Acknowledgment. The authors are indebted to Messrs. M. Freifelder and G. Stone for assistance with the pressure reactions, to Mr. William Washburn for infrared determinations, and to. Mr. E. F. Shelberg for microanalyses.

NORTH CHICAGO, ILL.

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

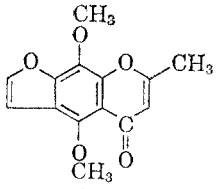
Synthesis in the Chromone Series. 5,8-Dimethoxy-2-substituted Chromones and Nitrogen Analogs

JOHN KOO[1]

Received November 1, 1960

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.

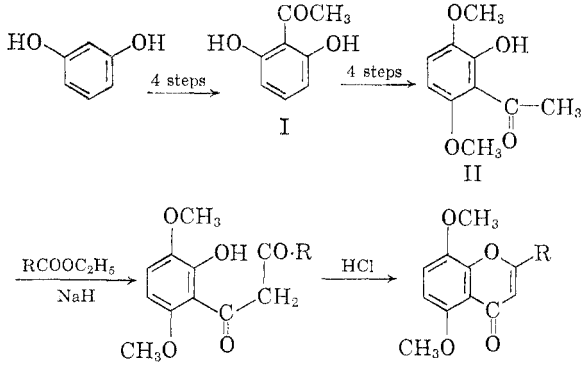
Khellin is the principal active component isolated[2] from the fruit of the Mediterranean plant, *Ammi visnaga*. Its structure has been elucidated as 5,8-dimethoxy-2-methyl-4′,5′-furo-6,7-chromone and its synthesis achieved.[2,3] For centuries the fruit of the plant has been employed as an antispasmodic 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).

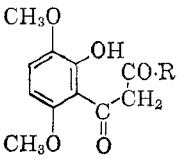
(5) G. Jongebreur, *Arch. Int. Pharm.*, **90**, 384 (1952).

(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).

TABLE I



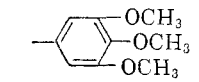
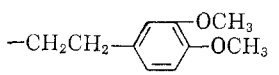
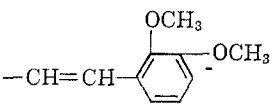
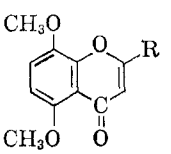
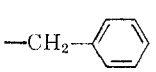
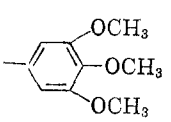
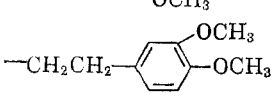
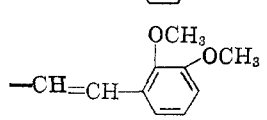
R	M.P.	Yield, %	Recryst. from	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
$-CH_2CH_3$	94–96	84	Ligroin	$C_{13}H_{16}O_5$	61.89	61.93	6.39	6.34
$-CH_2CH_2CH_3$	73–74	91	Ligroin	$C_{14}H_{18}O_5$	63.14	63.10	6.81	6.65
	142–144	87	Benzene–Petroleum ether	$C_{20}H_{22}O_8$	61.53	61.67	5.68	5.97
	117–118	89	Benzene-Ligroin	$C_{21}H_{24}O_7$	64.94	65.05	6.23	6.36
	156–157	78	Benzene–Petroleum ether	$C_{21}H_{22}O_7$	65.27	65.37	5.74	5.80
								

TABLE II



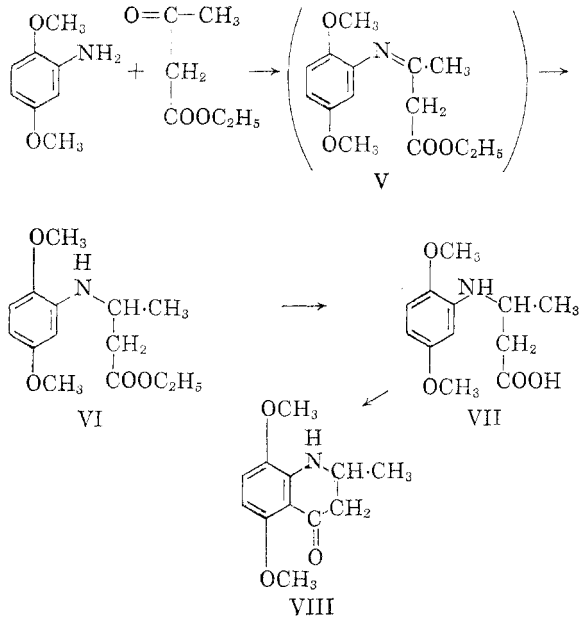
R	M.P.	Yield, %	Recryst. from	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
$-CH_2CH_3$	136–137	99	Benzene–Petroleum ether	$C_{13}H_{14}O_4$	66.65	66.69	6.02	6.06
$-CH_2CH_2CH_3$	102–103	81	Benzene–Petroleum ether	$C_{14}H_{16}O_4$	67.73	67.82	6.50	6.57
$-CH(CH_3)_2$	98–99	59	Petroleum ether	$C_{14}H_{16}O_4$	67.73	67.80	6.50	6.54
$-CH_2CH_2CH_2CH_3$	87–88	67	Petroleum ether	$C_{15}H_{17}O_4$	68.68	68.82	6.92	7.01
	133–135	34	Petroleum ether	$C_{18}H_{16}O_4$	72.96	73.24	5.44	5.38
	202–204	86	Benzene–Petroleum ether	$C_{20}H_{20}O_7$	64.50	64.86	5.41	5.79
	180–182	87	Benzene	$C_{21}H_{22}O_6$	68.09	68.07	5.99	6.00
	180–181	68	Benzene	$C_{21}H_{20}O_6$	68.47	68.65	5.47	5.33

probably because of the presence of a conjugating double bond in the side chain.

In exploring variations in the general structure of IV, it was thought that 5,8-dimethoxy-4-keto-1,2,3,4-tetrahydroquinaldine (VIII), which is a nitrogen analog of IV, might be of interest. Earlier, Johnson and his collaborators[9] and also Elderfield *et al*[10] reported the preparation of other 4-keto-1,2,3,4-tetrahydroquinolins. The present route appears to be more convenient:

(9) W. S. Johnson, E. L. Woroch, and B. G. Buell, *J. Am. Chem. Soc.*, **71**, 1901 (1949); W. S. Johnson and B. G. Buell, *J. Am. Chem. Soc.*, **74**, 4513 (1952).

(10) R. C. Elderfield and A. Maggiolo, *J. Am. Chem. Soc.*, **71**, 1906 (1949); R. C. Elderfield *et al.*, *J. Am. Chem. Soc.*, **68**, 1259 (1946).



V

VI VII

VIII

Condensation of 2,5-dimethoxyaniline and ethyl acetoacetate catalyzed by acetic acid yielded V, which was hydrogenated to give anilinobutyric ester (VI). The anilino acid (VII) was obtained by saponification of the ester (VI). It was then found that this type of anilinoacid could be cyclized directly with polyphosphoric acid, according to the general method for cyclizations,[11] to yield the desired 5,8-dimethoxy-4-keto-1,2,3,4-tetrahydroquinaldine (VIII). It seems of interest to note that previously reported[9,10] cyclization procedures for compounds similar to VIII required protection of the secondary amino- group by tosylation and subsequent removal of the tosyl group. Therefore, by eliminating two steps, this seems to offer a simpler and general procedure in the synthesis of quinoline derivatives.

EXPERIMENTAL[12,13]

Preparation of diketones (III, R represents a group listed in Table I). The condensation of 2,5-dimethoxy-6-hydroxyacetophenone with an appropriate ester is illustrated by the preparation of *1-(2,5-dimethoxy-6-hydroxybenzoyl)-2-butanone* (III. R = C_2H_5). To a solution of 2.4 g. of 2,5-dimethoxy-6-hydroxyacetophenone (II) in 25 ml. of ethyl propionate, was added 2.5 g. of sodium hydride in several portions with shaking during a 30-min. period. The mixture was then gently heated on the steam bath for 10 min. (for higher molecular weight esters the heating must be longer) and kept at room temperature overnight. The dark reaction mixture was poured into ice water with stirring and the solution was extracted once with ether. The aqueous phase part was acidified with dilute acetic acid, and the yellow oil that separated was extracted with ether. The ether solution was washed with cold water, dried over magnesium sulfate, filtered, and evaporated. The yellow oily residue soon solidified and weighed 2.6 g., m.p. 90–93°. It was recrystallized from ligroin to give bright yellow prisms, m.p. 94–96°.

Preparation of chromones (IV, R represents a group listed in Table II). The ring closure reaction is illustrated by the preparation of *5,8-dimethoxy-2-ethyl chromone* (IV. R = C_2H_5). To a 2.2 g. of the above diketone was added 15 ml. of concd. hydrochloric acid, and the mixture was stirred by hand for about 3 min. The dark, clear solution was poured into ice water and nearly neutralized with sodium hydroxide solution. The separated material was extracted with chloroform, which was dried over anhydrous magnesium sulfate, filtered and evaporated to yield 2.05 g. of pale yellow solid, m.p. 130–133°. Recrystallization from benzene-petroleum ether (30–60°) gave colorless needles, m.p. 136–137°.

Ethyl β-(2,5-dimethoxyanilino)butyrate (VI). To a solution of 38.3 g. of 2,5-dimethoxyaniline and 32.5 g. of ethyl acetoacetate in 100 ml. of benzene was added 1 ml. of glacial acetic acid. The solution was placed in a 300 ml. flask, fitted with a Dean-Stark trap, and refluxed for 10 hr., during which time 3.9 ml. of water was collected. The benzene and some unchanged ethyl acetate were distilled under reduced pressure. The dark residual condensation product V was not purified but dissolved in 150 ml. of ethanol, and 6 g. of palladium-on-carbon catalyst was added. The mixture was then hydrogenated at room temperature at 40 lb. pressure for 5 hr. The catalyst was filtered off and the ethanol was evaporated. The oily residue was distilled at 146°/0.4 mm. to yield 36 g. (54% for two steps) of a colorless oil. n_D^{25} 1.5284.

Anal. Calcd. for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.26. Found: C, 62.94; H, 7.79; N, 5.09.

β-(2,5-Dimethoxyanilino)butyric acid (VII). A mixture of 36 g. of the above ester and 200 ml. of 15% sodium hydroxide solution containing 30 ml. of ethanol was gently refluxed for 3 hr. After cooling, the alkaline solution was extracted with ether and then acidified with acetic acid. The oil that separated was extracted with benzene, washed with water, dried, and evaporated. The residue formed a dark, thick paste weighing 20 g. (62%). A small portion of this material was dissolved in ether and treated with hydrogen chloride gas. The hydrochloride that separated was recrystallized from absolute ethanol and ether to give colorless crystals, m.p. 172–173°.

Anal. Calcd. for $C_{12}H_{17}NO_4$·HCL: Cl; 12.86, N; 5.08. Found: Cl; 13.16; N; 4.93.

5,8-Dimethoxy-4-keto-1,2,3,4-tetrahydroquinaldine (VIII). A mixture of 16 g. of the crude acid VII and 150 g. of polyphosphoric acid was stirred and heated on a steam bath for 30 min. After cooling, the mixture was poured into 400 ml. of ice water and the solution was extracted with ether, which was dried and evaporated to give 1.5 g. of yellow product, m.p. 114–116°. The acidic aqueous solution was then neutralized with potassium carbonate until it became weakly basic and the solution was repeatedly extracted with ether. The combined ether extracts were dried and evaporated to give 4 g. of the product, m.p. 112–115°. The combined yield was 5.5 g. (36%).[14] A sample recrystallized from benzene-petroleum ether, formed bright yellow prisms, m.p. 117–118°.

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.30; H, 6.83; N, 6.12.

PHILADELPHIA 44, PA.

(11) J. Koo, *J. Am. Chem. Soc.*, **75**, 1891 (1953).

(12) All melting points are uncorrected.

(13) The experiments described here were carried out in 1953; later work in this field will appear in future publication.

(14) The percentage yield was obtained in the first and only experiment, and there is reason to believe that the yield can be considerably improved with some development.