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Furochromones and Coumarins. VI.[1] Demethylation of Xanthotoxin, Khellin and Khellol with Aniline Hydrochloride and Magnesium Iodide

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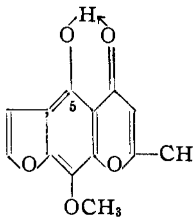
Examples of demethylation[2] reactions involving kellin, khellol and xanthotoxin are given, the importance of the facile demethylation of the latter leading to an intermediate in the preparation of medical imperatorin is stressed.

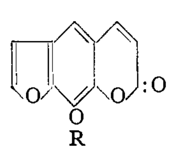
Demethylation of Xanthotoxin (IIb) and Khellin (IIIa) with Aniline Hydrochloride

The powdered fruits of *Ammi majus* are used in Egypt as a time-honored remedy for leukoderma; they contain, as active principles, xanthotoxin (IIb) and imperatorin[1a,1d] (IIc) which are now extracted and given as such.[3] This treatment avoids the unpleasant and dangerous side effects of the old one. Xanthotoxin and imperatorin are usually given in the ratio 2:1, and as the latter is only available in much smaller amount from the fruits, it is evident that the facile transformation of xanthotoxin into imperatorin is a problem of more than academic interest. It may be regarded as solved if a route from xanthotoxin to xanthotoxol (IIa) is found, since according to Späth and Holzen[4] xanthotoxol may be transformed into imperatorin with ease. A facile conversion of xanthotoxin into xanthotoxol is now described. It consists of heating the former with aniline hydrochloride and is superior technically to that effected by the action of magnesium iodide,[1d] the only other method so far found practicable.

Using the same method khellin (IIIa) was partially demethylated to IIId. Demethylation is believed to be connected with the methoxyl group in position 5, since the partially demethylated product is insoluble in alkali and stable toward ethereal diazomethane, characteristics which have also been observed in similar cases[5] and which are believed to be due to chelation I. This also explains the insolubility of IIId in alkali[6]

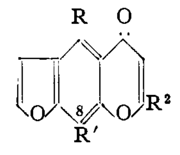


I



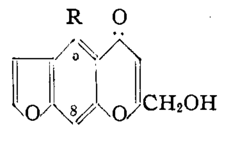
II

IIa, $R = H$ (xanthotoxol)
IIb, $R = CH_3$ (xanthotoxin)
IIc, $R = CH_2—CH{=}C(CH_3)_2$ (imperatorin)



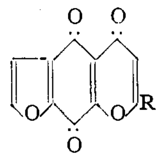
III

IIIa, $R = R' = OCH_3, R^2 = CH_3$ (khellin)
IIIb, $R = R' = OCH_3, R^2 = H$ (norkhellin)
IIIc, $R = R^1 = OH, R^2 = H$
IIId, $R = OH, R^1 = OCH_3, R^2 = CH_3$
IIIe, $R = OCH(CH_3)_2, R^1 = OCH_3, R^2 = CH_3$
IIIf, $R = OCH_3, R^1 = H, R^2 = CH_3$ (visnagin)
IIIg, $R = OH, R^1 = H, R^2 = CH_3$
IIIh, $R = OCH(CH_3)_2, R^1 = H, R^2 = CH_3$



IV

IVa, $R = OCH_3$ (khellol)
IVb, $R = OH$ (norkhellol)



V

Va, $R = H$
Vb, $R = CH_3$

Demethylation Effected with Magnesium Iodide.—Demethylation of khellin (IIIa to IIIc) may be effected by the action of magnesium iodide,[1c] in the absence of a solvent, followed by hydrolysis of the reaction product with dilute sulfuric acid. Using this method, we have for the first time demethylated khellol (IVa to IVb) and norkhellin[7] (IIIb to IIIc). IVb gives a color reaction with ferric chloride, forms a diacetate with acetic anhydride and may be methylated by methyl iodide in acetone to khellol (IVa). IIIb yields on oxidation with nitric acid the quinone Va which is orange, as is Vb.[1c]

Physiological Effect.—The partially demethylated khellin (IIId) was tested by Prof. G. V. Anrep (Cairo), to whom we wish to express our gratitude. He reports: "The spasmolytic action of the khellin derivative has been tested on the rectal caecum of the fowl and on the coronary circulation in the dog. With both methods the result was negative. Doses of the compound 10 times greater than those of

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[1] (a) A. Schönberg and A. Sina, *Nature*, **161**, 481 (1948); (b) THIS JOURNAL, **72**, 1611, (c) 3396, (d) 4826 (1950); (e) A. Schönberg and N. Badran, *ibid.*, **73**, 2960 (1951), are to be regarded as parts I–V.

[2] The word "demethylation" is used in this paper for the change $C–OCH_3 \rightarrow C–OH$(phenolic); in the field of naturally occurring furochromones and coumarins this change has often met with difficulties (J. R. Clarke and A. Robertson, *J. Chem. Soc.*, 302 (1949)).

[3] (a) Anis Abdel Malik, Gazette of the Faculty of Medicine, Cairo, Vol. XVI, No. 384 (May-August 1950); (b) Sidi and Bourgeois-Gavardin, *La Presse Medicale*, **60**, 421 (1952); (c) Abdel Moneim El Mofty, *J. Royal Egyptian Medical Association*, **35**, 1 (1952).

[4] E. Späth and H. Holzen, *Ber.*, **68**, 1123 (1935).

[5] A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 746 (1946).

[6] For examples of 5-hydroxychromones which are insoluble in alkali compare *inter alia* IIIg (this paper); 2,6-dimethyl-5-oxy-7-methoxychromones (H. Schmid, *Helv. Chim. Acta*, **32**, 814 (1949)) and 2,3-dimethyl-5-oxychromone (D. Pillon, *Bull. soc. chim.*, 326 (1952)).

[7] The use of the prefix "nor" facilitates the naming of many substances but leads to difficulties if used in connection with substances containing more than one methyl. Thus norkhellin has been proposed for both IIIb,[1b] and ($III, R = R^1 = OH; R_2 = CH_3$). (V. V. Sreerama Murti and T. R. Seshadri, *Proc. Indian Acad. Soc.*, **30**, 112 (1949).) We propose that in cases where the prefix "nor" alone is ambiguous, numbers and the prefix "di-nor," etc., be used. The following examples are self-explanatory: 2-nor-khellin (IIIb), 5-nor-khellin (IIId), 5,8-dinor-khellin ($III, R = R^1 = OH, R^2 = CH_3$), 2,5,8-trinor-khellin (IIIc), 1,7,7-trinor-camphane (for nor-camphane (C_7H_{12})).

khellin had no spasmolytic effect and caused no increase in the coronary blood flow."

Experimental

Demethylation Effected with Aniline Hydrochloride or β-Naphthylamine Hydrochloride. (a) Partial Demethylation of Khellin.—Two grams of khellin (1 mole) (IIIa) and aniline hydrochloride (2 moles) were finely powdered and the mixture heated (anisole-bath) in a vessel connected with a reflux condenser for 75 minutes. Evolution of gases was observed and the mixture turned orange. The cooled mixture was treated with water to dissolve excess of aniline hydrochloride and the residue was crystallized from benzene. 5-Hydroxy-8-methoxy-2-methylfuro-(4',5',6,7)-chromone (IIId)[8] forms yellow crystals, m.p. 196°, insoluble in 10% sodium hydroxide solution; the alcoholic solution gave with aqueous ferric chloride a deep green color; yield 1 g. *Anal.* Calcd. for $C_{13}H_{10}O_5$: C, 63.4; H, 4.0. Found: C, 63.4; H, 4.0.

The experiment was repeated using β-naphthylamine hydrochloride with similar results.

(b) **Visnagin (IIIf).**—The procedure was the same as in the case of khellin and aniline hydrochloride; 2-methyl-5-hydroxyfuro-(4',5'-6,7)-chromone (IIIg) was obtained m.p. 155°, insoluble in 10% sodium hydroxide solution. No depression of m.p. on admixture with an authentic sample.[1e] *Anal.* Calcd. for $C_{12}H_8O_4$: C, 66.7; H, 3.7. Found: C, 66.8; H, 3.8.

(c) **Xanthotoxin (IIb).**—The experiment was carried out as in the case of khellin and aniline hydrochloride but with stirring and in an atmosphere of carbon dioxide; the heating (about 40 minutes) was carried out by using a bath (initial bath temperature 180°, raising gradually at 205°). After cooling, the reaction product was treated with water; the insoluble residue was crystallized from dilute acetic acid. The yield was more than 50%; after further crystallization xanthotoxol (IIa) was obtained in crystals, m.p. 242°, no depression on admixture with an authentic sample.[1d] The alcoholic solution gave no color reaction with aqueous ferric chloride. IIa is soluble in 10% sodium hydroxide giving a yellow color, changing to brown-green.

Demethylation Effected with Magnesium Iodide. (a) Khellol.—A solution of 2 g. of khellol (1 mole) (IVa) in dry benzene was added to an ether-benzene mixture of magnesium iodide[9] (2 moles). The solvent was removed *in vacuo* and the residue dried in a vacuum at 130°, and kept at 160–165° (bath temperature) for 1.5 hours. After cooling, the solid was pulverized and decomposed with dilute sulfuric acid; the resulting product was filtered off, washed with water, treated with a dilute aqueous solution of sodium hydrogen sulfite to remove iodine and washed with water. The reaction product was, for further purification, transformed into its diacetate. One half gram of it was refluxed with 12 cc. of acetic anhydride for one hour; after cooling, crystals of the diacetate were formed which when recrystallized from alcohol had m.p. 198°, and gave a depression with IVb which has the same melting point. *Anal.* Calcd. for $C_{16}H_{12}O_7$: C, 60.7; H, 3.8. Found: C, 60.6; H, 3.5.

Hydrolysis.—One gram of the diacetate was boiled with 500 cc. of hydrochloric acid (5%) for one hour. The solution was filtered while hot; after cooling yellow crystals of norkhellol (IVb) formed and were recrystallized from water; m.p. 198°. It is insoluble in aqueous alkali and gives with concd. sulfuric acid, an orange color; the alcoholic solution gives a deep blue green color with aqueous ferric chloride. *Anal.* Calcd. for $C_{12}H_8O_5$: C, 62.1; H, 3.4. Found: C, 61.9; H, 3.7.

(b) **Norkhellin.**—One-half gram of norkhellin (IIIb) dissolved in 150 ml. of dry, hot benzene was added to a mixture of 10.5 g. of magnesium iodide in 100 ml. of ether and 100 ml. of benzene. The solvents were distilled off under vacuum (boiling water-bath), and the residue dried for 100 minutes under vacuum, the initial bath temperature being 130°, raising to 160°. The cold mixture was treated with dilute sulfuric acid, washed several times with water, then with a dilute solution of sodium bisulfite and then again with water. The dry product was crystallized from benzene m.p. 278°. 5,8-Dihydroxy-furo-(4',5',6,7)-chromone (IIIc) is difficultly soluble in hot alcohol and an alcoholic solution gave a green color with an aqueous solution of ferric chloride. It is soluble in aqueous alkali with a red-brown color. *Anal.* Calcd. for $C_{11}H_6O_5$: C, 60.5; H, 2.8. Found: C, 60.4; H, 3.0.

Oxidation of Norkhellin.—To 0.5 g. of norkhellin (IIIb) was added 5 cc. of nitric acid prepared by adding 12 ml. of water to 5 g. of nitric acid, sp. gr. 1.4; the mixture was stirred for five minutes and then allowed to stand for a further five minutes. Water was added, the precipitate filtered off, washed with water and refluxed with 5 ml. of acetone, allowed to cool, filtered and crystallized from acetone. Orange crystals of furo-4',5',6,7-chromone-5,8-quinone (Va) were obtained, m.p. 242°, with evolution of gases. *Anal.* Calcd. for $C_{11}H_4O_5$: C, 61.1; H, 1.8. Found: C, 61.0; H, 2.1.

Alkylation Reactions. (a) Khellol from IVb.—One gram of IVb was dissolved in 50 cc. of acetone, and 7 cc. of methyl iodide and 7 g. of potassium carbonate was added. The mixture was refluxed for 36 hours and filtered while hot. The acetone was distilled off in vacuum and the residue was crystallized from water and then from alcohol (charcoal). Khellol thus obtained gave no depression with the natural product and gave no color reaction with ferric chloride.

(b) **Khellin from IIId.**—The procedure was as previously described; the crude product was crystallized from hot water and proved to be khellin by its properties and mixed m.p.[8]

(c) **Isopropyl Iodide and IIId.**—A mixture containing 1 g. of IIId, 2 ml. of isopropyl iodide, 6 g. of potassium carbonate and 100 ml. of acetone was refluxed for 36 hours; the crude product was repeatedly crystallized from petroleum ether (b.p. 50–80°) until it gave no ferric chloride reaction. The m.p. of 2-methyl-5-isopropyloxy-8-methoxy-furo-4',5',6,7-chromone (IIIe)[8] is 94°. *Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.7; H, 5.5. Found: C, 66.4; H, 5.6.

(d) **2-Methyl-5-hydroxy-4',5',6,7-chromone (IIIg) and Methyl Iodide.**—The crude product was crystallized from water and then from alcohol and proved to be visnagin by mixed m.p. and properties.

(e) **IIIg and Isopropyl Iodide.**—The reaction mixture was refluxed for 42 hours; repeated crystallizations from benzine (b.p. 60–70°) (charcoal) until the ferric chloride reaction was negative gave 2-methyl-5-isopropyloxy-furo-4',5'-6,7-chromone (IIIh), m.p. 124°. *Anal.* Calcd. for $C_{15}H_{14}O_4$: C, 69.8; H, 5.4. Found: C, 69.9; H, 5.6.

(f) **Norkhellin IIIb from IIIc.**—The product from IIIc and methyl iodide was crystallized from ethyl alcohol (charcoal) and proved to be norkhellin; identification as above.

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(8) ADDED APRIL 22, 1953.—Compare H. Abu Shadi and T. O. Soine, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 325 and 403 (1952).

(9) A. Schönberg and R. Moubasher, *J. Chem. Soc.*, 462 (1944).