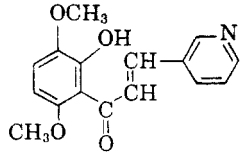
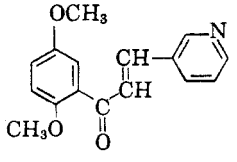
β-Pyridylacrylophenones. A New Class of Active Coronary Dilating Agents

Sir:

Among the physiological activities proposed[1] 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 dilating[3] and tranquilizing properties[4] accompanied by muscle relaxation actions. These facts suggested the possibility that β-substituted acrylophenones[5] 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.



I



II

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-pyridinecarboxaldehyde. 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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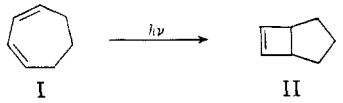
Photoisomerization of 3,5-Cycloheptadienones

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, $R_1 = CH_3$,



I II

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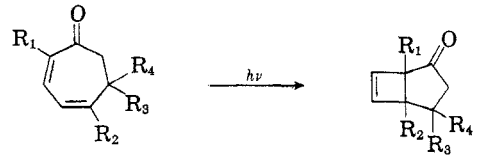
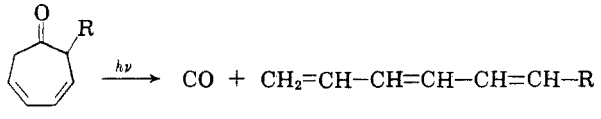
R_2 = H, R_3 = R_4 = CH_3)[4,5] and 4-methoxy-2,4-cycloheptadienone (III, R_1 = H, R_2 = OCH_3, R_3 = R_4 = H).[1]



III IV

Irradiation of 3,5-cycloheptadienones (V), however, follows a different course. Irradiation of a dilute solution of 2-methyl-3,5-cycloheptadienone (V, R = CH_3) in ether gives carbon monoxide (95%) and a mixture of geometric isomers of 1,3,5-heptatriene (VI, R = CH_3). The 1,3,5-heptatriene mixture, purified by preparative scale vapor phase



V VI

chromatography, showed (95% ethanol) λ_{max} 252 (26,800), 261 (36,400), and 271 mμ (28,900) and infrared maxima at 5.56, 6.11, 6.16, 7.29, and 11.19 μ and had the correct analysis for C_7H_{10}. Hydrogenation of VI gave *n*-heptane identical in infrared absorption and vapor phase chromatographic retention time with an authentic sample.

In similar fashion, irradiation of 3,5-cycloheptadienone (V, R = H) gives 1,3,5-hexatriene (VI, R = H; λ_{max} 247, 256, 267 mμ).[6]

This reaction is related to both the ring cleavage of 1,3-cyclohexadienes[7] and the elimination of carbon monoxide from saturated ketones.[8] The reaction proceeds smoothly in Pyrex vessels which must mean that the initial excitation involves the $n \rightarrow \pi^*$ transition of the carbonyl group.[9] This could involve an intramolecular transfer of energy from the triplet state of the carbonyl group to the diene system analogous to the intermolecular energy transfer between the low lying triplet state of benzophenone and acylic dienes.[11] Mechanisms involving cyclohexadiene are excluded by the formation of the trienes in Pyrex vessels. Further investigation of the mechanism of this transformation is in progress.

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