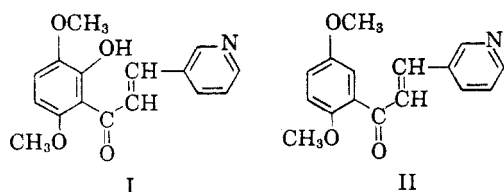


β -Pyridylacrylophenones. A New Class of Active Coronary Dilating Agents

Sir:

Among the physiological activities proposed¹ for the flavonoids are effects upon the vascular systems. The ability of compounds of this type to form chalcones under biological conditions is also significant.^{1,2} Khellin, which contains a chromone nucleus, has long been used as a vasodilator, and more recently it was reported that 5,8-dimethoxychromone derivatives possess potential coronary dilating³ and tranquilizing properties⁴ accompanied by muscle relaxation actions. These facts suggested the possibility that β -substituted acrylophenones⁵ with structures corresponding to those active chromones might also exhibit interesting pharmacological activities. Consequently, a series of β -substituted acrylophenones were synthesized, and their physiological properties were studied. A few of these compounds were found to exert a powerful coronary vasodilating activity with low toxicity. The syntheses and pharmacology of two representative compounds are reported here.



Condensation of 3,6-dimethoxy-2-hydroxyacetophenone^{4,6} with 3-pyridinecarboxaldehyde in the presence of piperidine or sodium hydroxide solution as catalyst gave 3,6-dimethoxy-2-hydroxy- β -(3-pyridyl)acrylophenone (I) as a yellow oil, the hydrochloride of which formed red needles, m.p. 233–234 dec. (*Anal.* Found for $C_{16}H_{15}NO_4 \cdot HCl$: C, 59.47; H, 5.07; N, 4.41.) In addition, an isomer produced by cyclization of I, namely, 5,8-dimethoxy-2-(3-pyridyl)chromanone, was also isolated in the form of colorless, fluffy needles; m.p. 170°. (*Anal.* Found for $C_{16}H_{15}NO_4$: C, 67.55; H, 5.44; N, 4.80.)

In order to learn whether the 2-hydroxy group of I was necessary for physiological activity, 2,5-dimethoxy- β -(3-pyridyl)acrylophenone (II) was subsequently synthesized by the analogous reaction of 2,5-dimethoxyacetophenone with 3-pyridinecar-

boxaldehyde. Its hydrochloride, formed as yellow needles, melted at 204–205° dec. (*Anal.* Found for $C_{16}H_{15}NO_3 \cdot HCl$: C, 62.71; H, 5.53; N, 4.65.)

Both I and II increased similarly the coronary flow in the Langendorf preparation of the excised cat heart, when 5 to 100 micrograms were introduced into the perfusion system at the aortic cannula. The coronary dilating action compares quantitatively very favorably with published data on similar action by Khellin. Doses of 5 to 10 mg./kg. given intravenously to the dog lowered the arterial pressure moderately. 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 II were 1000 mg./kg. and 55 to 68 mg./kg., respectively.⁷ These results indicate that the 2-hydroxy group of I is not essential for activity, but that its omission reduces the toxicity slightly. A further study of the correlation between structure and activity of the many substituted acrylophenones synthesized seems to indicate that the presence of the 3,6-dimethoxy and pyridyl groups are necessary to ensure a higher degree of coronary dilating action.

The present findings appear to provide a new approach in the search for more effective cardiovascular drugs.

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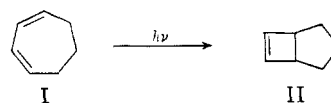
(7) The pharmacology study of these compounds by Dr. S. Krop and associates, A. Cameron, M. L. Greame, and E. Siegmund, Ethicon Inc., is gratefully acknowledged.

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Photoisomerization of 3,5-Cycloheptadienones

Sir:

The generality of the photoisomerization of cycloheptadienes to bicyclo[3.2.0]heptenes (I to II) has been well established for a variety of substituted cycloheptadienes^{1,2} as well as 1,3-cycloheptadiene (I).^{1,3} Among the substituted cycloheptadienes which undergo this type of photoisomerization are the conjugated dienones eucarvone (III, $R_1 = CH_3$,



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