β-Pyridylacrylophenones and Analogs

New Class of Active Coronary Dilating Agents

By JOHN KOO*

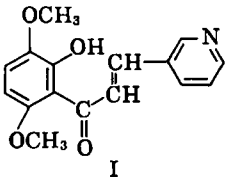
A series of β-pyridylacrylophenones and closely related analogs was synthesized by the condensation of pyridinecarboxaldehydes and other heterocyclic aldehydes with appropriate acetophenones in the presence of various catalysts. The proportions of various reaction products depended upon catalyst and reaction conditions. Several compounds of this type have been found pharmacologically to exhibit remarkable coronary dilating activity.

MANY CHROMONE derivatives exhibit interesting pharmacological activites. Khellin has long been used as a vasodilator (1, 2); recently, some 5,8-dimethoxychromone derivatives were found to exert a powerful coronary dilating (3) or central nervous system depressing action (4). Also, it has been reported (5, 6) that flavonoids possess the ability to form chalcones under certain biological conditions.

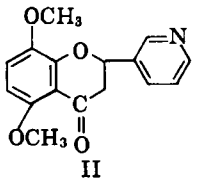
Our investigations in the chromone series (4, 7) therefore were extended to chalcone-type compounds—namely, heterocyclic acrylophenone, whose structures corresponded to some active chromones. Desirable structural features for pharmacological activity were a β-substituted heterocyclic radical, the presence of methoxy-groups, and a 2-hydroxy group in the acrylophenone structure.

The β-heterocyclic-acrylophenones reported here were synthesized according to the usual route for chalcones by condensation of a pyridyl or other heterocyclic carboxaldehyde with the appropriate acetophenone. Several synthetic methods employing various catalysts, solvents, and conditions were evaluated. The catalysts employed were sodium hydroxide in ethanol-water (8, 9), piperidine in absolute ethanol, piperidine in pyridine (10), and piperidine-acetic acid in benzene (11). Depending upon the catalyst and conditions used, similar reactants might form products different from those expected. Also, the reaction of the same acetophenone with different isomeric pyridine-carboxaldehydes using the same catalyst system under identical reaction conditions frequently produced different results. Two factors might be responsible for some difficulties encountered by us. First, the electronic effects of the heterocyclic moiety appeared to influence the course of reaction. Second, the presence of the hydroxy-group on the 2-position of the phenyl ring added the complication of possible ring closure.

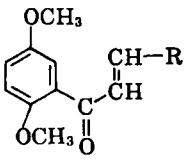
Condensation of 3,6-dimethoxy-2-hydroxyacetophenone[1] with 3-pyridinecarboxaldehyde in ethanol-water with sodium hydroxide as catalyst at 5° yielded the expected 3,6-dimethoxy-2-hydroxy-β-(3-pyridyl)-acrylophenone (I). Its hydrochloride was isolated as cherry-red needles. However, by using absolute ethanol as solvent in the presence of piperidine as catalyst under prolonged heating, the isomeric colorless 5,8-dimethoxy-2-(3-pyridyl)-chromanone (II) was obtained in addition to I.



I



II



III

IIIa, R = 

IIIb, R = 

IIIc, R = 

To study the relationship between the 2-hydroxy-group and the pharmacological activity of I and also to shorten the synthetic route, 2,5-dimethoxyacetophenone was employed in place of 3,6-dimethoxy-2-hydroxyacetophenone. By condensation of this compound with 4-pyridinecarboxaldehyde in pyridine or absolute ethanol with piperidine as catalyst, 2,5-dimethoxy-β-(4-pyridyl)-acrylophenone (III*a*) was then obtained.

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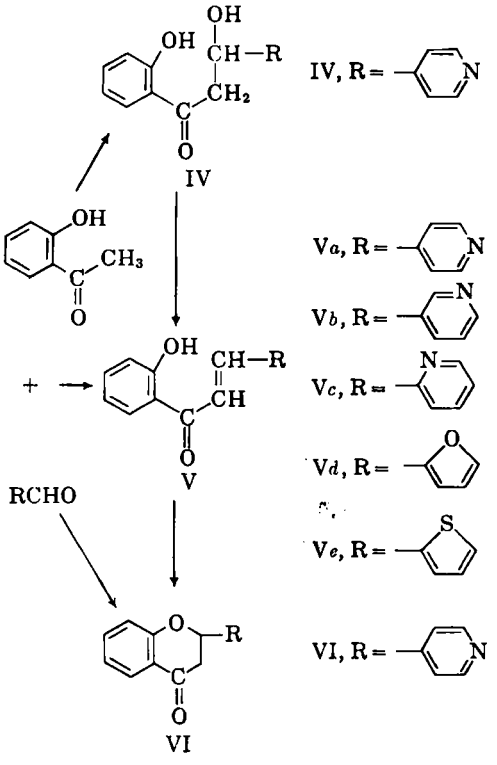
* Present address: Geigy Research Laboratories, Ardsley, N. Y.

[1] This compound was prepared according to the general route of Baker (12) in four steps from 2,6-dihydroxyacetophenone, which in turn was obtained in another four steps from resorcinol by following the method of Frye (13). However, the product of the first step, 4-methyl-7-hydroxy-coumarin, was produced more conveniently by using polyphosphoric acid instead of sulfuric acid as the condensing agent (14) and the last compound, 3,6-dimethoxy-2-hydroxyacetophenone, was obtained by an improved method of catalytic debenzylation of the corresponding benzyloxy-analog, as described under *Experimental*.

By an analogous reaction in absolute ethanol, using pyridine or benzene with piperidine or piperidine-acetic acid as catalyst, the 3-pyridyl isomer (III*b*) was obtained in better yields. Similarly, the 2-pyridyl isomer (III*c*) was obtained in absolute ethanol or pyridine in the presence of piperidine as catalyst.



For further pharmacological study, work was then extended to 2-hydroxy-β-heterocyclic-acrylophenones containing no methoxy-groups. Condensation of 2-hydroxyacetophenone and 4-pyridinecarboxaldehyde in ethanol-water with sodium hydroxide as catalyst gave both the colorless 2′,3-dihydroxy-3-(4-pyridyl)-propiophenone (IV) and its dehydration product, the yellow 2-hydroxy-β-(4-pyridyl)-acrylphenone (V*a*). When heated mildly with dilute hydrochloric or sulfuric acid or polyphosphoric acid, IV was promptly dehydrated to the yellow compound V*a*. However, the same condensation carried out in absolute ethanol or pyridine catalyzed with piperidine gave the colorless ring-closed product 2-(4-pyridyl)-chromanone (VI). Alternatively, when piperidine-acetic acid was used as catalyst in benzene solution for the same reaction, IV was the chief product which gradually changed to the yellow compound V*a* upon standing in air or in solution. The results of these experiments support the view that the mechanism of the reaction between a 2-hydroxyacetophenone and a heterocyclic aldehyde is first to form the ketol IV which then dehydrates to an acrylophenone V and finally undergoes ring closure to a chromanone VI. The state at which the reaction stops is strongly conditioned and catalyst dependent.

However, when 3- or 2-pyridylcarboxaldehyde was employed with sodium hydroxide at catalyst for the analogous condensation, the only product isolated was V*b* or V*c*. The preparation of the 2-furyl (V*d*) and the 2-thiophenyl (V*e*) analogs were similarly achieved using the usual aqueous ethanolic sodium hydroxide procedure for the condensation.

Pharmacology.—Pharmacological study[2] of these compounds showed that a few of them exhibited remarkable coronary dilating action with relatively low toxicity. Both compounds I and III*b* increased similarly the coronary flow in the Langendorf preparation of the excised cat heart, when 5 to 100 mcg. were introduced into the perfusion system at the aortic cannula. Quantitatively, the coronary dilating action compared favorably with published data by Khellin on similar action. The effect usually reached its maximum over approximately a 30-minute period. Doses of 5 to 10 mg./Kg. of these compounds given intravenously to the dog lowered the arterial pressure moderately, accompanied by a brief apnea, which was later followed by respiratory stimulation. Fighting of the Siamese fighting fish (*Beta splendens*) was suppressed in concentrations of 0.1 to 0.5 mcg./ml. of solution. Evipal sleeping time in mice was significantly prolonged by 250 mg./Kg. of III*b* orally, while compound I exhibited no significant action.

Compound III*a* also exerted coronary dilating action inconsistently at doses of about 2 to 6 mcg.; Evipal sleeping time was considerably potentiated. No consistent action on coronary flow was shown by IV. It was moderately hypotensive at about 5 to 20 mg./Kg. i.v. in dogs and potentiated Evipal sleeping time in mice considerably.

Compounds V*a*, V*b*, and V*c* increased coronary flow moderately at doses of about 50 to 100 mcg. They showed mild hypotensive action at about 2 to 10 mg./Kg. i.v. in dogs. Also, 2-hydroxy-5-chloro-β-(2-pyridyl)-acrylophenone, which was one of several previously known compounds synthesized for pharmacological study, exhibited moderate coronary dilating action by Langendorf preparation at doses of about 2 to 10 mcg. and was moderately hypotensive at levels of 2 mg./Kg. i.v. in dogs. The acute oral LD_{50} of I in mice was approximately 600 mg./Kg., and its acute intravenous LD_{50} was 52 mg./Kg. The acute oral and intravenous LD_{50} of III*b* were 1000 mg./Kg. and 55–68 mg./Kg.

A preliminary study of the correlation between structure and activity of many newly synthesized and some known heterocyclic-substituted acrylophenones seems to indicate that the presence of the 3,6-dimethoxy and 3-pyridyl groups are essential to insure a higher degree and greater consistency of coronary dilating action. The 2-hydroxy group does not appear to be necessary for the activity; its omission even reduces the toxicity moderately.

[2] The pharmacological study was made by Dr. S. Krop and associates.

EXPERIMENTAL[3]

3,6-Dimethoxy-2-hydroxyacetophenone.—To a solution of 14.3 Gm. of 2,5-dimethoxy-6-benzyloxyacetophenone (see *Footnote 1*) in 100 ml. of absolute ethanol was added 4 Gm. of 5% Pd on charcoal catalyst, and the mixture was hydrogenated at room temperature under 40 lb. pressure for 1.5 hours. It was then filtered, and the solution was evaporated to give 8.3 Gm. (95%) of a yellow crystalline solid, m.p. 60–61° [reported (12) m.p. 61°]. In our investigation the original hydrochloric-acetic acid procedure of debenzylation gave only about 70% yield of less pure material.

3,6-Dimethoxy-2-hydroxy-β-(3-pyridyl)-acrylophenone Hydrochloride (I).—(*a*) To a stirred solution of 1.8 Gm. of 3,6-dimethoxy-2-hydroxyacetophenone in 50 ml. of 10% NaOH aqueous ethanol (2:1) solution at 10° there was added 1.1 Gm. of 3-pyridinecarboxaldehyde. Stirring was continued for 5 hours while the solution was permitted to come to room temperature. The solution was acidified with dilute hydrochloric acid to pH 7, and the yellow oil which separated was extracted with ether. After drying over magnesium sulfate, the ether solution was treated with hydrogen chloride gas, causing a heavy precipitate to form. It was recrystallized first from ethanol-ether and then from aqueous ethanol to yield 0.2 Gm. (7%) of cherry-red needles, m.p. 233–234° dec.

Anal.—Calcd. for $C_{16}H_{16}ClNO_4$: C, 59.54; H, 5.31; N, 4.34. Found: C, 59.47; H, 5.09; N, 4.41.

(*b*) A solution of 3.92 Gm. of 3,6-dimethoxy-2-hydroxyacetophenone and 2.14 Gm. of 3-pyridinecarboxaldehyde in 60 ml. of absolute ethanol containing 16 drops of piperidine was gently refluxed for 3 hours. The reaction mixture was concentrated to a small volume, diluted with cold water, and repeatedly extracted with ether. After drying, the combined ether extracts were concentrated to a small volume. Some colorless material which separated was filtered off, and the ether solution was saturated with hydrogen chloride gas. The reddish paste which separated was recrystallized from absolute ethanol twice to give 0.75 Gm. (11%) of red needles. The melting point and mixed melting point with the material obtained from method (*a*) was 233–234° dec.

5,8-Dimethoxy-2-(3-pyridyl)-chromanone (II).—The colorless material obtained from the above experiment (*b*) weighed 0.5 Gm. (8%), m.p. 162–166°. It was recrystallized from dilute ethanol as long colorless needles, m.p. 170°. It was not soluble in dilute sodium hydroxide solution, and the infrared spectrum exhibited a strong carbonyl band at 5.9 μ.

Anal.—Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.55; H, 5.44; N, 4.80.

2,5-Dimethoxy-β-(4-pyridyl)-acrylophenone Hydrochloride (III*a*).—(*a*) A solution of 82 Gm. of 2,5-dimethoxyacetophenone, 50 Gm. of 4-pyridinecarboxaldehyde, and 14 ml. of piperidine in 200 ml. of absolute ethanol was refluxed gently for 55 hours. The dark solution was diluted with cold water and extracted with ether. The ether solution was washed with sodium bisulfite solution, dried over magnesium sulfate, and filtered. Introduction of hydrogen chloride gas to the ether solution yielded 75 Gm. (53%) of a yellow precipitate, m.p. 190–195°. It was recrystallized from absolute ethanol three times to give 17.5 Gm. (12%) of long bright-yellow needles, m.p. 229–230° dec.

Anal.—Calcd. for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.24; N, 4.58. Found: C, 62.63; H, 5.40; N, 4.62.

(*b*) A solution of 27 Gm. of 2,5-dimethoxyacetophenone, 16 Gm. of 4-pyridinecarboxaldehyde, 100 ml. of pyridine, and 15 drops of piperidine was heated on the steam bath for 8 hours. The pyridine was evaporated under reduced pressure, and the residue was diluted with water. The oily material was extracted with ether; the ether solution was washed with saturated sodium bisulfite, cold water, then extracted with 15% hydrochloric acid. On cooling, the acid solution 3.2 Gm. (7%) of yellow product separated, m.p. 220–225°. It was recrystallized from absolute ethanol twice to give bright fluffy needles, m.p. 228–230°. The mixed melting point with the sample obtained from method (*a*) showed no depression.

2,5-Dimethoxy-β-(3-pyridyl)-acrylophenone Hydrochloride (III*b*).—(*a*) A solution of 11 Gm. of 3-pyridinecarboxaldehyde and 18 Gm. of 2,5-dimethoxyacetophenone in 200 ml. of absolute ethanol was heated for 72 hours in the presence of 20 drops of piperidine. It was then worked up by the method (*b*) for compound III*a*. There was obtained 15.5 Gm. (49%) of bright-yellow needles, m.p. 204–205° dec.

Anal.—Calcd. for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.24; N, 4.58. Found: C, 62.71; H, 5.53; N, 4.65.

(*b*) By method (*b*) of III*a*, heating a solution of 11 Gm. of 3-pyridinecarboxaldehyde, 18 Gm. of 2,5-dimethoxyacetophenone in 150 ml. of pyridine, and 20 drops of piperidine for 5 hours yielded 11 Gm. (34%) of bright-yellow product. The melting point and mixed melting point with product from (*a*) were 204–205°.

(*c*) To a solution of 9 Gm. of 5.5 Gm. of 3-pyridinecarboxaldehyde and 9 Gm. of 2,5-dimethoxyacetophenone in 50 ml. of absolute ethanol was added 1 ml. of piperidine and 3 ml. of acetic acid. It was gently refluxed for 25 hours, then worked up as in method (*b*) of III*a*. The yield of product was 7.7 Gm. (49%), and the mixed melting points with sample from above experiments were 204–205° dec.

2,5-Dimethoxy-β-(2-pyridyl)-acrylophenone Hydrochloride (III*c*).—(*a*) A solution of 18 Gm. of 2,5-dimethoxyacetophenone, 10.7 Gm. of 2-pyridinecarboxaldehyde, and 20 drops of piperidine in 60 ml. of absolute ethanol was refluxed for 50 hours and then worked up as method (*a*) of III*b*. The yield of bright-yellow needles was 6.5 Gm. (41%), m.p. 189–190°.

Anal.—Calcd. for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.24; N, 4.58. Found: C, 62.82; H, 5.54; N, 4.86.

(*b*) The above experiment was repeated with pyridine instead of ethanol as solvent, yielding 2 Gm. (12%) of pure product.

2-Hydroxy-β-(4-pyridyl)-acrylophenone (V*a*).—To a stirred solution of 21.5 Gm. of 4-pyridinecarboxaldehyde in 300 ml. of 10% NaOH aqueous ethanol (2:1) solution was added dropwise 27.2 Gm. of 2-hydroxyacetophenone over a 1-hour

[3] Experiments were carried out during 1956 and early 1957. Melting points are uncorrected. Analyses were performed by Mr. E. R. Hoffman and staff, Research Division, Ethicon, Inc.

period. The stirring was continued at 5–10° for 8 hours and then at room temperature for 1 hour more. The reaction mixture was diluted with cold water, extracted with ether, and acidified with acetic acid to pH 6. The oily material which separated was shaken with ether. Some pale-yellow solid, which was not soluble in ether, was filtered out. The ether solution was first washed with sodium bisulfite solution, then with 10% hydrochloric acid solution. This acidic solution was made weakly basic with sodium carbonate solution. The heavy yellow precipitate that formed was filtered off, washed, and dried, yielded 25 Gm. (55%), m.p. 110–116°. It was recrystallized once from 70% ethanol to yield 3.5 Gm. (8%) pure product as long yellow needles, m.p. 124–125°. Concentration of the above filtrate yielded only a dark oil. It seemed likely that most of the crude product was decomposed during the recrystallization.

Anal.—Calcd. for $C_{14}H_{14}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.68; H, 4.92; N, 6.08.

2',3-Dihydroxy-3-(4-pyridyl)-propionphenone (IV).—(*a*) The pale-yellow material separated from the above experiment weighed 3.5 Gm. (7.5%), m.p. 141–145°. It was recrystallized twice from ethanol to give colorless needles, m.p. 147–149°.

Anal.—Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.36; H, 5.54; N, 5.85.

When this compound was warmed with dilute hydrochloric acid, sulfuric acid, or polyphosphoric acid, it was readily dehydrated to the yellow acrylophenone (V*a*).

(*b*) To a solution of 13.6 Gm. of 2-hydroxyacetophenone and 11 Gm. of 4-pyridinecarboxaldehyde in 200 ml. of benzene in a 500-ml. round-bottom flask fitted with a water-benzene separator, was added 4 ml. of acetic acid and 2 ml. of piperidine. The solution was refluxed for 20 hours and then washed with cold water, 30% sodium bisulfite solution, and again with water. The benzene was extracted with two 50-ml. portions of 20% hydrochloric acid solution. Upon standing at room temperature, some of the hydrochloride of IV separated and was filtered, weighing 2.1 Gm. (8%), m.p. 202–204°. It was recrystallized from ethanol-ether to provide cream-colored crystals, m.p. 205–206°.

Anal.—Calcd. for $C_{14}H_{14}ClNO_3$: N, 5.01; Cl, 12.67. Found: N, 4.78; Cl, 12.48.

The acid filtrate was neutralized with potassium carbonate solution, causing 4.5 Gm. (18%) of the free base of IV to precipitate, m.p. 145–148°. It was recrystallized once from benzene-petroleum ether to yield off-white material, m.p. 148–149° (deep-yellow melt). The mixed melting point with a sample from (*a*) was not depressed.

2-Hydroxy-β-(3-pyridyl)-acrylophenone (V*b*).—This compound was prepared from 22 Gm. of 3-pyridinecarboxaldehyde and 28 Gm. of 2-hydroxyacetophenone in 300 ml. of sodium hydroxide solution by the method of V*a*, giving 4.5 Gm. (10%) of yellow needles, m.p. 149–150° [reported (13) m.p. 161–162°].

Anal.—Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.40; H, 5.22; N, 6.15.

2-Hydroxy-β-(2-pyridyl)-acrylophenone (V*c*).—This compound was obtained from 10.7 Gm. of 2-pyridinecarboxaldehyde and 13.6 Gm. of 2-hydroxyacetophenone similarly by the method of V*a*, giving 14.5 Gm. (60%) of yellow product, m.p. 98–99° [reported (15) m.p. 101–102°].

Anal.—Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.86; H, 5.19; N, 6.05.

2-Hydroxy-β-(2-furyl)-acrylophenone (V*d*).[4]—The condensation of 14 Gm. of 2-hydroxyacetophenone and 10 Gm. of 2-furaldehyde in 150 ml. of 15% NaOH aqueous ethanol (2:1) gave 9 Gm. (42%) of long yellow needles, m.p. 109–110°.

Anal.—Calcd. for $C_{13}H_{10}O_3$: C, 72.98; H, 4.71. Found: C, 73.40; H, 5.01.

2-Hydroxy-β-(2-thiophenyl)-acrylophenone (V*e*).—This compound was obtained according to the above method from 4.6 Gm. of 2-hydroxyacetophenone and 3.8 Gm. of 2-thiophenecarboxaldehyde, giving 2.5 Gm. (37%) of yellow needles, m.p. 99–100°.

Anal.—Calcd. for $C_{13}H_{10}O_2S$: C, 67.80; H, 4.38; S, 13.92. Found: C, 67.97; H, 4.49; S, 13.60.

2-(4-Pyridyl)-chromanone (VI).—(*a*) To a solution of 10.7 Gm. of 4-pyridinecarboxaldehyde and 13.6 Gm. of 2-hydroxyacetophenone in 100 ml. of absolute ethanol was added 3 ml. of piperidine, and the solution was heated on a steam bath for 3 hours. The dark reaction mixture was then allowed to stand at room temperature for 1 week, during which time a yellow solid separated. It was filtered off, washed with a little cold water, and dried, 5.5 Gm. (24%), m.p. 210–215°. The crude material was recrystallized from 95% ethanol to give colorless needles, m.p. 224–225°.

Anal.—Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.93; N, 6.22. Found: C, 74.68; H, 4.83; N, 5.95.

(*b*) To a solution of 13.6 Gm. of 2-hydroxyacetophenone and 10.6 Gm. of 3-pyridinecarboxaldehyde in 150 ml. of pyridine was added 1 ml. of piperidine. The solution was gently refluxed on a steam bath for 3 hours, then diluted with cold water. The dark-red paste which separated was recrystallized from ethanol to give 3.5 Gm. (15%) of colorless needles, m.p. 225°. Neither of the products from the above experiments was soluble in dilute sodium hydroxide solution, and the mixed melting point was 224–225°. The infrared spectra of both materials were identical with a strong carbonyl band at 5.9 μ.

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[4] The preparation of this compound was mentioned in the earlier literature (16), but the material was neither characterized nor were experimental details given.