Central Nervous System Depressants. VII.[1] Pyridyl Coumarins

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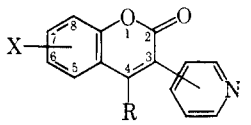
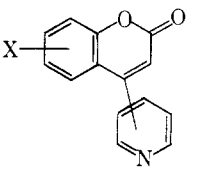
Coumarins substituted in the 3- and 4-positions by a pyridine ring have been prepared by modifications of the Pechmann, Knoevenagel, and Perkin reactions. These as well as several intermediates and derivatives have been tested for their effects on the central nervous system of mice. They are generally mild depressants, although some are stimulants. A few have antifungal activity *in vitro*.

Coumarins are known to have a variety of physiological activities including sedative properties.[2] Although a great number of substituted coumarins has been prepared including many with aromatic substituents in the 3- and 4-positions, very little work has been done on pyridyl coumarins (I and II).



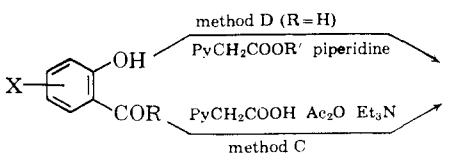
I



II

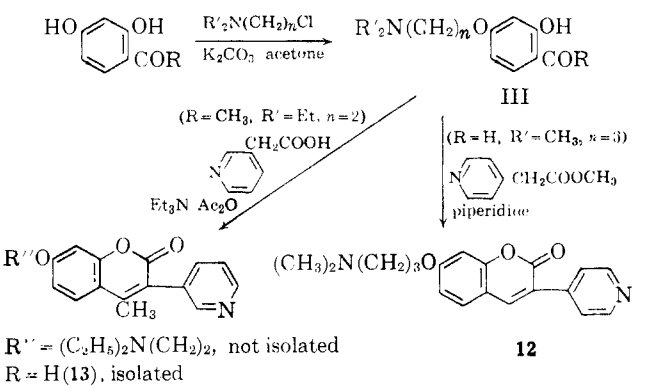
Pacheco and Gotto[3] describe a few hydroxyl-substituted 4-(3-pyridyl) coumarins (II) prepared by a modification of the Pechmann reaction, and Bragg and Wibberley[4] prepared the 3-(2- and 4-pyridyl) coumarins (I) by the Knoevenagel condensation. Neither of these reports describe any pharmacological properties. Our interest in coumarins[5] led us to prepare a number of pyridyl coumarins of types I and II and to study some of their pharmacological properties, especially their effects on the central nervous system (CNS).

These compounds, listed in Table I, were synthesized by three general methods. The 4-(4-pyridyl) coumarins (II) were prepared by the Pechmann reaction[6] in which the appropriate phenol was condensed with methyl β-oxo-4-pyridinepropionate in the presence of sulfuric (method A) or polyphosphoric acids (method B). In the one case (with resorcinol) in which a direct comparison was made, polyphosphoric acid was found to be superior (57% yield against 38%). Where applicable, the best method for preparing compounds of type I appeared to be the Knoevenagel condensation of salicylaldehydes with pyridylacetates in the presence of piperidine[4] (method D). The most general method for type I compounds is the Perkin reaction[7] using *o*-hydroxybenzaldehydes or *o*-hydroxyphenyl ketones with pyridylacetic anhydrides in the presence of bases (*e.g.*, triethylamine) (method C). In our work the anhydrides were prepared *in situ* from pyridylacetic acids and acetic anhydride.



6-Amino-3-(4-pyridyl)coumarin (**8**; I, R = H, X = 6-NH_2) was prepared by hydrogenation of the corresponding nitro compound (**7**). By using Raney nickel and hydrogen at low pressure, hydrogenation of the coumarin ring was avoided.

The dialkylaminoalkoxy-*o*-hydroxybenzaldehydes and acetophenones (III) needed to prepare pyridyl coumarins substituted by basic ether groups (I, R = H or CH_3, X = $R'_2N(CH_2)_nO$–) were readily prepared by selective monoalkylation of the corresponding dihydroxybenzaldehyde or acetophenone with dialkylaminoalkyl chlorides and potassium carbonate in acetone. The aldehyde (III, R = H, R′ = CH_3, n = 3) underwent extensive decomposition on distillation but the crude product was satisfactory for the Knoevenagel reaction giving the coumarin **12**. Since ketones are reported unsuccessful[4] for the Knoevenagel reaction the Perkin condensation was used with the basic acetophenone (III, R = CH_3, R′ = C_2H_5, n = 2). Although 4-methoxy-2-hydroxyacetophenone was satisfactory in this reaction, the analogous 4-(diethylaminoethoxy)-2-hydroxyacetophenone was cleaved and only 7-hydroxy-4-methyl-3-(3-pyridyl)coumarin (**13**) was isolated.



Pharmacology.—The pyridyl coumarins were tested for their CNS effects by gross observation of intact mice.[8] Although most of them showed depression at nearly the lethal dose, only three (Table I, **1**, **11**, and **18**) showed depression at less than half the LD_{50}. One of these (**1**) was suggestive of possible stimulant properties in that it inhibited monamine oxidase (MAO) *in vitro*.[9] One pyridyl coumarin (Table I, **15**) seemed to be a CNS stimulant giving an increase

(1) Paper VI of this series: R. B. Moffett, *J. Med. Chem.*, **7**, 319 (1964).
(2) S. M. Sethna and N. M. Shah, *Chem. Rev.*, **36**, 1 (1945).
(3) H. Pacheco and R. Gotto, *Bull. Soc. Chim. France*, 95 (1960).
(4) D. R. Bragg and D. G. Wibberley, *J. Chem. Soc.*, 5074 (1961).
(5) R. B. Moffett, *J. Med. Pharm. Chem.*, **5**, 335 (1962).
(6) S. Sethna and R. Phadke, *Org. Reactions*, **7**, 1 (1953).
(7) J. R. Johnson, *ibid.*, **1**, 210 (1942).
(8) R. B. Moffett, A. R. Manze, and P. H. Spay, *J. Med. Chem.*, **7**, 178 (1964).
(9) MAO oxidation studies are by Bio-Science Laboratories.

in motor activity of mice and inhibition of monamine oxidase *in vitro*.[9] Hydrochlorides of the two *o*-hydroxycarbonyl basic ether intermediates (III, R = H, R′ = CH_3, n = 3; and III, R = CH_3, R′ = C_2H_5, n = 2) also seemed to be stimulants on gross observation of intact mice. They also inhibited monamine oxidase *in vitro*[9] 46 and 38%, respectively, at 10^{-3} *M*. Two compounds (Table I, **4** and **5**) were found to be antifungal agents *in vitro*. The LD_{50} values of the pyridyl coumarins are given in Table I and other interesting pharmacology is indicated in the footnotes to this table.

Experimental[10]

3-(3-Pyridyl)coumarin (1).—A solution of 13.9 g. (0.1 mole) of 3-pyridylacetic acid, 12.2 g. (0.1 mole) of salicylaldehyde, 28.2 ml. (0.3 mole) of acetic anhydride, and 14 ml. (0.1 mole) of triethylamine was heated under nitrogen on a steam bath for 1 hr. and then in an oil bath at 180–195° for 2 hr. during which time the excess solvent evaporated. On cooling, the residue crystallized. This was dissolved in 150 ml. of dilute hydrochloric acid by warming, and was filtered and cooled. Crystalline hydrochloride separated which, however, was partly converted to free base either on washing with water or by drying. This was converted to the free base by dissolving in dilute sodium hydroxide, precipitating with acetic acid, collecting the solid, and drying, m.p. 167.5–169°. The filtrates were combined, made basic, and concentrated, giving additional free base. This was sublimed at 170° (bath) (0.01 mm.) giving a yellow solid which was crystallized from isopropyl alcohol, m.p. 167.5–169°. The total yield was 16.5 g.

3-(3-Pyridyl)coumarin N-Oxide (2).—A solution of 22.3 g. (0.1 mole) of 3-(3-pyridyl)coumarin in 100 ml. of acetic acid and 16 ml. of 30% hydrogen peroxide was heated at 70° for 16 hr. On cooling, the N-oxide crystallized and was collected, washed with water, and dried at 50° (0.3 ml.) giving 17.5 g. (75%) of nearly white solid, m.p. 276–278°. Recrystallization from dimethylformamide gave 15.7 g. of light tan silky needles with the same melting point.

Method D. 6-Chloro-3-(4-pyridyl)coumarin (3).—A solution of 37.3 g. (0.24 mole) of 5-chlorosalicylaldehyde, 30.2 g. (0.2 mole) of methyl 4-pyridylacetate, and 11.6 ml. of piperidine in 250 ml. of absolute ethanol was heated under reflux with stirring for 2 hr. After about the first 5 min. of heating a solid separated. After cooling the solid was collected, washed with ethanol, and dried, giving 47.9 g. of solid, m.p. 268.5–271.5°. This was recrystallized from 350 ml. of dimethylformamide giving 45.06 g. of light tan crystals, m.p. 271–272.5°.

6-Bromo-3-(2-pyridyl)coumarin (5).—To a mixture of 17.4 g. (0.1 mole) of 2-pyridylacetic acid hydrochloride, 20.1 g. (0.1 mole) of 5-bromosalicylaldehyde, and 75 ml. of acetic anhydride was added 28 ml. (0.2 mole) of triethylamine. The mixture became warm and turned dark. After heating under reflux with stirring for 18 hr., the mixture was cooled and poured into water giving a dark gum. This was extracted successively with boiling ether and acetone. The extracts were combined and evaporated and the residue was sublimed at 160–170° (bath) (0.01 mm.). The yellow solid sublimate was recrystallized from ethanol yielding 7.34 g. of yellow crystals, m.p. 177.5–188.5°.

6-Amino-3-(4-pyridyl)coumarin (8).—A suspension of 11.12 g. (0.0415 mole) of 6-nitro-3-(4-pyridyl)coumarin (**7**) in 150 ml. of ethanol was hydrogenated with two teaspoons of moist Raney nickel catalyst at 60 lbs. (4.22 kg./cm.²) starting pressure and room temperature. The theoretical 0.125 mole of hydrogen was absorbed in 1 hr. and the uptake nearly stopped. After cooling in the refrigerator, the solid (mixed with the catalyst) was collected. This solid was repeatedly extracted with hot dimethylformamide (180 ml.). The solution was diluted to 500 ml. with absolute ethanol and cooled, giving 5.93 g. of yellow solid, m.p. 253–255°. Concentration of the filtrates and dilution with ethanol yielded 3.0 g. more solid, m.p. 253–255.5°.

A small sample was sublimed at 220° (bath) (0.005 mm.) giving yellow solid which was recrystallized from methanol, m.p. 255–257°.

6-Acetamido-3-(4-pyridyl)coumarin (9).—A solution of 6.2 g. (0.026 mole) of 6-amino-3-(4-pyridyl)coumarin (**8**) in 150 ml. of acetic anhydride and 50 ml. of acetic acid was boiled for a few minutes, filtered, and cooled. The resulting yellow crystals were collected, washed with acetic anhydride, then with ethanol, and dried, giving 5.0 g. of yellow solid, m.p. 298–300°. A small sample recrystallized from Methyl Cellosolve had the same melting point.

5,7-Diacetoxy-3-(3-pyridyl)coumarin (10).—To a mixture of 30.4 g. (0.2 mole) of 2,4,6-trihydroxybenzaldehyde, 24.4 g. (0.2 mole) of 3-pyridylacetic acid, and 75 ml. of acetic anhydride was added 28 ml. (0.2 mole) of triethylamine. The temperature rose to 110°, the solid dissolved, and another solid crystallized. The mixture was heated in an oil bath to 190° for 4 hr. during which time the solvent evaporated. The resulting dark gum was boiled with methanol and after cooling the solid was collected, dissolved in dimethylformamide, and reprecipitated with water. The crude material was reacetylated by refluxing with acetic anhydride, treated with decolorizing charcoal, and cooled to give 27 g. of crystalline solid. This was sublimed at 220° (bath) (0.02 mm.) giving 12 g. of crystalline solid, m.p. 179–181°. An additional 5 g. of similar material was obtained from the filtrates. The total yield was recrystallized from methanol giving 15 g. of white silky needles, m.p. 182–183°.

5,6,7-Trimethoxy-3-(3-pyridyl)coumarin (11).—A solution of 10.61 g. (0.05 mole) of 2-hydroxy-4,5,6-trimethoxybenzaldehyde[11] and 9.15 g. (0.075 mole) of 3-pyridylacetic acid in 25 ml. of acetic anhydride and 7 ml. (0.05 mole) of triethylamine was heated with stirring under nitrogen on a steam bath for 1.5 hr. and then in an oil bath to 174° for 1.5 hr. Most of the solvent evaporated. The dark solution was poured into ice–water giving a gummy precipitate. The mixture was washed with ether and neutralized with sodium hydroxide. The precipitate was collected, dried, and sublimed at 185° (0.01 mm.) giving 2 g. of yellow solid. This was recrystallized from ethanol yielding 1.5 g. of nearly white crystals, m.p. 150.5–153.5°.

4-(γ-Dimethylaminopropoxy)salicylaldehyde.—A mixture of 41.5 g. (0.3 mole) of 2,4-dihydroxybenzaldehyde, 97 g. (0.7 mole) of potassium carbonate, 500 ml. of acetone, and 73 g. (0.6 mole) of γ-dimethylaminopropyl chloride was heated under reflux with stirring for 8 hr. After standing overnight and distilling most of the solvent, the mixture was dissolved in water and ether and acidified with hydrochloric acid. The aqueous layer was twice washed with ether and made basic (pH 7–8) with sodium hydroxide. The aqueous solution was well extracted with ether and then with methylene chloride. The organic solutions were washed with water and evaporated to dryness, giving 24.8 g. (37%) of a brown oil.

An attempt was made to distil the oily free base through a 20-cm. column. Most of it decomposed to a black solid; however, 1.6 g. of yellow liquid was obtained, b.p. 112° (0.07 mm.); $n^{25}D$ 1.5559. The infrared spectrum was practically identical with that of the undistilled oil.

Hydrochloride.—This distilled free base was dissolved in absolute ether and acidified with alcoholic hydrogen chloride giving 1.8 g. of nearly white solid, m.p. 172–174°. This was recrystallized from isopropyl alcohol giving 1.7 g. of nearly white crystals, m.p. 173.5–175°.

Anal. Calcd. for $C_{12}H_{18}ClNO_3$: C, 55.49; H, 6.98; Cl, 13.66; N, 5.39. Found: C, 55.42; H, 6.87; Cl, 13.86; N, 5.26.

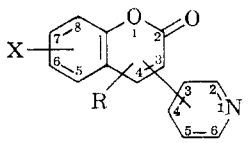
4-(β-Diethylaminoethoxy)-2-hydroxyacetophenone.—A mixture of 76.1 g. (0.5 mole) of 2,4-dihydroxyacetophenone, 138.2 g. (1.0 mole) of potassium carbonate, 600 ml. of acetone, and 104 g. (0.75 mole) of β-diethylaminoethyl chloride was heated under reflux with vigorous stirring for 5.5 hr. and allowed to stand for 5 days. After distillation of most of the solvent, the mixture was dissolved in ice–water and ether. The ether layer was twice extracted with 10% aqueous sodium hydroxide, dried over potassium carbonate, and evaporated to dryness, giving 17.4 g. of nearly colorless oil. Even though this had not dissolved in sodium hydroxide, it was essentially the desired monoether as shown by infrared spectroscopy. The basic aqueous solutions were acidified with hydrochloric acid and the solution was twice

(10) Melting points were taken in capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compounds showed no need for correction. Infrared, ultraviolet, and, in many cases, nuclear magnetic resonance spectra were obtained on these compounds. Unless otherwise noted they were in accordance with the proposed structures.

(11) W. J. Horton and M. G. Stout, *J. Org. Chem.*, **26**, 1221 (1961).

TABLE I

CHEMICAL AND PHARMACOLOGICAL PROPERTIES



Compd. no.	Position of pyridine on coumarin ring	Position of attachment on pyridine ring	R	X	Method of prepn.	Yield, %[a]	M.p., C.°[b]	Crystn. solvent[c]
1	3	3	4-H	H	C[e]	74	167.5–169	*i*-PrOH
2	3	3[d]	4-H	H(N-oxide)	[f]	75	276–278	DMF
3	3	4	4-H	6-Cl	D[e]	91	271–272.5	DMF
4	3	3	4-H	6-Br	D[e]	89	230–231	$MeO(CH_2)_2OH$
5	3	2	4-H	6-Br	C[e]	24	187.5–188.5	EtOH
6	3	2	4-H	$6\text{-}NO_2$	D	64	215–216.5	DMF
7	3	4	4-H	$6\text{-}NO_2$	D	75	270–271	DMF
8	3	4	4-H	$6\text{-}NH_2$	[g]	90	255–257	MeOH
9	3	4	4-H	$6\text{-}NHCOCH_3$	[h]	69	298–300	$MeO(CH_2)_2OH$
10	3	3	4-H	$5,7\text{-Di-}OCOCH_3$	C[e]	44	182–183	MeOH
11	3	3	4-H	$5,6,7\text{-Tri-}OCH_3$	C[e]	10	150.5–153.5	EtOH
12	3	4	4-H	$7\text{-}O(CH_2)_3N(CH_3)_2$	D[e]	35[i]	136–138	EtOH
13	3	3[j]	$4\text{-}CH_3$	7-OH	C[e]	28	313–315 dec.	H_2O
14	3	3	$4\text{-}CH_3$	7-OH	[k]	64[l]	257–258.5	$MeO(CH_2)_2OH$
15	3	3	$4\text{-}CH_3$	$7\text{-}OCH_3$	C[e]	51	138–141	EtOH
16	3	3	$4\text{-}C_6H_5$	7-OH	C[e]	40	288–290.5	$MeO(CH_2)_2OH$
17	4	4	3-H	7-OH	B[e]	57	307–312 dec.	$MeO(CH_2)_2OH$
18	4	4	3-H	$7\text{-}OCH_3$	B[e]	31	212–214.5	EtOH
19	4	4	3-H	$5,6,7\text{-Tri-}OCH_3$	A[e]	80	183–186	EtOH

[a] Unless otherwise stated, yields are calculated on material melting not less than two degrees below the highest melting point obtained. [b] See footnote 10. [c] DMF = dimethylformamide. [d] See paper V of this series (ref. 8) for methodology. [e] See Experimental for preparation. [f] Depression, chronic convulsions, loss of pinna reflex, and wobbly gait in mice at 300 mg./kg. Body temperature lowering in mice at 65 mg./kg. Decrease in motor activity of mice at 130 mg./kg. Monamine oxidase inhibition *in vitro* 44% at 10^{-3} *M*; see ref. 9. [g] N-oxide of 1. [h] See ref. 12. [i] A solution of 20.1 g. (0.1 mole) of 5-bromosalicylaldehyde, 30.2 g. (0.2 mole) of methyl 3-pyridylacetate, and 11.6 ml. of piperidine in 250 ml. of absolute ethanol was heated under reflux with stirring for 7 hr. [j] Antifungal *in vitro* against *Trichophyton rubrum*. Minimum inhibitory concentration 100 γ/ml. [k] Antifungal *in vitro* against *T. rubrum*. Mini-

extracted with ether. Evaporation of the ether yielded 14.0 g. of crude starting 2,4-dihydroxyacetophenone. The acid aqueous solution was neutralized (pH ~7–8) with sodium bicarbonate. The solution was concentrated *in vacuo* on a steam bath and the salts were well extracted with methanol. The methanol solution was evaporated to dryness and the residue was again extracted with methanol. After removal of the solvent the residue was boiled with benzene and filtered from salts. After removal of the benzene the two fractions of crude monoether were distilled giving 72.2 g. (57.6%) of nearly colorless oil, b.p. 115° (0.01 mm.); $n^{26}D$ 1.5398.

The infrared spectrum had little if any absorption in the OH region showing that if a phenolic hydroxyl is present it is highly chelated and therefore *ortho* to the carbonyl. The principal bands are at 2805, 1635, 1507, 1255, 1194, 1133, and 1070 cm.$^{-1}$. The ultraviolet spectrum indicates a phenolic group, showing a shift from neutral to basic medium. The principal bands are (in ethanol) at 227 mμ (ε 10,100), 234 (8500), 274 (16,000), and 313 (7400); (in 0.01 *N* ethanolic KOH) at 228 mμ (ε 19,900), 238 (17,700), 274 (10,050), and 353 (8700). The nuclear magnetic resonance spectrum clearly shows the phenolic hydroxyl and only one diethylaminoethoxy group.

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57; O, 19.10. Found: C, 66.64,[12] H, 8.37,[12] N, 5.42; O, 19.57.[12]

Hydrochloride.—A 10-g. sample of the free base in absolute ether was acidified with ethanolic hydrogen chloride yielding 11.75 g. of white crystalline solid, m.p. 153–154.5°. A sample recrystallized from ethyl methyl ketone had the same melting point.

Anal. Calcd. for $C_{14}H_{22}ClNO_3$: C, 58.42; H, 7.71; Cl, 12.32. Found: C, 58.35; H, 7.85; Cl, 12.44.

Attempt to Prepare 7-(β-Diethylaminoethoxy)-4-methyl-3-(3-pyridyl)coumarin. Isolation of 7-Hydroxy-4-methyl-3-(3-pyridyl)coumarin Hydrochloride (13).—A solution of 25.1 g. (0.1 mole) of 4-(β-diethylaminoethoxy)-2-hydroxyacetophenone and 13.9 g. (0.1 mole) of 3-pyridylacetic acid in 28.2 ml. (0.3 mole) of acetic anhydride was heated under reflux for 16 hr. The dark solution was poured into ice–water and neutralized (pH ~6) with sodium hydroxide. The dark insoluble gum was dissolved in dilute hydrochloric acid, filtered, and partly neutralized (pH ~3) with sodium hydroxide. The resulting solid was recrystallized from aqueous dimethylformamide and then from water with decolorizing charcoal treatment, giving 1.33 g. of cream-colored crystals, m.p. 313–315° dec. This was found by analysis and infrared spectrum to be 7-hydroxy-4-methyl-3-(3-pyridyl)coumarin hydrochloride. By evaporating the filtrate to dryness *in vacuo*, fractionating the solids with alcohol, and finally recrystallizing from water an additional 6.75 g. of this hydrochloride was obtained.

Free Base (14).—A 0.5 g. sample of the hydrochloride was made basic with sodium hydroxide and neutralized with acetic acid (pH ~6) giving a solid which was sublimed at 220° (bath) (0.005 mm.) giving 0.4 g. of solid. This was recrystallized from Methyl Cellosolve, yielding 0.28 g. of nearly white crystals, m.p. 257–258.5°.

7-Methoxy-4-methyl-3-(3-pyridyl)coumarin (15).—A solution of 33.2 g. (0.2 mole) of 2-hydroxy-4-methoxyacetophenone and 27.8 g. (0.2 mole) of 3-pyridylacetic acid in 56.4 ml. (0.6 mole) of acetic anhydride and 28 ml. (0.2 mole) of triethylamine was heated under reflux for 18 hr., cooled, and poured into ice–water. After neutralizing with sodium hydroxide the resulting partly crystalline solid was extracted with benzene and methylene chloride. The extracts were washed with sodium carbonate solution and water and the solvent was evaporated giving 59 g. of dark oil, which crystallized on standing. This was sublimed at 190° (bath) (0.02 mm.). After removing a liquid forerun, 33 g. of solid was obtained. This was recrystallized from ethanol giving 27 g. of light yellow crystals, m.p. 138–141°.

7-Hydroxy-4-phenyl-3-(3-pyridyl)coumarin (16).—A solution of 21.4 g. (0.1 mole) of 2,4-dihydroxybenzophenone and 12.2 g. (0.1 mole) of 3-pyridylacetic acid in 56.4 ml. (0.6 mole) of acetic anhydride and 28 ml. (0.2 mole) of triethylamine was heated under reflux for 3 days. On pouring the dark solution into water a black gum was obtained. The aqueous solution was decanted and the gum was boiled with 300 ml. of ethanol, allowed to stand

(12) This analysis by Huffman Microanalytical Laboratories.

Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Other elements, % Calcd.	Other elements, % Found	Mouse LD_{50}, mg./kg.[d]
$C_{14}H_9NO_2$	75.32	75.33	4.06	3.76	6.28	6.57	O, 14.34	O, 14.16	650[f]
$C_{14}H_9NO_3$	70.29	70.60	3.79	3.56	5.86	5.85	O, 20.06	O, 20.23[h]	1780
$C_{14}H_8ClNO_2$	65.25	65.40	3.13	3.24	5.44	5.29	Cl, 13.76	Cl, 13.98	1780
$C_{14}H_8BrNO_2$	55.65	55.80	2.67	3.08	4.64	4.68	Br, 26.45	Br, 26.66	420[j]
$C_{14}H_8BrNO_2$	55.65	55.74	2.67	2.45	4.64	4.82	Br, 26.45	Br, 26.34	560[k]
$C_{14}H_6N_2O_4$	62.69	62.84	3.00	2.85	10.44	10.38	O, 23.86	O, 23.04[h]	1780
$C_{14}H_8N_2O_4$	62.69	62.62[h]	3.00	3.13[h]	10.44	10.22	O, 23.86	O, 23.78[h]	1780
$C_{14}H_{10}N_2O_2$	70.58	70.59	4.23	4.05	11.76	11.75			560
$C_{15}H_{12}N_2O_3$	68.56	68.28	4.32	4.39	9.99	9.89			>1000
$C_{18}H_{13}NO_6$	63.72	63.67	3.86	3.72	4.13	4.12			770
$C_{17}H_{15}NO_5$	65.17	65.06	4.83	4.62	4.47	4.46			>1000[l]
$C_{19}H_{20}N_2O_3$	70.35	70.29	6.22	6.29	8.64	8.50			560
$C_{15}H_{12}ClNO_3$[o]	62.18	62.40[h]	4.18	4.33[h]	4.84	5.11	Cl, 12.24	Cl, 12.06	560
$C_{15}H_{11}NO_3$	71.14	70.95	4.38	4.51	5.53	5.59	O, 18.95	O, 18.94[h]	
$C_{16}H_{13}NO_3$	71.90	71.70	4.90	4.79	5.24	5.06			>1000[q]
$C_{20}H_{13}NO_3$	76.18	76.23	4.15	4.11	4.44	4.39	O, 15.22	O, 16.35[h]	1780
$C_{14}H_9NO_3$	70.29	70.44	3.79	3.60	5.86	6.02	O, 20.06	O, 20.04[r]	>1000
$C_{15}H_{11}NO_3$	71.14	71.03	4.38	4.41	5.53	5.79	O, 18.95	O, 19.61[h]	1780[t]
$C_{17}H_{15}NO_5$	65.17	65.06	4.83	4.87	4.47	4.60			>1000[u]

mum inhibitory concentration 10 γ/ml. [l] Depression at 300 and extreme depression at 1000 mg./kg. Body temperature lowering and decrease in motor activity of mice at 200 mg./kg. [m] Crude (undistilled) 4-(γ-dimethylaminopropoxysalicylaldehyde) was used in this preparation and the yield is based on this crude starting material. [n] Hydrochloride salt. [o] *Anal.* Calcd.: O, 16.57. Found: O, 16.55. See ref. 12. [p] Yield of free base from hydrochloride (**13**). [q] Increase in motor activity of mice at 200 mg./kg. and 45% inhibition of monamine oxidase at 10^{-3} *M*; see ref. 9. [r] This analysis by Clark Microanalytical Laboratory. [s] The crude product was sublimed. [t] Depression in mice at 300 mg./kg. [u] Depression in mice at 1000 mg./kg. and in rats at 500 mg./kg. Decrease in motor activity and protection against lethal doses of epinephrine in mice at 200 mg./kg.

overnight, and filtered. On long standing, large crystals mixed with some gum separated. This was collected, giving 14.5 g. of dark solid. A 2-g. sample was sublimed up to 270° (bath) (0.005 mm.) giving 1.85 g. of light yellow solid. Two recrystallizations from ethanol were carried out by boiling with a large excess of solvent, filtering, concentrating, and cooling, furnishing 0.68 g. of pale yellow crystals, m.p. 288–290.5°. The bulk of the dark crystals was recrystallized from Methyl Cellosolve to yield 11.2 g. of tan crystals, m.p. 286–288°. An additional 1 g. was obtained by subliming and recrystallizing the filtrate.

Methyl β-Oxo-4-pyridinepropionate.—A mixture of 1.45 l. (6.5 moles) of 25% methanolic sodium methoxide, 1.5 l. of toluene, and 5.4 l. of dry benzene in a 12-l. flask was slowly distilled with stirring through a Vigreux column until the methanol was removed. The column was replaced by a reflux condenser and a mixture of 617 g. (4.5 moles) of methyl isonicotinate and 667 g. (9.0 moles) of methyl acetate was added slowly under reflux during 2.5 hr. After refluxing for an additional 18 hr. and cooling, the sodium derivative was collected on a filter and washed with benzene and hexane. The solid was dissolved in water and neutralized with acetic acid. The product was extracted with ether and dried over sodium sulfate. Filtration and removal of the solvent gave 250.7 g. of solid which was recrystallized twice from 95% ethanol yielding 160 g. (20%) of nearly white crystals, m.p. 76–78°.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.24; H, 5.15; N, 7.77.

Method A. 5,6,7-Trimethoxy-4-(4-pyridyl)coumarin (19).—A mixture of 1.84 g. (0.01 mole) of 3,4,5-trimethoxyphenol,[13] 1.8 g. (0.01 mole) of methyl β-oxo-4-pyridinepropionate, and 5 ml. of 75% (by weight) sulfuric acid was stirred and shaken for 8 hr. and allowed to stand for 2 days. The red solution was poured into ice–water and made basic with sodium hydroxide. The precipitate was collected, washed with water, and dried, giving 2.5 g. of tan solid, m.p. 182–184°. This was recrystallized from 40 ml. of ethanol giving 2.27 g. of white crystals, m.p. 183–186°.

Method B. 7-Hydroxy-4-(4-pyridyl)coumarin (17).—A mixture of 18.0 g. (0.1 mole) of methyl β-oxo-4-pyridylpropionate, 11.0 g. (0.1 mole) of resorcinol, and 75 g. of polyphosphoric acid was stirred at 70–90° for 30 min. The red mixture was well washed with water and dried, yielding 22.76 g. of orange solid, m.p. 282–294° dec. This was dissolved in 120 ml. of dimethyl sulfoxide, treated with decolorizing charcoal, filtered, and diluted with water at the boiling point until crystallization started. After cooling, 11.6 g. of yellow crystals was obtained, m.p. 297–306°. The aqueous acid solution was neutralized (pH ~6) with sodium hydroxide giving 6 g. of solid which after recrystallization from aqueous dimethyl sulfoxide as above yielded 2.1 g. of solid, m.p. 290–300° dec. The total yield was 13.7 g. A sample was recrystallized from Methyl Cellosolve and sublimed at 250° (0.005 mm.) to yield yellow crystals, m.p. 307–312 dec.

A run using sulfuric acid in place of polyphosphoric acid (method A) gave only 38% yield.

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