2-Pyridones: 1-(Heterocyclic)-1,2-dihydro-2-oxopyridine-5-carboxylic Acids and Derivatives

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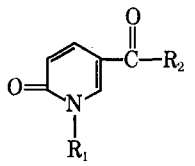
A series of derivatives including esters, amides, and substituted amides of 1-(heterocyclic)-1,2,-dihydro-2-oxopyridine-5-carboxylic acids have been synthesized. The 1-(heterocyclic) moiety has been varied as pyridine, thiazole, and thiadiazole units. The compounds were prepared for an evaluation of their effect upon the central nervous system.

A SERIES of potentially useful central nervous system depressants which are substituted 1-(aminophenyl)-2-pyridones have been synthesized (1). The study has been extended to 1-(heterocyclic)-2-pyridones, in which the heterocyclic moiety is the pyridine, thiazole, or the thiadiazole nucleus, as shown:



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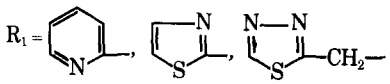
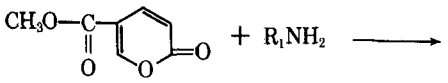


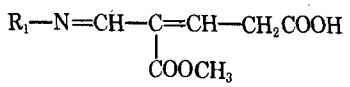
R_2 = hydroxy, alkoxy, amino, substituted amino, phenyl

These compounds are listed in Table I.

In general, the compounds were prepared by the condensation of methyl coumalate (II) with the appropriate heterocyclic amine to form an open-chain Schiff base (III) (2).



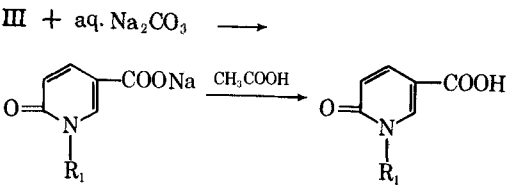
II



III

The Schiff base was then cyclized by heating in a basic solution, usually aqueous sodium carbonate. Cyclization (3, 4) was accompanied by the hydrolysis of the ester group, and the acid was isolated by acidification with glacial acetic acid, as shown in Scheme I.

The acids thus obtained were converted to the various amides and substituted amides through the



Scheme I

intermediate acid chloride which was produced by the addition of thionyl chloride to a suspension of the acid in chloroform or benzene; the acid chloride then was caused to react with the appropriate amine.

The methyl esters were prepared by saturating at 0° a mixture of the respective acid in methanol with hydrogen chloride gas and then refluxing for several hours.

The ketone (Table I, compound *23*) was formed from the appropriate acid chloride by a Friedel-Crafts reaction with benzene.

The methiodides of several of the compounds (Table I, *2, 10, 16, 18*) were prepared by warming the solution of the base in dimethylformamide with methyl iodide.

EXPERIMENTAL

General Procedure for Preparation of 1-(Heterocyclic)-2-pyridone-5-carboxylic Acids (I)

A solution of 0.2 mole of methyl coumalate in 80 ml. of ethanol was added rapidly to a stirred solution of 0.2 mole of the appropriate heterocyclic amine in 60 ml. of ethanol. The Schiff base precipitated either immediately or after 0.5 hr. The mixture was allowed to stand overnight, after which the solid was collected and washed with ethanol.

Ten grams of the Schiff base was added to 100 ml. of 15% aqueous sodium carbonate. The mixture was heated with stirring at 60–70° for 5–10 min., cooled to room temperature, filtered, and acidified to pH 5 with glacial acetic acid. The solid which formed was collected by filtration and washed with 10% acetic acid. After having been dried in the oven at 100°, the product was recrystallized from glacial acetic acid.

General Procedure for Preparation of 1-(Heterocyclic)-2-pyridone-5-carboxamides (II)

A. Preparation of Acid Chlorides.—To a slurry of 0.05 mole of the appropriate carboxylic acid in 100 ml. dry chloroform at 0–5° was added 0.2 mole of thionyl chloride. After addition, the mixture was allowed to warm spontaneously. A vigorous reaction started at 20–30°. When the reaction subsided, the mixture was refluxed 0.5 hr. The chloroform and excess thionyl chloride were removed by distillation under reduced pressure. Then two

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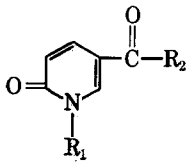
TABLE I.—COMPOUNDS STUDIED



Compd.	R_1	R_2	Yield, %	M.p., °C.[c]	Procedure	Recrystallizing Solvent[a]	Formula	Anal., Calcd.	Anal., Found
1	2-Thiazolyl	OH	20	264–265	I	1	$C_9H_6N_2O_3S$	C, 48.64 H, 2.70 N, 12.61 S, 14.41	48.71 2.69 12.55 14.81
2	2-Thiazolyl	OH (methiodide)	73	244.5–246.5	V	2	$C_9H_6N_2O_3S \cdot CH_3I$	I, 34.85	34.62
3	2-Thiazolyl	OCH_3	4	161–163	III	3	$C_{10}H_8N_2O_3S$	C, 50.85 H, 3.39 N, 11.86 S, 13.56	51.20 3.47 11.60 13.61
4	2-Thiazolyl	NH_2	75	268–269.5	IIB*2*	9	$C_9H_7N_3O_2S$	C, 48.91 H, 3.19 N, 19.02	48.40 3.44 19.12
5	2-Thiazolyl	$N(CH_2CH_3)_2$	40	141.5	IIB*1*	4	$C_{13}H_{15}N_3O_2S$	C, 56.30 H, 5.45 N, 15.15	56.42 5.37 15.15
6	2-Thiazolyl	1-Pyrrolidino	47	204.5–206.5	IIB*2*	5	$C_{13}H_{13}N_3O_2S$	C, 56.71 H, 4.76 N, 15.26	56.73 4.94 15.24
7	4-Methyl-2-pyridyl	OH	65	259–261	I	1	$C_{12}H_{10}N_2O_3$	C, 62.61 H, 4.35 N, 12.17	62.45 4.52 12.01
8	4-Methyl-2-pyridyl	OCH_3	54	212.5–213	III	3	$C_{13}H_{12}N_2O_3$	C, 63.92 H, 4.95 N, 11.47	63.36 4.79 11.44
9	2-Pyridyl	OH	27	277–279	I	1	$C_{11}H_8N_2O_3$	C, 61.11 H, 3.70 N, 12.96	61.34 4.07 12.98
10	2-Pyridyl	OH (methiodide)	60	266–266.5	V	2	$C_{11}H_8N_2O_3 \cdot CH_3I$	I, 35.45	35.18
11	2-Pyridyl	OCH_3	54	163–164.5	III	3	$C_{12}H_{10}N_2O_3$	C, 62.60 H, 4.38 N, 12.17	62.80 4.70 12.16
12	2-Pyridyl	1-Pyrrolidino	52	183.5–184.5	IIB*1*	3	$C_{16}H_{16}N_3O_2$	C, 66.90 H, 5.61 N, 15.61	67.15 5.85 15.61
13	2-Pyridyl	1-Morpholino	40	199.5–200	IIB*1*	4	$C_{15}H_{15}N_3O_3$	C, 63.15 H, 5.30 N, 14.73	63.06 5.48 14.47
14	2-Pyridyl	$N(CH_2CH_3)_2$	44	149.5–150	IIB*1*	10	$C_{15}H_{17}N_3O_2$	C, 66.40 H, 6.32 N, 15.49	66.81 6.37 15.38
15	2-Pyridyl	2-Pyridylamino	28	281–281.5	IIB*2*	6	$C_{16}H_{12}N_4O_2$	C, 65.75 H, 4.14 N, 19.17	66.36 4.68 19.18
16	2-Pyridyl	2-Pyridylamino (dimethiodide)	77	233–234.5	V	2	$C_{16}H_{12}N_2O_2 \cdot 2CH_3I$	I, 44.10	44.69
17	2-Pyridyl	3-Pyridylamino	48	266.5–268	IIB*2*	6	$C_{16}H_{12}N_4O_2$	C, 65.75 H, 4.14 N, 19.17	65.24 4.27 19.38
18	2-Pyridyl	3-Pyridylamino methiodide	76	284.5–285	V	2	$C_{16}H_{12}N_4O_2 \cdot CH_3I$	C, 47.01 H, 3.48 N, 12.90	47.12 3.53 12.78
19	2-Pyridyl	2-Tetrahydrofurylmethylamino	54	193–193.5	IIB*2*	4	$C_{16}H_{17}N_3O_3$	C, 64.20 H, 5.72 N, 14.04	64.87 6.03 14.00
20	2-Pyridyl	NH_2	33	246–249	IIB*2*	11	$C_{11}H_9N_3O_2$	C, 61.39 H, 4.22 N, 19.53	61.47 4.34 19.48
21	2-Pyridyl	1-Methyl-4-piperazinyl	44	152.5–153	IIB*1*	2	$C_{16}H_{18}N_4O_2$[b]	C, 61.99 H, 6.23 N, 18.07	61.86 6.48 18.95
22	2-Pyridyl	$NHCH_2CH_2N(CH_2CH_3)_2$	30	141.5–142.5	IIB*3*	7	$C_{17}H_{22}N_4O_2$	C, 64.94 H, 7.05 N, 17.82	65.13 7.15 17.68
23	2-Pyridyl	Phenyl	40	168–168.5	IV	1	$C_{17}H_{12}N_2O_2$	C, 73.90 H, 4.38 N, 10.14	73.52 4.30 10.35
24	2-(1,3,4-Thiadiazolyl-methyl)	OH	11	254.5–256	I	1	$C_9H_7N_3O_3S$	C, 45.57 H, 2.97 S, 13.51	46.14 3.00 13.74
25	2-(1,3,4-Thiadiazolyl-methyl)	OCH_3	55	213–213.5	III	8	$C_{10}H_9N_3O_3S$	C, 47.80 H, 3.61 S, 12.77	47.75 3.34 12.99
26	2-(1,3,4-Thiadiazolyl-methyl)	$N(CH_2CH_3)_2$	67	200–201	IIB*3*	4	$C_{13}H_{16}N_4O_2S$	C, 53.41 H, 5.51 S, 10.97	54.25 5.64 11.26

[a] Recrystallizing solvents: 1, glacial acetic acid; 2, water; 3, methanol; 4, isopropanol; 5, ethanol; 6, methyl cellosolve; 7, ethyl acetate; 8, dioxane; 9, 50% 2 and 50% 4; 10, 80% 2 and 20% 5; 11, 30% 2 and 70% 4. [b] Analysis is for ⅔ mole water, confirmed by Karl Fischer analysis. [c] All melting points are corrected. They were determined on the Fischer-Johns melting point apparatus.

successive additions of 50 ml. of dry benzene were made, each followed by distillation under reduced pressure to remove last traces of the thionyl chloride.

B. Preparation of the Carboxamides.—*Procedure 1.*—To a slurry of the above acid chloride in 100 ml. of dry chloroform was added 0.2 mole of the respective amine. The mixture was slowly heated to reflux and refluxed 2 hr. The cooled mixture was extracted with 3 *N* hydrochloric acid. The acid solution was washed with chloroform and then adjusted to pH 8 with solid sodium carbonate. The solid was collected by filtration, washed with water, and recrystallized from the appropriate solvent.

Procedure 2.—The acid chloride, prepared as above, was slurried in 100 ml. of dry benzene, and to the slurry at 10–15° was added 0.2 mole of the respective amine. The mixture then was refluxed 5 hr., cooled, and then filtered. The solid was slurried in water, collected by filtration, and washed with water until the wash was colorless. The solid was dried at 70° and recrystallized from the appropriate solvent.

Procedure 3.—The procedure was the same as described for *Procedure 2* except that the water slurry of the product was adjusted to pH 10 with 15% aqueous sodium carbonate before filtration.

Preparation of Methyl Esters of 1-(Heterocyclic)-2-pyridone-5-carboxylic Acids (III)

A mixture of 0.02 mole of the respective carboxylic acid and 100 ml. methanol was saturated at 0° with hydrogen chloride gas. It was then refluxed 3 hr. The methanol and excess hydrogen chloride were removed under reduced pressure. The residue was dissolved in 50 ml. water and the solution adjusted to pH 8 with concentrated ammonium hydroxide. The solid that formed was collected by filtration, washed with water, dried, and recrystallized from methanol.

Preparation of 1-(2-Pyridyl)-5-benzoyl-2-pyridone (IV) (Table I, Compound 23)

The acid chloride from 20 Gm. (0.0924 mole) of 1-(2-pyridyl)-2-pyridone-5-carboxylic acid was prepared as described above. The acid chloride was slurried in 250 ml. of dry benzene, the slurry was cooled to 10°, and to it at 10–15° was added slowly, 49.0 Gm. (0.3696 mole) of aluminum chloride. The mixture was heated slowly. Evolution of hydrogen chloride gas was slow until 35°, at which temperature evolution became vigorous. Heat was applied so that the reaction remained vigorous up to reflux temperature. The reaction then rapidly subsided. The dark red solution was refluxed 1 additional hour, allowed to cool to room temperature, and to stand overnight.

The mass was then poured onto a mixture of 400 Gm. of ice and 75 ml. of concentrated hydrochloric acid. A tan precipitate was formed. When the complex was completely decomposed, the solid was collected by filtration, slurried in water, and adjusted to pH 10 with 15% aqueous sodium carbonate. The yellow-green solid was collected by filtration, dried at 70°, and recrystallized from glacial acetic acid.

Preparation of Methiodides (V)

To a solution of 0.1 mole of the substituted pyridone in 500 ml. of dimethylformamide was added 0.5 mole methyliodide, and the resulting solution was heated at 60–70° for 16 hr. The solid methiodide was filtered from the cooled solution and thoroughly washed with acetone. It was recrystallized from water.

PHARMACOLOGY

In general, little potentially useful activity upon the central nervous system was disclosed by the compounds in this series. One possible exception might be compound *26*, which exhibited weak analgesic activity in both the hot-plate method ED_{50} 375 (337–416) mg./Kg. p.o. and the tail clip technique ED_{50} 360 (330–394) mg./Kg. p.o. The oral LD_{50} in mice was 1600 (1280–2000) mg./Kg.

Attention is also directed to compounds *21* and *22* which increased femoral and coronary blood flow, the potency being approximately one-fourth that of papaverine. These compounds also induced mild central nervous system stimulation without a corresponding increase in blood pressure.

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