Furo-chromones and -Coumarins. XIII. The Dicoumarol Analogs of Bergapten, Isopimpinellin and Pimpinellin

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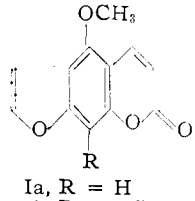
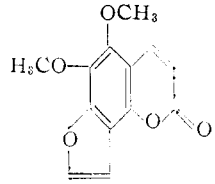
RECEIVED JUNE 1, 1955

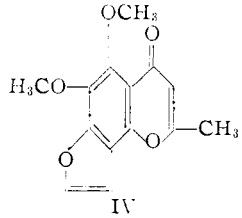
As bergapten (Ia), isopimpinellin (Ib) and pimpinellin (II) are substances of known physiological action (comp. the photodynamical action of Ia,[1] the molluscicidal action of Ia and Ib,[2] and the well known poisonous character of these three natural furocoumarins to fish[3]), and as dicoumarol is an anticoagulant of great medical interest, it seemed advisable to prepare the dicoumarol analogs of the mentioned furocoumarins.



Ia, R = H
b, R = OCH_3



II



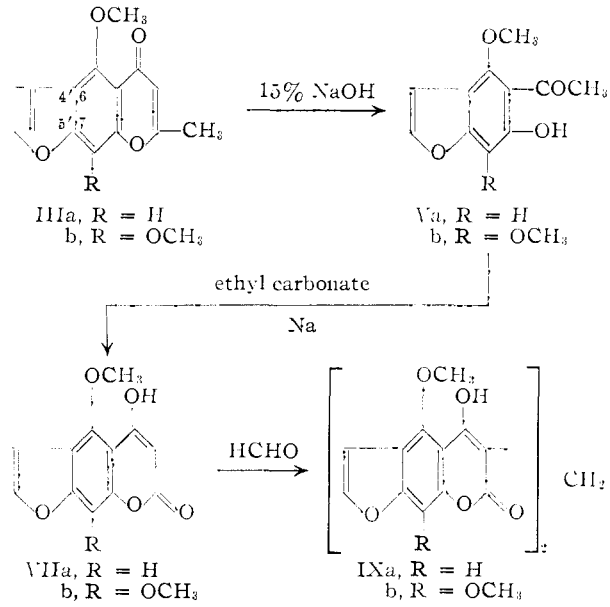
IV

The synthesis of these derivatives of dicoumarol starting with the corresponding coumarins is impossible, or at least very difficult. We have found a suitable way starting with visnagin (IIIa) and khellin (IIIb), two natural chromones which are now easily available from the Egyptian plant *Ammi visnaga* (L.), and isokhellin (IV) prepared synthetically from khellin.[4]

As an example, the synthesis of 3,3'-methylene-bis-(4-hydroxy-5-methoxyfuro-4',5',6,7-coumarin) (IXa) from visnagin (IIIa) has been carried out as follows.[5,6] An analogous series of reactions starting with isokhellin (IV) yields the dicoumarol derivative X.

While the alkaline hydrolysis of visnagin (IIIa) to visnaginone (Va) and of khellin (IIIb) to khellinone (Vb) are already known, it seems that the hydrolysis of isokhellin (IV) to isokhellinone (VI) has not yet been published.

The new 4-hydroxycoumarin derivatives VIIa and VIIb have been methylated with methyl iodide in the presence of acetone and potassium carbonate. Although the methylation of 4-hydroxycoumarins by this method has been reported to give the 4-



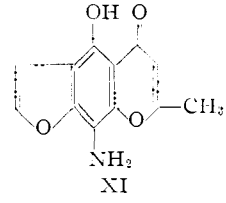
IIIa, R = H
b, R = OCH_3

Va, R = H
b, R = OCH_3

VIIa, R = H
b, R = OCH_3

IXa, R = H
b, R = OCH_3

methoxy products,[5] a discussion of this point is necessary because 4-hydroxycoumarins also may react as 2-hydroxychromones; thus, the methylation of 4-hydroxycoumarin with diazomethane has been reported[7] to yield the two possible methyl ethers (*viz.*, 4-methoxycoumarin and 2-methoxychromone) of which the chromone, but not the coumarin is soluble in cold moderately concentrated mineral acids. We have found that the products of methylation obtained under the stated conditions are insoluble in cold acids in accordance with the coumarin structure. The alkaline hydrolysis of these 4-methoxycoumarins led to visnaginone (Va) and khellinone (Vb), respectively.



XI

Color Test.—It has been found that the alcoholic solutions of the furocoumarins xanthotoxin, imperatorin, bergapten and isopimpinellin give with 8-amino-5-hydroxy-2-methylfuro-4',5',6,7-chromone (XI),[8] in the presence of alkali, a deep violet color which may be used for colorimetric work. Details concerning such use will be given in a later publication. The structurally related furochromones visnagin and khellin do not give this test.

Experimental[9]

Isokhellinone (VI).—Isokhellin (IV)[4] (1 g.) was refluxed for 1 hour with 50 ml. of 15% sodium hydroxide solution. The chromone dissolved giving a yellow solution which was cooled and acidified with hydrochloric acid. The deposit of isokhellinone (VI) which was thus obtained crystallized

(1) H. Kuske, *Arch. Derm. Syph.*, **178**, 112 (1938); L. Musajo, G. Rodighiero and G. Caporale, *Bull. soc. chim. biol.*, **36**, 1213 (1954).

(2) A. Schönberg and N. Latif, THIS JOURNAL, **76**, 6208 (1954).

(3) E. Späth and F. Kuffner, *Monatsh.*, **69**, 75 (1936).

(4) J. R. Clarke and A. Robertson, *J. Chem. Soc.*, 302 (1949); S. K. Mukerjee and T. R. Seshadri, *J. Sci. Ind. Research (India)*, **13B**, 400 (1954).

(5) Comp. J. Boyd and A. Robertson, *J. Chem. Soc.*, 174 (1948).

(6) Comp. C. F. Huebner and K. P. Link, THIS JOURNAL, **66**, 656 (1944).

(7) F. Arndt, L. Loewe, R. Un and E. Ayça, *Chem. Ber.*, **84**, 319 (1951).

(8) A. Schönberg and N. Badran, THIS JOURNAL, **73**, 2960 (1951).

(9) 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.

TABLE I

Starting material	Reacn. prod.[a] and m.p., °C.		Formula of the reacn. prod.	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Yield, %	Dicoumarol derivative: Reacn. prod.[e] and m.p.,[f] °C.		Formula of the reacn. prod.	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	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.

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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

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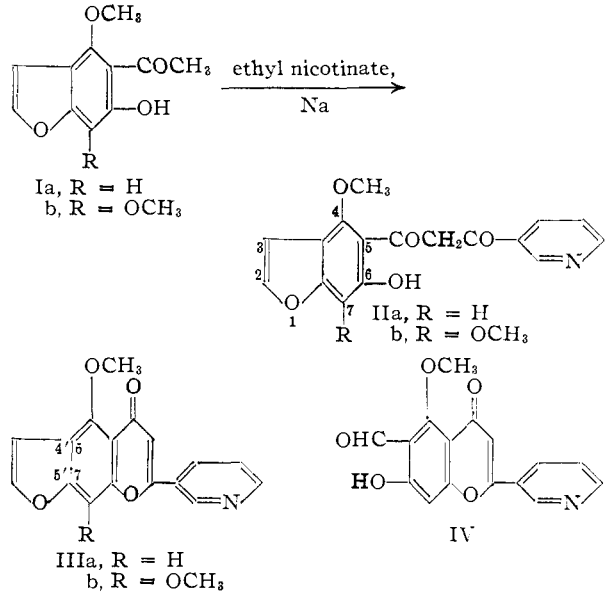
RECEIVED JUNE 1, 1955

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]



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).