CH_2); ir (nujol): 3170, 2730, 1700, 1622, 1600, 1120, 758 cm^{-1}; ms: m/e 267 (M^+), 250, 239, 211, 183, 154.

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.93; H, 4.84; N, 5.25.

5-Hydroxy-3-oxo[1]benzopyrano[3,4-*e*]cyclopenta[*b*]pyridine (**23**).

3-Formylchromone (**1**) (1.74 g., 10 mmoles), 3-amino-2-cyclopenten-1-one (**22**) (13) (0.97 g., 10 mmoles) and 20 ml. of pyridine were reacted as described for the quinoline (**21**). To the resulting brown-red solution was added 80 ml. of water. The precipitated crystals were filtered and washed with 10 ml. of methanol to give beige crystals (2.7 g.), m.p. 228-234°. Further purification was achieved by dissolving the crystals in 750 ml. of ethyl acetate, followed by treatment with activated charcoal and reducing to a volume of about 200 ml. to give colorless crystals (**23**) (1.5 g., 59%), m.p. > 230° dec.; nmr (DMSO-d_6): 8.32 (1H, dd, J = 8, 2), 8.02 (1H, s), 7.72 (1H, d, J = 6, OH), 7.49 (1H, dt, J = 2, 8), 7.18 (1H, dt, J = 2, 8), 7.10 (1H, dd, J = 8, 2), 6.57 (1H, d, J = 6, C*H*OH), 3.10-3.33 (2H, m), 2.68-2.88 (2H, m); ir (nujol): 3130, 2920, 1715, 1600, 1585 cm^{-1}.

Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.08; H, 4.52; N, 5.61.

4-Oxo-6-ethoxy-1,2,3,4-tetrahydro-6*H*-[1]benzopyrano[4,3-*b*]quinoline (**24**).

The alcohol obtained above (**21**) (8.0 g., 30 mmoles), 200 ml. of absolute ethanol and 20 ml. of 8*N* hydrochloric acid in ethanol were heated under reflux for 6 hours, cooled to room temperature and rotary evaporated. The residue was treated with ice and 120 ml. of 2*N* aqueous sodium hydroxide followed by extraction with 3 × 100 ml. of methylene chloride. The combined organic portions were dried (magnesium sulfate) and rotary evaporated to give a yellow oil (10.1 g.). Silica gel (200 g.) column chromatography using methylene chloride as eluent and crystallization from ether-petroleum ether yielded a light-yellow product (**24**) (6.5 g., 74%), m.p 100-101°; nmr (deuteriochloroform): 8.36 (1H, dd, J = 8.2), 8.18 (1H, s), 7.41 (1H, dt, J = 2,8), 7.15 (1H, dt, J = 2, 8), 7.05 (1H, dd, J = 8, 2), 6.13 (1H, s, CHOEt), 3.88 (2H, m, OCH_2), 3.19 (2H, t, J = 6, CH_2), 2.7 (2H, t, J = 6, CH_2), 2.17 (2H, m, CH_2), 1.17 (3H, t, J = 7, CH_3); ir (dichloromethane): 2970, 2890, 1690, 1620, 1590, 1075, 995 cm^{-1}.

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.08; H, 5.78; N, 4.79.

4,6-Dioxo-1,2,3,4-tetrahydro-6*H*-[1]benzopyrano[4,3-*b*]quinoline (**25**).

To an ice cooled solution of pyridinium chlorochromate (16.2 g., 75 mmoles) in 50 ml. of pyridine was added a solution of the above alcohol (**21**) (13.5 g., 50 mmoles) in 60 ml. of pyridine. The red reaction mixture was stirred at room temperature for 24 hours. The resulting mixture was treated with water and saturated aqueous sodium bicarbonate. The brown precipitate was filtered off and extracted with 3 × 300 ml. of methylene chloride. The combined extracts were rotary evaporated to give brown crystals. Silica gel column chromatography using methylene chloride as eluent gave after crystallization from methylene chloride-ether a colorless product (**25**) (8.5 g., 64%), m.p. 244-247° dec.; nmr (deuteriochloroform + DMSO-d_6): 8.93 (1H, s), 8.57 (1H, dd, J = 8, 2), 7.7 (1H, dt, J = 2, 8), 7.45 (1H, dt, J = 2, 8), 7.37 (1H, dd, J = 8, 2), 3.35 (2H, t, J = 6), 2.78 (2H, t, J = 6), 2.27 (2H, m); ir (dichloromethane): 3070, 2960, 2880, 1750, 1700, 1640, 1630, 1580, 1175 cm^{-1}.

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.31; H, 4.06; N, 5.26.

4-Oxo-1,2,3,4-tetrahydro-6*H*-[1]benzopyrano[4,3-*b*]quinoline (**26**).

The above alcohol (**21**) (11.2 g., 42 mmoles), 150 ml. of glacial acetic acid and 50 ml. of 57% aqueous hydroiodic acid were heated under reflux for 1.5 hours. The dark reaction mixture was cooled to room temperature, poured on ice and saturated aqueous sodium hydrogen sulfite and extracted with 3 × 300 ml. of methylene chloride. The combined organic layers were washed with water, dried (sodium sulfate) and rotary evaporated to give reddish crystals (8.9 g.). Silica gel column chromatography using methylene chloride as eluent followed by crystallization from methylene chloride-ether-petroleum ether afforded a colorless product (**26**) (8.0 g., 76%), m.p. 152-154°; nmr (deuteriochloroform): 8.26 (1H, dd, J = 8, 2), 7.96 (1H, s), 7.34 (1H, dt, J = 2, 8), 7.07 (1H, dt, J = 2, 8), 6.94 (1H, dd, J = 8, 2), 5.20 (2H, s), 3.17 (2H, t, J = 6), 2.68 (2H, t, J = 6), 2.17 (2H, m); ir (dichloromethane): 3070, 3000, 2900, 1685, 1620, 1590, 1475, 1360, 1230, 1040 cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.22; N, 5.58. Found: C, 76.36; H, 5.26; N, 5.57.

Ethyl 5-Hydroxy-3-methyl-5*H*-[1]benzopyrano[4,3-*b*]pyridine-3-carboxylate (**28b**) (5).

To a suspension of 3-formylchromone (**1**) (3.5 g., 20 mmoles) in 75 ml. of DMF was added 3-aminocrotonic acid ethyl ester (2.6 g., 20 mmoles). The reaction was stirred for 2 hours at 80° and then cooled to room temperature. The dark red solution was poured onto ice and diluted with water. The precipitate was filtered, washed with water, dissolved in 800 ml. of warm methylene chloride, dried (sodium sulfate) and reduced to a volume of about 300 ml. The crystals formed were filtered off and washed with ether to give a colorless product (**28b**) (2.4 g., 42%), m.p. 200-203°; nmr (DMSO-d_6): 8.27 (1H, dd, J = 8, 2), 8.19 (1H, s), 7.66 (1H, s, OH), 7.45 (1H, dt, J = 2, 8), 7.15 (1H, dt, J = 2, 8), 7.08 (1H, dd, J = 8, 2), 6.53 (1H, s, C*H*OH), 4.35 (2H, q, J = 7), 2.82 (3H, s), 1.35 (3H, t, J = 7); ir (nujol): 3070, 2960, 1715, 1585, 1240, 995, 760 cm^{-1}.

Anal. Calcd. for $C_{16}H_{15}O_4N$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.13; H, 5.33; N, 4.83.

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