sapogenins, and the possibility now exists of monitoring these steroid transformation reactions by gas chromatography. The techniques should be equally useful in biochemical or biological studies involving sapogenins and other steroids.

LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS
NATIONAL HEART INSTITUTE
BETHESDA 14, MARYLAND
W. J. A. VANDENHEUVEL
E. C. HORNING

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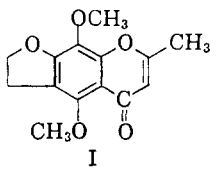
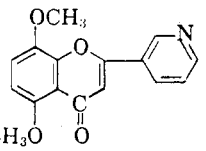
New Classes of Active Central Nervous System Depressing and Stimulating Agents

Sir:

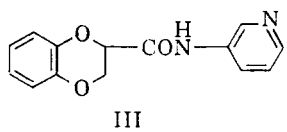
Khellin (I), a principal active component isolated from the fruit of the Mediterranean plant, *Ammi visnaga*, has been shown to possess a direct relaxing action on visceral smooth muscle and has been used frequently in the treatment of coronary deficiency disease.[1] A few synthetic 5,8-dimethoxychromones, which may be regarded as defuro-khellin derivatives, appeared recently in animal testing to have greater activity than khellin itself.[2] Also, it is of interest to note that one of the chief actions of many of the psychotherapeutic agents currently used in medical practice is to induce muscular relaxation[3] both in animals and humans. In the light of these facts, it was thought that some 5,8-dimethoxychromones, with selected substituents in the 2 position might have similar physiological effects.



I



II



III

Since late 1952 we have been working with the 5,8-dimethoxychromones and analogs.[4] Among many compounds of this type synthesized, one, 5,8-dimethoxy-2-(3-pyridyl)chromone(II), was found to be the most active as a central nervous system depressant. To our knowledge this is the first demonstration that a chromone possesses this type of activity.

Condensation of 2,5-dimethoxy-6-hydroxyacetophenone[5] with ethyl nicotinate in the presence of sodium hydride gave 3,6-dimethoxy-2-nicotinylacetophenol as bright yellow needles m.p. 120–121°. (*Anal.* Found for $C_{16}H_{15}NO_5$: C, 63.93; H, 5.02; N, 4.76). Treatment of this material with sulfuric acid in ethanol resulted in ring closure to yield the desired product (II) as pale yellow to colorless needles, m.p. 178–179° (*Anal.* Found for $C_{16}H_{13}NO_4$: C, 67.80; H, 4.63; N, 4.76).

Oral administration of II (50 mg./kg.) to mice greatly reduced spontaneous motility and increased evipal sleeping time from four to five times, while meprobamate, one of the most widely used psychopharmacologic agents, was needed in much larger doses (110–200 mg./kg.) in order to exhibit an equal effect. Also, the ataractic suppression of II against aggressive behavior in mice required a dose of 70 mg./kg. instead of 200 mg./kg. for meprobamate.[6] These tests indicated that II is about three times as potent as meprobamate. Meanwhile, II was found to be three times less toxic than that of meprobamate. Similarly, a very potent tranquilizing action was observed[7] by administration of II to fighting fish, cats, dogs and monkeys.

In exploring variations in the structure of II, it was recalled that the 1,4-benzodioxan ring system has a formal structural relation to that of chromone. Therefore, an extended series of compounds of this type was prepared.[8–10] *N*-(3-Pyridyl)-1,4-benzodioxan-2-carboxamide (III), m.p. 154–155° (*Anal.* Found for $C_{14}H_{12}N_2O_3$: C, 65.47; H, 4.80; N, 10.88), obtained by the acylation of 3-amino-pyridine with 1,4-benzodioxan-2-carbonyl chloride,[8] has been found[7] for the first time to exhibit outstanding central nervous system stimulating action as an analep-

(1) G. V. Anrep *et al.*, *J. Pharm. and Pharmacol.*, **1**, 164 (1949) and *Am. Heart J.*, **37**, 531 (1949); K. Samaan *et al.*, *J. Pharm. and Pharmacol.*, **1**, 538 (1949); E. N. Silber *et al.*, *J. Clin. Invest.*, **30**, 1046 (1951); L. A. Nalefski *et al.*, *Circulation*, **5**, 851 (1952); R. C. Kory *et al.*, *Am. Heart J.*, **50**, 308 (1955).

(2) G. Jongebreur, *Arch. intern. pharmacodynamic*, **90**, 384 (1952).

(3) For drugs belonging to this category see New and Nonofficial Drugs, evaluated by A.M.A. Council on Drugs, page 676 (1960).

(4) The first paper of this series not including compounds reported here is in press [J. Koo, *J. Org. Chem.*, in press].

(5) This compound was prepared by modification of the method of W. Baker (*J. Chem. Soc.*, 1922 (1939)] in four steps from 2,6-dihydroxyacetophenone, which in turn was obtained in another four steps according to the general direction of A. Russel and J. R. Frye [*Org. Syntheses*, Coll. Vol. III, 282 (1955)]. However, the first-step product, 4-methyl-7-hydroxycoumarin, was synthesized by following an improved procedure of J. Koo [*Chem. & Ind.*, 445 (1955)].

(6) C. Y. Yen, R. L. Stanger, and N. Millman, *Arch. intern. pharmacodynamic*, **123**, 179 (1960); L. Cook and E. Weidleg, *Federation Proc.*, **19**, 22 (1960).

(7) The pharmacology study by Dr. S. Krop and his associates, Mrs. M. Graeme and Mrs. E. Siegmund, of the pharmacology department, Ethicon, Inc., is gratefully acknowledged; the details will be published by them later.

(8) J. Koo, *et al.*, *J. Am. Chem. Soc.*, **77**, 5373 (1955).

(9) J. Koo, *et al.*, *Chem. & Ind.*, 832 (1958).

(10) J. Koo, *J. Org. Chem.*, in press.

tic. It remarkably increased the rate and depth of respiration of anesthetized dogs and cats at a dosage as low as 5 mg./kg. (intravenous injection) as compared to 12.5 to 37.5 mg./kg. required for the well known drug nikethamide. Thus, III appears to be pharmacologically a few times more effective than nikethamide. Despite a somewhat higher toxicity, in an over-all evaluation, III compares favorably with nikethamide. The contrasting activities exhibited by II and III are indeed surprising and significant.

RESEARCH DIVISION
ETHICON, INC.
SOMERVILLE, N. J.

JOHN KOO[11]

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(11) Present address: Geigy Research Laboratories, Ardsley, N. Y.