[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

gem-Difluorosteroids

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Several new types of fluorosteroids have been prepared by adaptation of a known method using sulfur tetrafluoride to replace ketonic oxygen by fluorine. 3,3-Difluoro and 17,17-difluoro compounds in the androstane series are described as well as 3,3-difluoro and 20,20-difluoro derivatives of C_{21} steroids. Ease of fluorination, reflected in yields of products, was greatly dependent on the site and nature of the carbonyl function undergoing reaction.

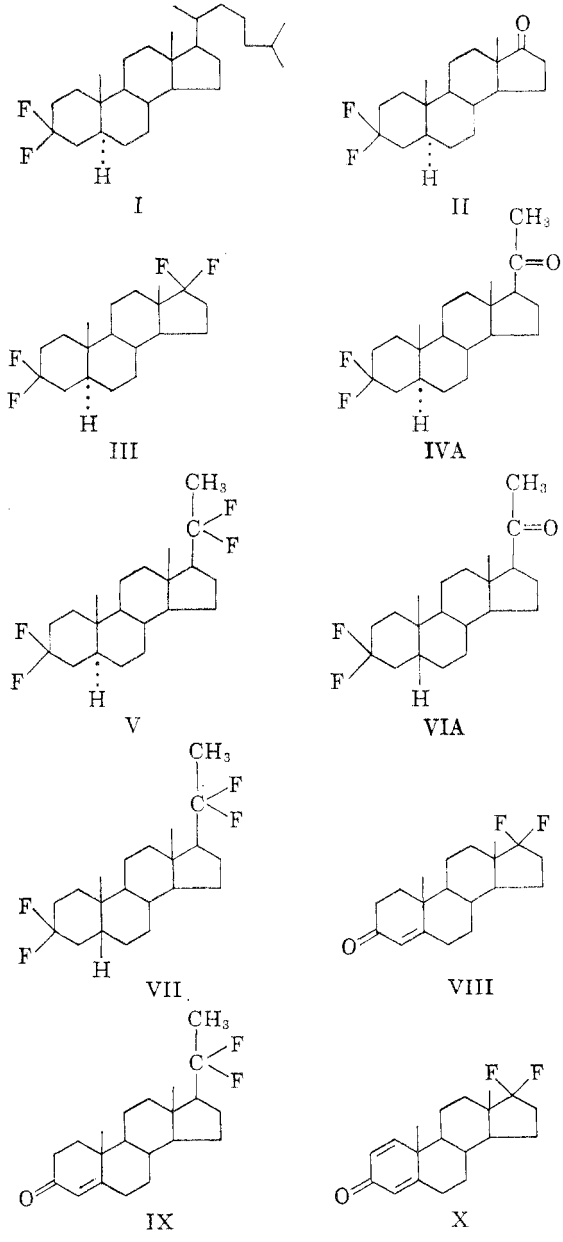
The introduction of fluorine into the steroid molecule has, in a number of cases, resulted in remarkable and useful modification of physiological activities.[1] Since certain desoxy analogues of steroidal hormones have been shown to possess some physiological activity,[2] it was hoped that certain *gem*-difluorosteroids, with fluorine substitution at sites occupied by carbonyl groups in the naturally occurring hormones, might be of therapeutic value. The recent report of sulfur tetrafluoride as a reagent for the preparation of *gem*-difluorides by replacement of carbonyl oxygen by fluorine[3] suggested a convenient route to such steroids.

Fluorination experiments were carried out with several types of diketosteroids to determine the extent to which reactivity differences of carbonyl groups at different positions in the steroid nucleus could be exploited to effect selective fluorination.

5α-Androstane-3,17-dione, 5α-pregnane-3,20-dione, and 5β-pregnane-3,20-dione (Table I) all gave mixtures of di- and tetrafluorinated products. In these cases the difluoroketones which were fluorinated at C_3 predominated in molar ratios of 3:1, 7:1, and 4:1 respectively.

In contrast to the relative ease of fluorination at C_3 with the saturated ketones, no characterizable products of fluorination at C_3 were isolated from 3-ketones having α,β-unsaturation. Treatment of androst-4-ene-3,17-dione, progesterone, and androsta-1,4-diene-3,17-dione with sulfur tetrafluoride resulted in the isolation, in low yields, of 17,17-difluoroandrost-4-en-3-one (VIII), 20,20-difluoropregn-4-en-3-one (IX), and 17,17-difluoroandrosta-1,4-dien-3-one (X), respectively.

With the exception of the difluorinated products obtained from 5α-pregnane-3,20-dione and 5β-pregnane-3,20-dione, structural assignments are based on infrared absorption patterns. The frequency of the carbonyl absorption characterized the nature of the ketone function in the difluoroketones[4] and thus determined the site of fluorination.



The lack of resolution of steroidal 3- and 20-keto absorptions precluded structural assignments by means of infrared to the difluorinated products

(1) *Cf.*, L. F. Fieser and M. Fieser, *Steroids*, Reinhold Publishing Co., New York, 1959, pp. 593, 682–6.

(2) *Cf.*, M. S. de Winter, C. M. Siegmann, and S. A. Szpilfogel, *Chem. & Ind. (London)*, 905 (1959).

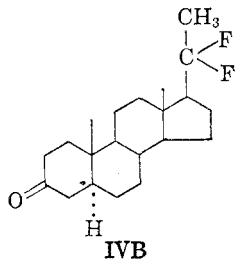
(3) W. R. Hasek, W. C. Smith, and V. A. Englehardt, *J. Am. Chem. Soc.*, 82, 543 (1960).

(4) R. N. Jones and F. Herling, *J. Org. Chem.*, 19, 1252 (1954).

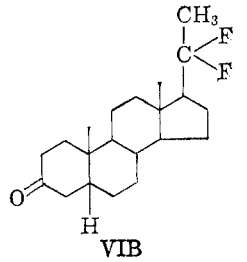
TABLE I

Starting Material	Catalyst	Products	Yield, %	$[\alpha]_D^{23}$	M.P.	ν_{max} (cm.$^{-1}$)	Formula	Calcd. C	Calcd. H	Calcd. F	Found C	Found H	Found F
Cholestan-3-one	HF	I	32	+24°	109–111	—	$C_{27}H_{46}F_2$	79.37	11.35	9.28	79.28	11.42	8.97
5α-Androstane-3,17-dione	HF	II	37	+92	123–124	1730	$C_{19}H_{28}F_2O$	73.56	9.02	12.25	73.67	9.07	12.18
		III	11	+7	84–85	—	$C_{19}H_{28}F_4$	68.65	8.49	22.86	69.12	8.63	21.93
5α-Pregnane-3,20-dione	HF	IVA	33	+88	145–147	1703	$C_{21}H_{32}F_2O$	74.51	9.53	11.23	74.76	9.82	11.04
		V	5	+12	120–121	—	$C_{21}H_{32}F_4$	69.96	8.95	—	69.80	8.67	—
5β-Pregnane-3,20-dione	HF	VIA	29	+87	100–102	1706	$C_{21}H_{32}F_2O$	74.51	9.53	11.23	74.58	9.47	11.26
		VII	7	+20	104–106	—	$C_{21}H_{32}F_4$	69.96	8.95	21.08	70.13	9.20	21.27
Androst-4-ene-3,17-dione	A HF	VIII	3	+82	179–182	1668 1622							
	B BF_3	VIII	10	+82	181–183	1668 1622	$C_{19}H_{26}F_2O$	74.00	8.50	—	73.84	8.41	—
Progesterone	BF_3	IX	2	+94	108–110	1672 1620	$C_{21}H_{30}F_2O$	74.95	8.99	11.29	75.15	8.95	11.55
Androstra-1,4-diene-3,17-dione	BF_3	X	3	+33	116–117	1673 1630 1613	$C_{19}H_{24}F_2O$	74.48	7.90	12.40	74.27	8.10	12.77

resulting from the pregnanediones. Two products were possible in each case: the 3,3-difluoro 20-ketones IVA and VIA from 5α- and 5β-pregnane-3,20-dione, respectively, or the 20,20-difluoro 3-ketones, IVB and VIB.



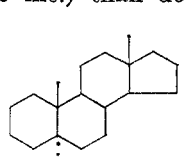
IVB



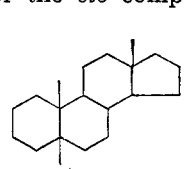
VIB

Assignment of structures IVA and VIA, respectively, to the difluoro ketones resulting from fluorination of 5α-pregnane-3,20-dione and 5β-pregnane-3,20-dione was made on the basis of their NMR spectra (Table II). As methyl ketones, both IVA and VIA must exhibit a singlet in their NMR spectra due to C_{21}-methyl protons. On the other hand, the C_{21}-methyl proton absorptions of IVB and VIB would be multiplets due to spin-spin coupling with the two fluorine atoms at C_{20}. Both difluoro ketones isolated show three distinct singlet absorptions attributable to C_{18}-, C_{19}-, and C_{21}-methyl protons. In both cases, the position of the C_{21}-methyl proton absorption is in good agreement with the value reported by Shoolery and Rogers for C_{21}-methyl 20-ketosteroids.[5]

The positions of the C_{18}- and C_{19}-methyl proton absorptions of IVA and VIA are compared in Table II with those reported by Shoolery for 5α-pregnane-3,20-dione and 5β-pregnane-3,20-dione.[5] It is of interest that while the chemical shift of the C_{19}-methyl protons of the diketones is independent of the nature of the A/B ring junction, the absorption of the C_{19}-methyl protons of the A/B-*trans* difluoro ketone (IVA) lies at higher field (11 c.p.s.) than does the corresponding A/B-*cis* compound (VIA). A similar dependence of the chemical shift of the angular methyl absorption on the nature of the ring junction has been reported for androstane (XI) and its 5-epimer (XII).[6] The absorption of the C_{19}-methyl protons of the A/B-*trans* compound (XI) lies at higher field (7 c.p.s. at 60 mc.) than does that of the *cis* compound



XI



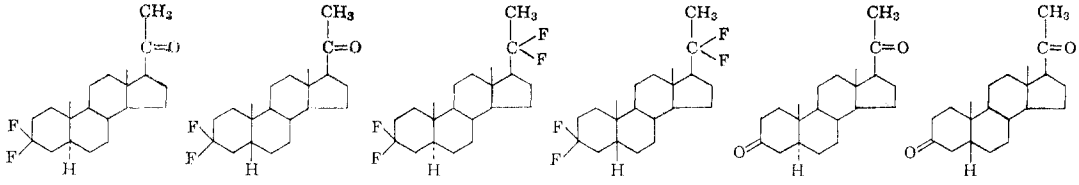
XII

(5) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, 80, 5121 (1958).

(6) J. A. Pople, W. G. Schneider, and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance Spectra*, McGraw-Hill, New York, N. Y., 1959, pp. 291–2.

TABLE II

NUCLEAR MAGNETIC RESONANCE SPECTRA[a]



Methyl Protons	IVA[b]	VIA[b]	V[b]	VII[b]	c	c
C_{21}	125	126	—	—	128	128
C_{19}	49	60	52	60	62	62
C_{18}	36	37	52	49	38	40

[a] C.p.s. relative to tetramethylsilane at 60 mc., measured in the direction of decreasing field. [b] Determined in ethanol-free chloroform solution using tetramethylsilane as an internal standard. [c] Calculated from the data of Shoolery and Rogers[5] using the value of 385 ± 1 c.p.s. reported by L. L. Smith *et al.* for the position of the tetramethylsilane peak measured relative to benzene as an external reference.[7]

(XII), while the chemical shift of the C_{18}-methyl protons is the same for both compounds.

The NMR spectra of 3,3,20,20-tetrafluoro-5α pregnane (V) and 3,3,20,20-tetrafluoro-5β-pregnane (VII) were also measured. Neither compound showed an absorption maximum at or near 125 c.p.s. (relative to tetramethylsilane), and no singlet absorption other than those attributable to the angular methyls was evident. The 5α-pregnane derivative showed only a single peak at 52 c.p.s. due to the overlapping absorptions of the C_{18} and C_{19} methyl protons. That this was the case was indicated by a comparison of the absorptions of the C_{18} angular methyl of 3,3,20,20-tetrafluoro-5β-pregnane (VII) and the C_{19} angular methyl of 3,3-difluoro-5α-pregnan-20-one (IVA) which should lie in essentially the same environments, respectively, as the C_{18} and C_{19} methyls of V. Both absorptions lie at the same frequency, which is in reasonable agreement with that found for the angular methyl absorption of V.

In addition, it was found that, for V, the ratio of the area of absorption, other than that of the angular methyl groups, to the area of the peak attributed to the overlapping angular methyls was 3.44. The corresponding ratio for VII, using the sum of the areas of the angular methyl peaks was 3.6. The calculated value for this quantity is 4.3. The ratio of the areas of the two angular methyl peaks of VII was found to be 1.0.

The C_{19} angular methyl of the A/B-*trans* tetrafluoride (V), thus, lies at approximately 8 c.p.s. higher field than does that of the A/B-*cis* compound (VII), an effect similar to that observed with the 3,3-difluoro ketones (IVA and VIA).

The effect of acid catalysis on sulfur tetrafluoride fluorination has been reported.[3] It was also reported that Lewis acids such as boron trifluoride have a much greater specific catalytic effect than do Bronsted acids such as hydrogen fluoride. In the present work, acid catalysis was found necessary in all cases. The hydrogen fluoride catalyst was generated *in situ* by the reaction of ethanol, added to the solvent, with the sulfur tetrafluoride reagent.

Attempted fluorination of cholestan-3-one in ethanol-free chloroform or in ether led to almost quantitative recovery of starting material. When the fluorination was carried out in chloroform containing 0.75% ethanol, the infrared spectrum of the crude product showed complete absence of carbonyl absorption and 3,3-difluorocholestane (I) was isolated in 32% yield.

Under the conditions used to effect complete fluorination of cholestanone, fluorination of 5α-androstan-3,17-dione at C_3 was incomplete. The infrared spectrum of the crude product showed strong carbonyl absorptions characteristic of both 3- and 17-ketone groups. When the reaction was carried out in chloroform containing 3% ethanol, under otherwise identical conditions, the infrared spectrum showed no trace of absorption characteristic of the 3-keto function, and 3,3-difluoro-5α-androstan-17-one (II) was isolated in 37% yield together with 11% of 3,3,17,17-tetrafluoro-5α-androstane (III).

Fluorinations of 5α- and 5β-pregnane-3,20-dione were also carried out in chloroform containing 3% ethanol. Yields of difluorinated and tetrafluorinated products are recorded in Table I.

Fluorination of androst-4-ene-3,17-dione in chloroform containing 3% ethanol yielded 3% of 17,17-difluoroandrost-4-en-3-one (VIII) with recovery of a large amount of starting material. Using boron trifluoride as catalyst and employing a somewhat shorter reaction time, 10% of VIII was isolated, but there was considerable resinification and low recovery of starting material.

In view of the higher isolated yield of VIII using boron trifluoride, this catalyst was employed in the fluorinations of progesterone and androsta-1,4-

(7) L. L. Smith, M. Marx, J. J. Garbarini, T. Foell, and J. J. Goodman, *J. Am. Chem. Soc.*, **82**, 4616 (1960).

diene-3,17-dione. In both cases there was considerable resinification and the yields of the difluorides (IX) and (X) were low.

This study is being continued with other ketosteroids. It is apparent that by adjustment of reaction conditions, ketones of different reactivities may be converted into the *gem*-difluoro derivatives. Although bioassay of the substances described in this report is incomplete, several of the difluoroketosteroids tested have mild androgenic activity. Substances VIA and VIII have some additional effects on endocrine balance.

EXPERIMENTAL

The fluorinations were carried out in a stainless steel hydrogenation cylinder. The gaseous reagents were introduced by means of a gas buret using bromobenzene as the displaced liquid.

Ethanol-free chloroform, used in runs employing boron trifluoride as the acid catalyst, was prepared by washing reagent chloroform with concentrated sulfuric acid.[8]

Melting points were taken by the capillary tube method and are uncorrected. Infrared spectra were taken on chloroform solutions using a Perkin-Elmer Model 21 spectrophotometer. The NMR spectra were taken on a Varian nuclear magnetic resonance spectrometer at 60 mc. using tetramethylsilane as an internal reference. Optical rotations were measured in a 1 dm. tube at 23° using freshly-distilled chloroform solvent.

Neutral alumina of activity III (Woelm) and Davison silica gel, 100–200 mesh, were used for the chromatographic separations.

The procedures in which hydrogen fluoride was used as the acid catalyst are illustrated for the fluorinations of 5α-pregnane-3,20-dione and androst-4-ene-3,17-dione. The use of boron trifluoride is illustrated for the fluorination of androst-4-ene-3,17-dione.

3,3-Difluoro-5α-pregnan-20-one (IVA) *and 3,3,20,20-tetrafluoro-5α-pregnane* (V). 5α-Pregnane-3,20-dione (2.0 g.) and 20 ml. of chloroform containing 3% ethanol were heated at 40° for 15 hr. with 10.6 g. of sulfur tetrafluoride.[3] The gaseous reactants and products were stripped and the residue was washed into a 500-ml. separatory funnel with five 50-ml. portions of chloroform. The resulting chloroform solution was washed with two 100-ml. portions of water, 100 ml. of 5% sodium bicarbonate solution, two 100-ml. portions of water, and dried over anhydrous magnesium sulfate. The chloroform was stripped under aspirator pressure on the steam bath leaving 2.47 g. of a partially crystalline, dark brown solid.

The product was heated with 50 ml. of boiling ethanol and the mixture was treated with carbon and filtered through Celite. The carbon-Celite mat was washed with 80 ml. of boiling ethanol and the washings were added to the original ethanol filtrate. The ethanol was stripped under aspirator pressure on the steam bath leaving 1.48 g. of a dark orange, crystalline solid.

This material was chromatographed on 50 g. of alumina. Elution with 1:10 benzene–petroleum ether (b.p. 68–70°) yielded 1.3 g. of an orange, crystalline solid, m.p. 130–136°, which was rechromatographed on 80 g. of silica gel. Elution with 1:5 chloroform–petroleum ether yielded 120 mg. of a white, crystalline solid. The infrared spectrum of this material showed no significant absorption between 1500 and 2700 cm.$^{-1}$ A portion of this material (83.4 mg.) was recrystallized from ethanol–water solution to yield 72.2 mg. of 3,3,20,20-tetrafluoro-5α-pregnane, m.p. 120–121°.

Anal. Calcd. for $C_{21}H_{32}F_4$: C, 69.96; H, 8.95. Found: C, 69.80; H, 8.67.

Elution with chloroform yielded 1.1 g. of a light orange, crystalline solid. This material was recrystallized from ethanol to yield 710 mg. of 3,3-difluoro-5α-pregnan-20-one, white crystals, m.p. 143–147°, ν_{max}1703 cm.$^{-1}$ The analytical sample, prepared by further recrystallization from ethanol, melted at 145–147°.

Anal. Calcd. for $C_{21}H_{32}F_2O$: C, 74.51; H, 9.53; F, 11.23. Found: C, 74.76; H, 9.82; F, 11.04.

17,17-Difluoroandrost-4-en-3-one (VIII). *Run* A. Two grams of androst-4-ene-3,17-dione and 20 ml. of chloroform containing 3% ethanol were heated at 40° for 15 hr. with 10.6 g. of sulfur tetrafluoride. The reaction mixture was allowed to cool to room temperature and the gaseous reactants and products were stripped. The chloroform extraction was carried out in the usual manner to yield 2.41 g. of a black tar.

The product was dissolved in 80 ml. of boiling ethanol, treated with carbon and filtered through Celite. The carbon–Celite mat was washed with 80 ml. of boiling ethanol and the washings were combined with the original ethanol filtrate. The ethanol was stripped on the steam bath under aspirator pressure leaving 1.45 g. of a black tar which crystallized on standing. The infrared spectrum of this material showed strong absorption peaks at 1730, 1668, and 1622, cm.$^{-1}$

This material was chromatographed on 100 g. of alumina. Elution with 1:1 benzene–petroleum ether yielded 89.8 mg. of a white, crystalline solid, m.p. 166.5–174°, ν_{max} 1668, 1622 cm.$^{-1}$ This material was recrystallized from ethanol-water solution to yield 69.6 mg. of 17,17-difluoroandrost-4 en-3-one, m.p. 178.5–182°.

Elution with benzene yielded 1.02 g. of a crystalline solid, ν_{max} 1730, 1668, and 1622 cm.$^{-1}$ This was recrystallized from acetone–petroleum ether to yield 660 mg. of androst-4-ene-3,17-dione, m.p. 171–172°, lit.,[9] m.p. 172. 5–173.5°.

Run B. Androst-4-ene-3,17-dione (2.1 g.) was heated at 40° for 10 hr. with 20 ml. of ethanol-free chloroform, 8 g. of sulfur tetrafluoride, and 0.4 g. of boron trifluoride. The reaction mixture was allowed to cool to room temperature and the gaseous reactants and products were stripped. The chloroform extraction was carried out in the usual manner to yield 1.15 g. of a black, crystalline solid. A large amount of a chloroform-insoluble black resin adhered to the walls of the reaction vessel and was discarded.

The product was heated with 80 ml. of boiling ethanol and the ethanol solution was treated with carbon and filtered through Celite. The carbon–Celite mat was washed with three 25-ml. portions of boiling ethanol and the washings were added to the original ethanol filtrate. The ethanol was stripped under aspirator pressure on the steam bath leaving 0.611 g. of a brown oil which readily crystallized on cooling.

This material was chromatographed on 70 g. of alumina. Elution with 1:1 benzene–petroleum ether yielded 277 mg. of a pale yellow, crystalline solid. This was recrystallized from ethanol–water solution to yield 227.3 mg. of 17,17-difluoroandrost-4-en-3-one, m.p. 178–180.5°, ν_{max} 1668, 1622 cm.$^{-1}$ For analysis this material was recrystallized twice from ethanol-water solution to yield 160 mg., m.p. 181–182.8°.

Anal. Calcd. for $C_{19}H_{26}F_2O$: C, 74.00; H, 8.50. Found: C, 73.84; H, 8.41.

Elution with 1:10 chloroform–benzene yielded 192 mg. of a white crystalline solid, m.p. 160–168.5°, ν_{max} 1730, 1668 1622 cm.$^{-1}$

(8) A. I. Vogel, *A Textbook of Practical Organic Chemistry*, Longmans, Green and Co. Ltd., London, 2nd Ed., 1951, p. 174.

(9) Elsevier, *Encyclopedia of Organic Chemistry*, Springer-Verlag, Berlin, 1959, 14s, p. 2880.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, NATIONAL DRUG CO.]

Synthesis in the Chromone Series. 5,8-Dimethoxy-2-substituted Chromones and Nitrogen Analogs

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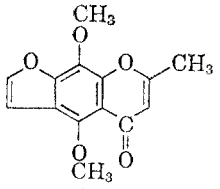
A series of 5,8-dimethoxy-2-substituted chromones was synthesized and a nitrogen analog, 5,8-dimethoxy-4-keto-1,2,3,4-tetrahydroquinaldine, was prepared more conveniently by direct cyclization of the corresponding acid with polyphosphoric acid than by previously reported methods.

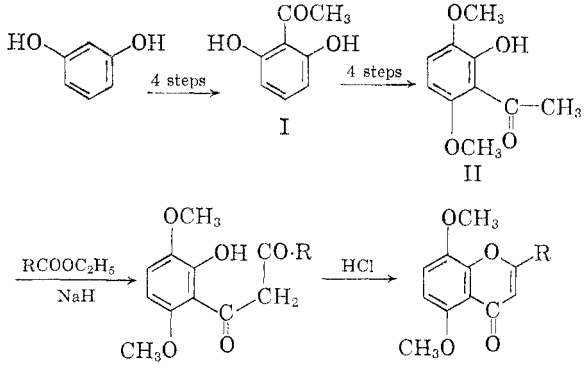
Khellin is the principal active component isolated[2] from the fruit of the Mediterranean plant, *Ammi visnaga*. Its structure has been elucidated as 5,8-dimethoxy-2-methyl-4′,5′-furo-6,7-chromone and its synthesis achieved.[2,3] For centuries the fruit of the plant has been employed as an antispasmodic by Egyptian natives in treating renal colic. In recent years, Khellin has been shown in various pharmacological studies[4] to be a potent relaxant to smooth muscle, and the coronary arteries are affected tremendously by this relaxant action.



Khellin

Accordingly, the structure of Khellin contains a chromone nucleus, and some synthetic chromones have shown characteristic Khellinlike action. Especially the 5,8-dimethoxy-2-methyl chromone, which differs from Khellin by the absence of the condensed furan ring, has been found[5] to be even more active than Khellin itself. As part of a search for new and more effective compounds with Khellinlike activity, a series of 5,8-dimethoxy-2-substituted chromones were synthesized for pharmacological study.

2,5-Dimethoxy-6-hydroxyacetophenone, the common starting material in these syntheses, was obtained according to the method of Baker[6] in four steps from 2,6-dihydroxyacetophenone, which, in turn, was prepared in another four steps from resorcinol by following the general procedure of Frye,[7] except for the first step product, 4-methyl-7-hydroxycoumarin, which was obtained more conveniently by using polyphosphoric acid instead of sulfuric acid as the condensing agent.[8]



R represents a group listed in table I

III

R represents a group listed in table II

IV

Condensation of 2,5-dimethoxy-6-hydroxyacetophenone (II) with an appropriate ester in the presence of sodium hydride provided the diketones (III) listed in Table I. Most of these diketones are yellow solids, and the yields were generally good to excellent. However, a few appeared as yellow oils, which were directly used for ring closure without further purification.

Treatment of the diketones III with concentrated hydrochloric acid for a short period produced the desired chromones (IV) in fair to good yields. All these chromones, listed in Table II, were colorless solids except 2-(2′,3′-dimethoxystyryl)-5,8-dimethoxychromone, which appeared as yellow needles,

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

(2) E. Späth and W. Gruber, *Ber.*, **71**, 106 (1938).

(3) R. A. Baxter, *et al.*, *J. Chem. Soc.*, S 30 (1949); T. S. Gardner *et al.*, *J. Org. Chem.*, **15**, 841 (1950); A. Schonberg and A. Sina, *J. Am. Chem. Soc.*, **72**, 1611, 3396 (1950).

(4) G. V. Anrep *et al.*, *J. Pharm. & Pharmacol.*, **1**, 164 (1949); *Am. Heart J.*, **37**, 531 (1949); K. Samaan *et al.*, *J. Pharm. & Pharmacol.*, **1**, 538 (1949).

(5) G. Jongebreur, *Arch. Int. Pharm.*, **90**, 384 (1952).

(6) W. Baker, *J. Chem. Soc.*, 1922 (1939).

(7) J. R. Frye, *Org. Syntheses*, **Coll. Vol. III**, 282 (1955).

(8) J. Koo, *Chemistry and Industry*, 455 (1955).