TABLE I

Starting material	Reacn. prod.[a] and m.p., °C.		Formula of the reacn. prod.	Carbon, %		Hydrogen, %		Yield, %	Dicoumarol derivative						
				Calcd.	Found	Calcd.	Found		Reacn. prod.[e] and m.p.,[f] °C.		Formula of the reacn. prod.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Va	VIIa[b]	245	$C_{12}H_8O_5$	62.1	61.8	3.4	3.7	90	IXa[g]	280	$C_{25}H_{16}O_{10}$	63.0	62.7	3.4	3.4
Vb	VIIb[c]	205–206	$C_{13}H_{10}O_6$	59.5	59.2	3.8	3.9	60	IXb[h]	276	$C_{27}H_{20}O_{12}$	60.4	60.0	3.7	4.1
VI	VIII[d]	182–183	$C_{13}H_{10}O_6$	59.5	60.0	3.8	3.8	60	X[i]	252	$C_{27}H_{20}O_{12}$	60.4	60.0	3.7	3.8

[a] Solvent for crystallization, alcohol; all are colorless substances soluble in dilute sodium carbonate solution and giving a negative ferric chloride reaction. [b] 4-Hydroxybergapten. [c] 4-Hydroxyisopimpinellin. [d] 4-Hydroxypimpinellin. [e] All are colorless substances difficultly soluble in alcohol; the yields are practically quantitative. [f] All fuse with a brown melt and evolution of gas. [g] 3,3'-Methylene-bis-(4-hydroxy-5-methoxyfuro-4',5',6,7-coumarin). [h] 3,3'-Methylene-bis-(4-hydroxy-5,8-dimethoxyfuro-4',5',6,7-coumarin). [i] 3,3'-Methylene-bis-(4-hydroxy-5,6-dimethoxyfuro-4',5',8,7-coumarin).

from dilute alcohol as yellow prisms, m.p. 54° (reported m.p. for VI prepared by another method, 56°[10]), yield 0.75 g.

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.0; H, 5.1. Found: C, 61.3; H, 5.0.

Condensations with Ethyl Carbonate. Visnaginone (Va) Taken as an Example.—A mixture of Va (5 g.), ethyl carbonate (20 g.) and sodium metal powdered under toluene (3 g.) was shaken until a green solution was obtained and then heated on a steam-bath for 45 minutes. After the reaction was over, the solidified reaction mixture was cooled, dissolved in 120 ml. of cool water and extracted with ether. The aqueous solution, on acidification with dilute hydrochloric acid, yielded a colorless precipitate of VIIa (see Table I).

Reaction of the 4-Hydroxycoumarins with Formaldehyde. VIIa Taken as an Example.—A solution of VIIa (0.5 g.) in excess of boiling alcohol was treated with a mixture of 10 ml. of alcohol and 2 ml. of 40% formaldehyde. The mixture was boiled gently for a few minutes and cooled; the dicoumarol derivative (IXa) separated as colorless crystals (see Table I).

Methylation of VIIa.—One-half gram of VIIa was refluxed for 8 hours with a mixture of methyl iodide (3 ml.), acetone (50 ml.) and anhydrous potassium carbonate (4 g.). The reaction mixture then was filtered while hot and the crude **4-methoxybergapten**, obtained by evaporation of the solvent, crystallized from acetone as colorless needles, m.p. 191–192°. It was insoluble in 4% sodium hydroxide and in cold 50% sulfuric acid and 20% hydrochloric acid; the crude product did not contain any amount of organic substance soluble in these acids.

Anal. Calcd. for $C_{13}H_{10}O_5$: C, 63.4; H, 4.0. Found: C, 63.5; H, 4.1.

4-Methoxybergapten (200 mg.) was refluxed for 30 minutes with a mixture of 40 ml. of ethanol and 40 ml. of 4% sodium hydroxide; on acidification after evaporation of the alcohol, yellow visnaginone (Va), m.p. 108–110°, was precipitated.

Methylation of VIIb.—Methylation of VIIb under the conditions described for VIIa led to **4-methoxyisopimpinellin**, which crystallized from acetone as colorless needles, m.p. 211–212°.

Anal. Calcd. for $C_{14}H_{12}O_6$: C, 60.9; H, 4.3. Found: C, 60.5; H, 4.2.

The alkaline hydrolysis of 4-methoxyisopimpinellin, carried out under the conditions described for 4-methoxybergapten, led to khellinone (Vb), m.p. 98–100°.

Color Test for Furocoumarins.—When to 2 ml. of an alcoholic solution of one of the furocoumarins mentioned below are added, in succession, 1 ml. of a 0.1% solution of 8-amino-5-hydroxy-2-methylfuro-4',5',6,7-chromone (XI)[8] and 10 ml. of an alkaline buffer solution at *p*H 11.6, a violet color is produced gradually and can be measured colorimetrically. The test is given with solutions of 1:100,000 of xanthotoxin and imperatorin and is sensitive to 0.02 mg. of these furocoumarins. The color given by bergapten and isopimpinellin is less intense, while coumarin itself does not give a measurable color under the stated conditions. The structurally related furochromones khellin and visnagin do not give this test.

FACULTY OF SCIENCE, CAIRO UNIVERSITY
AND THE MEMPHIS CHEMICAL CO.
CAIRO, EGYPT

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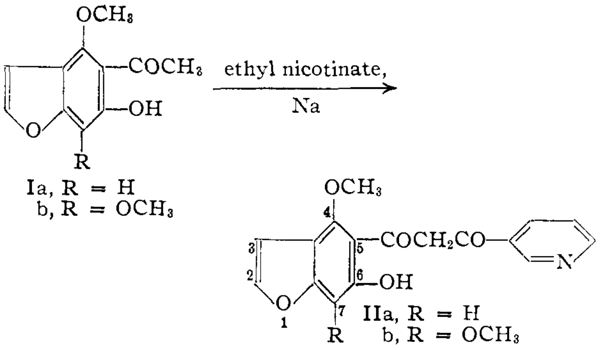
[10] H. Abu-Shady and T. Soine, *J. Am. Pharm. Ass., Sci. Ed.*, **41**, 403 (1952).

Furo-chromones and -Coumarins. XIV. 2-(3'-Pyridyl) Analogs of Khellin and Visnagin

BY ALEXANDER SCHÖNBERG, NASRY BADRAN AND NICOLAS A. STARKOWSKY

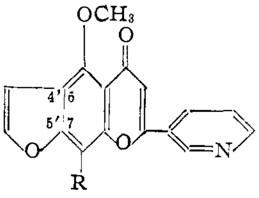
RECEIVED JUNE 1, 1955

The condensation of the products of the alkaline hydrolysis of visnagin and khellin, *i.e.*, visnaginone (Ia) and khellinone (Ib) with ethyl nicotinate to the corresponding diketones (IIa and IIb), followed by the cyclization to the corresponding 2-(3'-pyridyl)-chromones (IIIa and IIIb) was undertaken with the hope of obtaining pharmacologically active products, as 2-(3'-pyridyl)-chromone already has been claimed to possess a spasmolytic action even higher than that of khellin.[1]

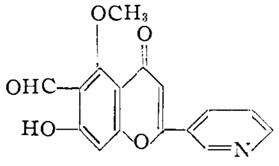


Ia, R = H
b, R = OCH3

IIa, R = H
b, R = OCH3



IIIa, R = H
b, R = OCH3



IV

The condensations with ethyl nicotinate have been carried out as directed by Schönberg and Sina[2] for the condensation of khellinone with ethyl acetate. The diketones which were first obtained (IIa and IIb) were then cyclized by being refluxed with an alcoholic solution of sulfuric acid to the corresponding 5-methoxy-2-(3'-pyridyl)-furo-4',5',6,7-chromone (IIIa) and 5,8-dimethoxy-2-(3'-pyridyl)-furo-4',5',6,7-chromone (IIIb). These furochromone derivatives were very sparingly soluble in water and their salts with mineral acids, such as the hydrochlorides, sulfates, etc., which could be prepared

[1] G. Jongebreur, Thesis, Utrecht, 1950; Dutch Patent 70,267; *cf. C. A.*, **47**, 6445 (1953).

[2] A. Schönberg and A. Sina, THIS JOURNAL, **72**, 1611 (1950).

easily by the standard methods were so readily hydrolyzed by water that the free furochromones precipitated from the aqueous solutions of their salts almost at once. By treatment with hot alcoholic potassium hydroxide for a short time, the pyridylchromones IIIa and IIIb gave back the corresponding diketones IIa and IIb.

The 2-pyridyl derivative corresponding to visnagin (*i.e.*, IIIa) could be oxidized easily with chromic acid to 6-formyl-7-hydroxy-5-methoxy-2-(3′-pyridyl)-chromone (IV). This reaction, proceeding with the opening of the furan ring and the production of a formylchromone already has been found to occur with visnagin,[3a] khellol[3b] and 5-methoxyfuro-4′,5′,6,7-flavone.[3c]

The pyridylchromones have been found to respond to the usual test for flavones[4]: they give an orange or red color when reduced with magnesium and hydrochloric acid in alcoholic solution.

Experimental[5]

Condensation of Visnaginone (Ia) with Ethyl Nicotinate.—A solution of 6.5 g. of Ia in 30 g. of ethyl nicotinate was treated with 1.6 g. of powdered sodium (prepared under toluene). After the initial reaction has subsided, the mixture was refluxed on a water-bath for 2 hours. It was then left to stand overnight, treated with ice and water and extracted with ether. The aqueous solution, after being freed from ether by a stream of air, was acidified with dilute hydrochloric acid; the crystalline precipitate of **5-nicotinoylaceto-4-methoxy-6-hydroxybenzofuran (IIa)** was filtered off, washed with water and crystallized from dilute ethanol as orange crystals, m.p. 135–136° (red melt), yield 6 g. IIa dissolved in dilute hydrochloric acid and in 4% sodium hydroxide solution, and gave an orange red color with concentrated sulfuric acid; its ferric chloride reaction was brown.

Anal. Calcd. for $C_{17}H_{13}O_5N$: C, 65.6; H, 4.2; N, 4.5. Found: C, 65.4; H, 4.0; N, 4.3.

5-Methoxy-2-(3′-pyridyl)-furo-4′,5′,6,7-chromone (IIIa).—One gram of IIa was refluxed for 30 minutes with a solution prepared by mixing 18 ml. of 92% sulfuric acid with ethanol to make 100 ml. The deep yellow solution thus obtained was cooled, diluted with 100 ml. of water and treated with excess of 20% sodium carbonate solution. The crystalline IIIa which separated out was recrystallized from ethanol as colorless needles, m.p. 226° (brown melt), yield 0.7 g. IIIa was insoluble in cold 4% sodium hydroxide, sparingly soluble in cold ethanol and acetone, and soluble in chloroform and 50% sulfuric acid; in the case of the latter solvent, the free furochromone was reprecipitated on dilution with water. IIIa had a negative ferric chloride reaction and gave an orange-red color on treatment with concentrated sulfuric acid. When magnesium turnings were added to a pale yellow alcoholic solution of IIIa, containing a drop of concentrated hydrochloric acid, as red color was gradually developed.

Anal. Calcd. for $C_{17}H_{11}O_4N$: C, 69.6; H, 3.7; N, 4.8. Found: C, 69.9; H, 3.7; N, 4.5.

The yellow crystalline **hydrochloride of IIIa** was prepared by dissolving the substance in acetone and adding the calculated amount (1 mol.:1 mol.) of 5 *N* hydrochloric acid; the salt which separated out decomposed with evolution of gas above 230°.

IIIa (0.5 g.) was added to a warm solution of 1.2 g. of potassium hydroxide in 10 ml. of alcohol and the mixture was gently warmed to its boiling point and shaken at this temperature for a few minutes until a clear solution was obtained. This was then cooled, diluted with its volume of water and neutralized with dilute acetic acid to give a red precipitate of IIa.

Condensation of Khellinone (Ib) with Ethyl Nicotinate.—Six and one-half grams of khellinone was condensed with ethyl nicotinate in the presence of sodium, using the same procedure and amounts as for the preparation of IIa. **5-Nicotinoylaceto-4,7-dimethoxy-6-hydroxybenzofuran (IIb)** crystallized from dilute ethanol as orange crystals, m.p. 129–130°, yield 5.9 g. IIb was insoluble in water and soluble in dilute hydrochloric acid and 4% sodium hydroxide; it gave a brown ferric chloride reaction and dissolved in concentrated sulfuric acid with a brown-red color.

Anal. Calcd. for $C_{18}H_{15}O_6N$: C, 63.4; H, 4.4; N, 4.1. Found: C, 63.7; H, 4.5; N, 3.9.

5,8-Dimethoxy-2-(3′-pyridyl)-furo-4′,5′,6,7-chromone (IIIb).—One gram of IIb was cyclized to IIIb by using the same procedure as in the cyclization of IIa. The pale yellow needles of IIIb, m.p. 213–214° (brown-red melt). obtained in 65% yield, gave a negative ferric chloride reaction and dissolved in concentrated sulfuric acid with a red color. IIIb was very sparingly soluble in water, moderately soluble in alcohol, and freely soluble in chloroform and glacial acetic acid. The magnesium–hydrochloric acid test, done under the conditions described for IIIa, gave a red color.

Anal. Calcd. for $C_{18}H_{13}O_5N$: C, 66.9; H, 4.0; N, 4.3. Found: C, 67.3; H, 3.9; N, 3.9.

The hydrochloride of IIIb was prepared by the addition of the calculated amount (1 mol.:1 mol.) of 5 *N* hydrochloric acid to a solution of IIIb in acetone, m.p. 233° dec., and the sulfate by recrystallizing IIIb from ethanol containing excess of sulfuric acid, m.p. 250° (red-brown melt). These yellow crystalline salts dissolved in water giving pale yellow solutions from which the free base precipitated spontaneously on keeping for a few minutes.

The conversion of IIIb back to IIb was effected by alcoholic potassium hydroxide as described for IIIa.

Oxidation of IIIa with Chromic Acid.—One gram of IIIa dissolved in 20 ml. of glacial acetic acid was treated with stirring and at room temperature (20°) with 4 ml. of 25% sulfuric acid and 6.6 ml. of 30% sodium dichromate. The mixture warmed up to about 40°, while its color was changing from yellow to deep brown. After standing for 30 minutes, the mixture was diluted with 120 ml. of water and extracted with 50 ml. of chloroform. The chloroform extract then was washed with water and extracted with 20 ml. of 4% sodium hydroxide. The yellow alkaline extract yielded on acidification with dilute acetic acid colorless **6-formyl-7-hydroxy-5-methoxy-2-(3′-pyridyl)-chromone (IV)**, which was filtered off and crystallized from ethanol as hairy yellowish crystals, m.p. 223° (dec., evolution of gas), yield 0.6 g. IV was insoluble in water and dilute acetic acid and sparingly soluble in alcohol and acetone. It gave a red ferric chloride reaction and dissolved in both 4% sodium hydroxide and concentrated sulfuric acid with a yellow color; a deep orange color was produced when an alcoholic solution of IV was mixed with an alcoholic solution of *p*-phenylenediamine. The magnesium–hydrochloric acid test done as with IIIa gave an orange color.

Anal. Calcd. for $C_{16}H_{11}O_5N$: C, 64.7· H, 3.7; N, 4.7. Found: C, 64.9; H, 3.7; N, 4.7.

Oxime of IV.—A mixture of 0.2 g. of IV, 0.2 g. of hydroxylamine hydrochloride, 0.4 g. of sodium acetate and 300 ml. of ethanol was refluxed for one hour and cooled. The crystalline oxime which separated out had m.p. 253° (brown melt) and was very sparingly soluble in alcohol; its ferric chloride reaction was red-brown.

Anal. Calcd. for $C_{16}H_{12}O_5N_2$: N, 9.0. Found: N, 8.7.

FACULTY OF SCIENCE, CAIRO UNIVERSITY
AND THE MEMPHIS CHEMICAL CO.
CAIRO, EGYPT

Benzoylcyanamide from Ethyl Benzoylthioncarbamate

BY GLENN S. SKINNER AND H. C. VOGT

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In an attempt to condense N-benzoyl-O-ethylisourea with ethyl malonate in alcoholic sodium ethox-

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(3) (a) A. Schönberg, N. Badran and N. A. Starkowsky, THIS JOURNAL, **75**, 4992 (1953); (b) **77**, 1019 (1955); (c) **77**, 5390 (1955).

(4) For references to the reaction of flavones with magnesium and hydrochloric acid, see T. A. Geissman and R. O. Clinton, *ibid.*, **68**, 700 (1946).

(5) All melting points are uncorrected. For the ferric chloride reactions, a drop of an aqueous solution of ferric chloride was added to the substance dissolved in 95% ethanol. Elementary microanalyses were made by Drs. Weiler and Strauss, Oxford.