test for nitrogen and a negative test for carbylamine. Of this quantity 470 mg. was recrystallized from methanol, and the 171 mg. that separated was recrystallized from water. The 45 mg. thus obtained melted at 191–192° with darkening and evolution of gas (20 mg. required 3.30 ml. of 0.0502 N alkali, therefore, neutral equivalent = 121). In attempts to find a better crystallizing solvent, all the acid was lost, except that the aqueous mother liquor yielded about 25 mg., which melted at 193–194° with darkening and evolution of gas.

Anal. Calcd. for $C_{11}H_{13}O_4N$: C, 59.10; H, 5.83; N, 6.28; mol. wt., 223. Found: C, 59.15, 58.72; H, 5.85, 5.75; N, 6.15, 6.01; mol. wt. (above titration), 242.

The isoelectric point of a small quantity of the acid obtained from another experiment was determined by electrometric titration to be *p*H 2.92.

Isolation of Dicarboxylic Acid Half-Ester.—After ether extraction, the acidified hydrolysate described above was neutralized and evaporated but it failed to yield the expected polyhydroxy nucleus. The residue was finally digested with several portions of hot absolute methanol from which, upon the addition of three to four volumes of acetone, a colorless, hygroscopic, amorphous precipitate was separated. It gave a positive test for nitrogen. The product is presumed to be the salt of the half-ester of the dicarboxylic acid described above, but it did not form a definite amide or *p*-phenylphenacyl ester.

Isolation of Polyhydroxy Nucleus of Wilfordine.—In another experiment 4 g. of wilfordine was saponified with barium hydroxide in 90% methanol, and the reaction mixture was diluted with water. The excess barium was precipitated with carbon dioxide, removed from solution, and washed with water and methanol. The washings were combined with the filtrate and the methanol was removed. The hydrolysate was acidified and continuously extracted with ether. The aqueous residue then was made alkaline and saponified a second time. The reaction mixture was adjusted to *p*H 2.92 and, after the volume had been reduced to about 5 ml., it was diluted with 100 ml. of boiling ethanol. The ethanol solution was filtered hot, and the solvent was removed under reduced pressure. The thick, sirupy residue contained nitrogen. It was dissolved in a little water, and required 53.35 ml. of 0.1059 N barium hydroxide (eq. to 631 mg. of dibasic acid) for neutralization to cresol red. Removal of the solvent yielded a sirupy residue containing the barium salt. This residue was digested with four portions of boiling methanol (A), which were filtered from the insoluble part (B). The residue obtained on removal of the solvent from the combined filtrates (A) was dissolved in a few milliliters of water, and just enough sulfuric acid was added to precipitate all the barium. The barium sulfate was separated and the filtrate was evaporated to dryness. The residue thus obtained crystallized when treated with methanol. The crystals were filtered and added to the crystalline fractions obtained as described below, and the methanol filtrate was evaporated. The resulting residue was digested with several portions of boiling acetone, which were filtered. The acetone-insoluble portion (1.2 g.), presumably the half-ester, was set aside. The acetone filtrates were combined, and when the solvent was removed 200 mg. of crystals was obtained.

The methanol-insoluble portion (B) was dissolved in a little water, and the barium was precipitated by the careful addition of dilute sulfuric acid. The barium sulfate was separated and the solvent was removed leaving a residue that was dissolved in a few milliliters of hot methanol and diluted with 3 volumes of acetone. The solution crystallized when cooled and the crystals (35 mg.) were separated. The solvent was removed from the mother liquor and the residue was digested with several portions of hot acetone and then set aside. The acetone solutions were combined, filtered, and reduced to a small volume from which, after cooling, an additional 15 mg. of the crystalline product was obtained.

The four portions of crystalline material were combined and recrystallized four times from equal volumes of methanol–acetone. The separated crystals weighed 170 mg. and the combined mother liquors yielded an additional 35 mg. of the same product which contained neither nitrogen nor sulfur and melted very unsharply, 245–270° (dec.), when heated in the usual manner. However, when plunged into a bath previously heated to 306° and then heated at 4 to 5° per minute, the sample melted at 309–310° with decomposition.

Anal. Calcd. for $C_{15}H_{26}O_{10}$: C, 49.18; H, 7.15. Found: C, 49.03, 49.38, 49.32; H, 7.29, 7.35, 7.05.

Summary

A crystalline, insecticidally active alkaloid has been isolated from the roots of *Tripterygium wilfordii* Hook. This compound has been designated wilfordine and it has been found to be an ester alkaloid consisting of a polyhydroxy nucleus esterified with 5 moles of acetic acid, 1 mole of benzoic acid, and 1 mole of a nitrogen-containing dicarboxylic acid.

BELTSVILLE, MARYLAND RECEIVED JUNE 22, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, FOUAD I UNIVERSITY]

Khellin and Allied Compounds

BY ALEXANDER SCHÖNBERG AND ALY SINA

Khellin, obtained from the fruits of *Ammi visnaga* (L), has attracted interest, being an antispasmodic and a coronary vasodilator of promise, in the treatment[1] of angina pectoris and bronchial asthma. Comparatively little is known about the chemistry of khellin,[2] its derivatives and analogs. The aim of this paper is to fill this gap; by the preparation of a number of such derivatives, a study of the relationship between chemical constitution and physiological activity was rendered possible.

Khellin (IIIb) being a chromone derivative with a methyl group in position 2, might be expected to condense with aromatic aldehydes as do other 2-methylchromones.[3] This is indeed the case; thus the action of anisaldehyde and sodium alcoholate lead to the formation of the yellow 2-(*p*-methoxybenzylidene)-khellin (IIIf). Khellin gave an orange perchlorate.

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[1] Anrep, Barsoum, Kenawy and Misrahy, *British Heart J.*, **8**, 171 (1946); *Lancet*, **I**, 557 (1947).

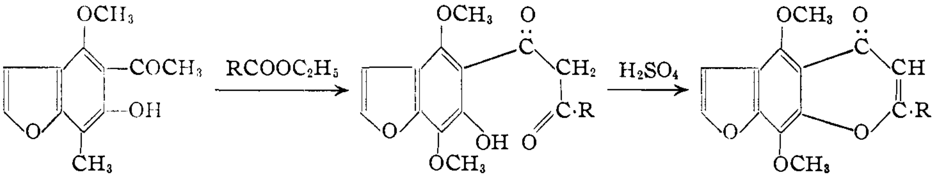
[2] Mustapha, *Compt. Rend. Acad. Sci., Paris*, **89**, 442 (1879); Fantl and Salem, *Biochem. Z.*, **226**, 166 (1930); Späth and Gruber, *Ber.*, **71**, 106 (1938).

[3] Heilbron, Barnes and Morton, *J. Chem. Soc.*, **123**, 2559 (1923).

Synthesis of Analogs of Khellin.—This was achieved by starting with khellinone (I), easily obtained by the action of alkali on khellin.[4] When (I) was treated with the ethyl esters of propionic and benzoic acid in the presence of sodium, (IIb) and (IIc), respectively, were obtained. Norkhellin (IIIa) and *n*-2-propylnorkhellin (IIId) were obtained by allowing (I) to react similarly with the ethyl esters of formic and *n*-butyric acids, respectively, and treating the reaction products with 30% sulfuric acid. In a similar manner the 2-ethyl and 2-phenyl derivatives of (IIIa) were obtained from (IIb) and (IIc).

The partial synthesis of khellin was effected by following a similar route (I → IIa → IIIb) by using ethyl acetate. The new analogs of khellin gave the same color reaction as khellin with concentrated sulfuric acid (orange).

The condensation product (IId) obtained from (I) and ethyl oxalate, yielded ethyl norkhellin-2-carboxylate (IIIg) either by the action of alcoholic hydrochloric acid, or by heating in a vacuum above its melting point. Norkhellin when treated with alkali gave khellinone (I).



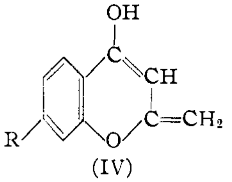
(I) (33%)[1]

(II or enolic form)
IIa, R = CH_3 (5%)
IIb, R = C_2H_5 (inact.)
IIc, R = C_6H_5[a]
IId, R = $COOC_2H_5$

(III)
IIIa, R = H (55%)
IIIb, R = CH_3 (100%)
IIIc, R = C_2H_5 (75%)
IIId, R = C_3H_7-*n*
IIIe, R = C_6H_5[a]
IIIf, R = $CH{=}CHC_6H_4OCH_3$[a]
IIIg, R = $COOC_2H_5$

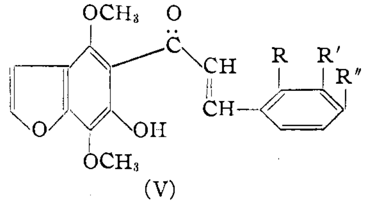
[a] Not sufficiently soluble in Tyrode solution.

A Color Reaction of 2-Methyl-γ-pyrones.—A red color reaction of khellin with potassium hydroxide was described[5,6] which was also used for the colorimetric estimation of khellin. We have found that a reddish-violet color reaction (under conditions described in the experimental part) is also developed when certain simple 2-methyl-γ-pyrones are treated with potassium hydroxide, *e. g.*, 2,6-dimethylpyrone, 2,6-dimethylchromone, 2,3-dimethylchromone, 2-methyl-7-methoxychromone (or the corresponding ethyl or propyl ethers) and visnagin. The presence of a methyl group in position 2 is essential as no such color is given with chromone, 6-methylchromone, flavone, norkhellin (IIIa) and 2-phenylnorkhellin (IIIe). The hydrolysis products of khellin, ω-acetokhellinone (IIa) and khellinone (I), do not give this color test. 2-Ethyl- and 2-propylnorkhellin give a brownish-red color which is weaker in intensity than that developed with khellin. As the violet substance could not be isolated, its constitution is doubtful. In this respect, it should be pointed out that the methyl group (or substituted methyl group) in position 2 in γ-pyrones and in chromones has a reactive hydrogen atom (compare IV).



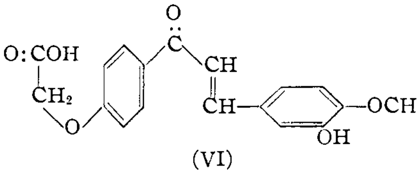
(IV)

Condensation of Khellinone and Visnaginone (VII) with Aromatic Aldehydes.—These condensations, *e. g.*, with anisaldehyde, *p*-dimethylaminobenzaldehyde, piperonal and vanillin resulted in the formation of the corresponding colored chalkones having the constitution Va-Vd, respectively, in the case of khellinone.



(V)
Va, R = R′ = H; R″ = OCH_3
Vb, R = R′ = H; R″ = $N(CH_3)_2$
Vc, R′R″ = —O·CH_2·O—; R = H
Vd, R = H; R′ = OCH_3; R″ = OH

It should be mentioned that some of the chalkones, *e. g.*, (Vd) are similar in structure to chalkones showing vitamin P activity,[7] *e. g.*, (VI).



(VI)

These chalkones are under investigation for vita-

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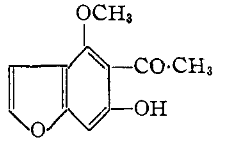
[4] Späth and Gruber, ref. 2.

[5] Fahmy and El-Keiy, *Reports Pharmaceutic. Soc., Cairo*, **3**, 36 (1931); Abdel Rahman, M. Pharm. Thesis, Fac. of Medicine, Fouad I University, Cairo, 1943.

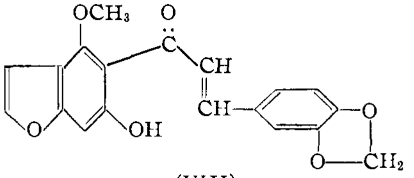
[6] Anrep, Kenawy, Barsoum and Fahmy, *Gazz. Fac. of Medicine, Cairo*, XIV, No. 1, March (1947).

[7] Hughes and Parkes, Jubilee Volume dedicated to E. C. Barell by the scientific workers of La Roche Company, 1946, p. 225.

min P activity. Similarly, we have condensed visnaginone (VII) with piperonal and obtained 5-(3′,4′-dioxymethylenebenzalaceto)-4-methoxy-6-hydroxybenzofuran (VIII).

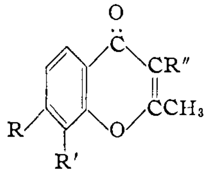


(VII) (20%)[6]



(VIII)

Physiological Effect of Khellin and Allied Compounds.—A number of 2-methyl-γ-pyrones, including some chromones which show similarity in their constitution to khellin, have been prepared and their activity tested and the results are shown below.



(IX)

IXa, R = CH_3, R′ = R″ = H (22%)
IXb, R = CH_3, R′ = H; R″ = CH_3 (15%)
IXc, R = OCH_3, R′ = R″ = H (10%)
IXd, R = R′ = OCH_3, R″ = H (20%)
IXe, R = OC_2H_5, R′ = R″ = H (27%)
IXf, R = OC_3H_7-*n*, R′ = R″ = H (30%)
IXg, R = OC_4H_9-*n*, R′ = R″ = H (30%)
IXh, R = OC_3H_5, R′ = R″ = H (30%)
IXk, R = OH, R′ = R″ = H (< 10%)
Flavone (15%)
Meconic acid (< 10%)
2,6-Dimethylpyrone (3%)

The antispasmodic effect of these compounds was tested by Prof. G. V. Anrep and A. R. Fahmy in the Department of Physiology of this University, using the rectal caecum of the fowl as a test object, with an accuracy of about 10%. The compounds were dissolved in Tyrode solution in 0.5 millimolar concentration and the activities reported beside the formulas refer to equimolecular amounts.

It should be stressed that chromone derivatives without a furan ring (comp. IX) as well as benzofuran derivatives containing no pyrone ring (comp. I) show activity. The importance of methyl or ethyl group in the 2-position of norkhellin should be stressed (comp. IIIa-c) this recalls the importance of the methyl group in the case of 1,4-naphthoquinones (vitamin K activity), 2,8-diaminoacridine (antibacterial action) and in the sulfonamide field, lately summarized by Platt and Sharp.[8] Similar results have been reported by Mauss[9] in connection with antibilharzial activity of 4-methyl derivatives of xanthone and thioxanthone.

Experimental

Condensation of Khellin with Anisaldehyde.—One-half gram of khellin and 0.27 g. of anisaldehyde were dissolved in 10 cc. of absolute alcohol. 0.05 gram of sodium was dissolved in 5 cc. of absolute alcohol and the two solutions were mixed, after being well cooled in ice. A colorless precipitate came down which was redissolved by slight warming and the mixture was left at room temperature overnight, acidified with acetic acid and diluted with water and then allowed to stand. The formed precipitate was filtered off, washed with water, pressed over porous plate, washed with a little benzine and finally crystallized from methyl alcohol as yellow needles, m. p. 171°, giving an orange melt. (IIIf) gave a reddish-brown color with sulfuric acid.

Anal. Calcd. for $C_{22}H_{18}O_6$: C, 69.84; H, 4.76. Found: C, 70.34; H, 4.96.

Action of Perchloric Acid on Khellin.—One-half gram of khellin was dissolved in 15 cc. of dry benzene and to the solution was gradually added 1.5 cc. of 60% perchloric acid, with vigorous shaking after each addition, when orange needles were formed. The crystals were filtered off and washed with dry benzene and had a m. p. about 180° with decomposition and evolution of gas.

Anal. Calcd. for $(C_{14}H_{12}O_5)_2 \cdot HClO_4$: C, 54.14; H, 4.06; Cl, 5.71. Found: C, 54.19; H, 4.06; Cl, 5.19.

Khellinone from Khellin.—Two grams of khellin was boiled with potassium hydroxide (2 g. in 20 cc. water) for one hour, on which the solid dissolved, gradually giving a yellow colored solution; on acidification with dilute hydrochloric acid it gave a crystalline precipitate which was filtered off, washed with water and crystallized from methyl alcohol as dark yellow needles of (I) m. p. 99–101° (yield about 90%).

ω-Acetokhellinone from Natural Khellin.[10]—A solution of 25 g. of potassium hydroxide in 200 cc. of absolute alcohol at 70° was poured onto 10 g. of khellin. The mixture was shaken for fifteen minutes without further heating during which time all khellin was dissolved and the solution acquired a deep wine-red color. It was then acidified with 60 cc. of glacial acetic acid, a liter of distilled water was added and the mixture cooled in the ice-chest, when crystals of (IIa) were formed (8.5 g.). After washing with water the substance was first crystallized from alcohol and then from a mixture of acetone and petroleum ether as colorless crystals of (IIa) m. p. 88–93°. Mixed m. p. with an authentic sample of (IIa) obtained from khellinone and ethyl acetate gave no depression. A dilute alcoholic solution of (IIa) gave with ferric chloride a red color. (The analysis was done by Mr. Charles Childes.)

Anal. Calcd. for $C_{14}H_{14}O_6$: C, 60.43; H, 5.03. Found: C, 60.52; H, 5.21.

(IIa) was converted back into khellin, by heating 1 g. with 30 cc. of dilute sulfuric acid (16 cc. of 98% sulfuric acid mixed with 70 cc. of water) in a vessel fitted with a reflux condenser on a water-bath for one hour. The resulting deep orange solution was poured into excess water and allowed to stand, when crystals were obtained which, after recrystallization from methyl alcohol, proved by m. p. and mixed m. p. determinations to be khellin (IIIb).

Khellin from Khellinone.—9.4 grams of khellinone was dissolved in 20 g. of ethyl acetate and to the warm solution a suspension of 3.7 g. of powdered sodium metal (prepared under xylene) in dry ether was gradually added. A violent reaction took place which was slowed down, when necessary, by external cooling. The mixture was left overnight and then treated with ice and water and then extracted three times with ether. The alkaline solution

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[8] Platt and Sharp, *J. Chem. Soc.*, 2129 (1948).

[9] Mauss, *Ber.*, **81**, 19 (1948).

[10] This experiment was carried out by Nasry Badran.

after being freed from ether by a stream of air, was acidified with dilute hydrochloric acid and the crystalline precipitate filtered off, washed with water, pressed over a porous plate and crystallized from alcohol as colorless crystals, m. p. 85–93°, giving a deep yellow melt. ω-Acetokhellinone (IIa) gave in alcoholic solution a red color with aqueous ferric chloride.

Anal. Calcd. for $C_{14}H_{14}O_6$: C, 60.43; H, 5.03. Found: C, 60.70; H, 5.05.

On boiling the benzene solution of the colorless (IIa) for ten minutes and then concentrating, yellow crystals were obtained, m. p. 112–113°, which may be reconverted into the colorless form m. p. 85–93° by crystallizing from dilute alcohol. This is probably a case of keto-enol or ring-chain tautomerism. The following is the analysis of the yellow form, which behaves toward ferric chloride in the same way as the colorless form.

Anal. Calcd. for $C_{14}H_{14}O_6$: C, 60.43; H, 5.03. Found: C, 60.32; H, 5.04.

When 1 g. of the colorless form of (IIa) was treated with dilute sulfuric acid as previously described and pouring the reaction mixture into sodium carbonate solution, a colorless precipitate came down which was filtered off, washed with water and crystallized from methyl alcohol as colorless crystals of (IIIb) m. p. 148–149° undepressed by admixture with an authentic sample (yield almost quantitative).

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.62; H, 4.62. Found: C, 64.17; H, 4.64.

Action of Ethyl Formate on Khellinone.—In a flask fitted with a reflux condenser, 4.7 g. of khellinone was dissolved by the aid of gentle heat in 10 cc. of ethyl formate and to the warm solution 1.8 g. of powdered sodium suspended in 50 cc. of dry ether was gradually added; the reaction mixture was then treated as in the case of khellinone and ethyl acetate, when colorless crystals were obtained from alcohol; m. p. 165–170° with decomposition and evolution of gas. With sulfuric acid the crystals turned orange and gave a yellow solution. A dilute alcoholic solution of the crystalline compound gave gradually with ferric chloride a red brown color.

Norkhellin (IIIa).—(a) One gram of the crystals, m. p. 165–170°, was heated for two hours with 50 cc. of dilute sulfuric acid and the mixture treated as in the case of (IIa). The reaction product (IIIa) was crystallized from alcohol as colorless crystals, m. p. 182°. With sulfuric acid (IIIa) turned orange and gave a yellow solution.

Anal. Calcd. for $C_{13}H_{10}O_5$: C, 63.14; H, 4.07. Found: C, 63.65; H, 4.21.

(b) One-half gram of the crystals was refluxed with 25 cc. of alcoholic sulfuric acid (16.6 cc. 98% sulfuric acid mixed with alcohol and made up to 100 cc.) for thirty minutes; the orange solution was diluted with 100 cc. of water and then added to excess sodium carbonate solution. The colorless precipitate was filtered off, washed with water and then crystallized from alcohol as colorless crystals of (IIIa), m. p. 182° undepressed with the sample obtained in (a).

Action of Alkali on Norkhellin (IIIa).—0.05 gram of (IIIa) was refluxed with 10 cc. of potassium hydroxide solution (1 g. in 10 cc. water). The brownish-yellow solid was filtered, acidified with hydrochloric acid and the precipitate formed filtered off, washed with water and crystallized from methyl alcohol as brownish-yellow crystals of (I), m. p. 99° undepressed by admixture with an authentic sample of khellinone.

Action of Ethyl Propionate on Khellinone.—4.7 grams of khellinone was dissolved in 12 cc. of warm ethyl propionate and to the warm solution 1.8 g. of powdered sodium suspended in dry ether were gradually added. The mixture was then treated as in the case of ethyl acetate and khellinone. (IIb) crystallized from alcohol as colorless crystals m. p. 96° giving a deep yellow melt. With sulfuric acid the crystals turned orange and gave a yellow solution. Aqueous ferric chloride gave with an alcoholic solution of (IIb) a red color.

Anal. Calcd. for $C_{15}H_{16}O_6$: C, 61.64; H, 5.48. Found: C, 61.46; H, 5.41.

2-Ethylnorkhellin (IIIc).—One gram of (IIb) was treated with aqueous sulfuric acid as in the case of ethyl formate and khellinone and the reaction product was washed with water and crystallized from methyl alcohol as colorless crystals of (IIIc), m. p. 126°. The color reaction with sulfuric acid was the same as in the case of (IIb).

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.7; H, 5.1. Found: C, 65.24; H, 4.82.

Action of Ethyl Benzoate on Khellinone.—4.7 grams of khellinone and 18 g. of ethyl benzoate were condensed in the presence of 1.9 g. of powdered sodium, as in the case of ethyl acetate and khellinone. On acidification of the mixture with hydrochloric acid, an oil was obtained which was washed repeatedly with water, then rapidly with alcohol and finally crystallized from alcohol as yellow crystals of (IIc), m. p. 185° giving a red melt. With sulfuric acid the crystals turned red and gave an orange solution.

Anal. Calcd. for $C_{19}H_{16}O_6$: C, 67.06; H, 4.71. Found: C, 66.65; H, 5.0.

2-Phenylnorkhellin (IIIe).—(IIc) was treated with alcoholic sulfuric acid as in the case of the condensation product of ethyl formate and khellinone, when yellow crystals of (IIIe) were obtained from alcohol, m. p. 176–177°. With sulfuric acid (IIIe) behaved as (IIc).

Anal. Calcd. for $C_{19}H_{14}O_5$: C, 70.81; H, 4.35. Found: C, 71.06; H, 4.41.

2-*n*-Propylnorkhellin (IIId).—The oily diketone which was obtained by the condensation of 4.7 g. of khellinone with 12 g. of *n*-ethyl butyrate in the presence of 2 g. of powdered sodium, as in the case of ethyl acetate and khellinone, was treated with alcoholic sulfuric acid as (IIc) when (IIId) was obtained as colorless crystals, m. p. 93–94°, from benzine (40–60°). With sulfuric acid (IIId) gave an orange yellow solution. It is easily soluble in benzene and alcohol in the cold, difficultly soluble in petroleum ether (40–60°).

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.55. Found: C, 66.65; H, 5.54.

Action of Ethyl Oxalate on Khellinone.—In a flask fitted with a reflux condenser, 3 g. of khellinone was dissolved in 6 g. of warm ethyl oxalate and to the mixture was gradually added a suspension of 1.2 g. of powdered sodium in dry ether. When the initial vigorous reaction subsided, the mixture was refluxed on a water-bath for one hour and then left overnight. The reaction mixture was treated as in the case of ethyl acetate and khellinone and then acidified with acetic acid; the colorless crystalline precipitate that came down was filtered off, washed with water and recrystallized from methyl alcohol as colorless crystals of (IId) m. p. 161° giving a red-brown melt. Ferric chloride in alcoholic solution gave a reddish-brown color. Sulfuric acid gave an intense red-brown color.

Anal. Calcd. for $C_{16}H_{16}O_8$: C, 57.14; H, 4.76. Found: C, 57.58; H, 4.88.

Ethyl Norkhellin-2-carboxylate (IIIg).—(a) 0.3 gram of (IId) was dissolved in 10 cc. of hot alcohol, 1.5 cc. of hydrochloric acid (sp. gr. 1.18) was added and the mixture left overnight at room temperature. Yellow needles formed which were recrystallized from alcohol and had a m. p. 132° giving a yellow melt. (IIIg) gave no reaction with ferric chloride and was insoluble in cold aqueous sodium hydroxide. With sulfuric acid it gave a red color.

Anal. Calcd. for $C_{16}H_{14}O_7$: C, 60.38; H, 4.40. Found: C, 60.21; H, 4.52.

(b) 0.2 gram of (IId) was heated in vacuum at 210° (bath temperature) for five minutes. The reddish melt after cooling was crystallized from a mixture of benzene and alcohol when yellow crystals of (IIIg) were obtained m.p. 132° undepressed by admixture with the substance obtained in (a). Sulfuric acid gave a red color.

Anal. Calcd. for $C_{16}H_{14}O_7$: C, 60.38; H, 4.40. Found: C, 60.59; H, 4.43.

Condensation of Khellinone with Aromatic Aldehydes

(a) **Anisaldehyde.**—One-half gram of khellinone was dissolved together with 0.25 g. of anisaldehyde in 10 cc. of alcohol and the warm solution treated with 2 cc. of 50% sodium hydroxide solution and left overnight. The solution was diluted with water and the precipitated solid that separated was filtered off, washed with dilute hydrochloric acid several times on the filter, pressed and then crystallized from alcohol as yellow-brown prisms, of Va, m. p. 137°. It gave with sulfuric acid a brown color.

Anal. Calcd. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.08. Found: C, 67.64; H, 5.37.

(b) **Piperonal.**—One-half gram of khellinone and 0.3 g. of piperonal was dissolved in 5 cc. of 95% alcohol and then treated with 2 cc. of 50% sodium hydroxide solution. The mixture was warmed on a water-bath until a deep red cake of crystals was formed and then left overnight. The reaction mixture was diluted with water and the crystalline precipitate (Vc) filtered off, washed on the filter with dilute hydrochloric acid and then crystallized from alcohol as deep red crystals, m. p. 154°.

Anal. Calcd. for $C_{20}H_{16}O_7$: C, 65.2; H, 4.4. Found: C, 65.03; H, 4.32.

(c) **Vanillin.**—One-half gram of khellinone and 0.3 g. of vanillin were dissolved in 5 cc. of warm alcohol; to the warm solution was added a hot sodium hydroxide solution (2 g. of sodium hydroxide in 2 cc. of water) on which a vigorous reaction took place and the solution became deep orange. By shaking for a few minutes, an orange precipitate was formed; the reaction mixture was left overnight, acidified with dilute hydrochloric acid, cooled in ice and the precipitate filtered off; it was recrystallized from dilute alcohol and finally from a small amount of alcohol as orange crystals of (Vd) m. p. 135°, giving with sulfuric acid a brown color. (Vd) is soluble in dilute alkali, easily soluble in alcohol, difficultly soluble in petroleum ether.

Anal. Calcd. for $C_{20}H_{18}O_7$: C, 64.9; H, 4.8. Found: C, 64.9; H, 4.8.

(d) **Dimethyl-*p*-aminobenzaldehyde.**—One-quarter gram of khellinone and 0.15 g. of the aldehyde were condensed as described in the case of (c). The alkaline mixture was acidified with dilute hydrochloric acid, when a clear solution was obtained. Addition of a slight excess of ammonia led to the formation of a precipitate which was recrystallized from alcohol as deep red crystals of (Vb), m. p. 145°. It gave a brown solution with concentrated sulfuric acid and an orange solution with dilute hydrochloric acid.

Anal. Calcd. for $C_{21}H_{21}O_5N$: C, 68.6; H, 5.7; N, 3.8. Found: C, 68.75; H, 5.65; N, 4.08.

Condensation of Visnaginone (VII) with Piperonal.—One-half gram of (VII)[11] and 0.3 g. of piperonal were dissolved in 5 cc. of alcohol and then treated with 2 cc. of 50% sodium hydroxide solution as described in the case of piperonal and khellinone. (VIII) was crystallized from alcohol as orange crystals, m. p. 139°, which gave with sulfuric acid an orange-red color.

Anal. Calcd. for $C_{19}H_{14}O_6$: C, 67.45; H, 4.14. Found: C, 67.42; H, 4.31.

Preparation of Ethers of 2-Methyl-7-hydroxychromone

(a) **Methyl Ether.**—2-Methyl-7-hydroxychromone (IXk) was suspended in dry ether, treated with an excess of an ethereal solution of diazomethane and left overnight in ice. The ethereal solution was concentrated, cooled in ice, on which colorless crystals of 2-methyl-7-methoxychromone (IXc) were obtained, and recrystallized from petrol (80–90°); m. p. 114–115°. Kostanecki and Rozycki[12] gave m. p. 113°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.5; H, 5.26. Found: C, 69.83; H, 5.35.

(b) **Ethyl Ether.**—(IXk) was treated with an excess of an ethereal solution of diazoethane as described in (a), on which 2-methyl-7-ethoxychromone (IXe) was obtained in colorless crystals[12] from petrol (90–100°), m. p. 123–124°.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.59; H, 5.88. Found: C, 70.44; H, 5.61.

(c) ***n*-Propyl Ether.**—Nine-tenths gram of (IXk) (1 mol) was dissolved in 30 cc. of hot absolute alcohol containing 0.3 g. of potassium hydroxide; 1 g. of *n*-propyl iodide was then added and the mixture refluxed for eight hours. The mixture was cooled, filtered from potassium iodide and the filtrate evaporated to dryness in a vacuum. The residue was then crystallized from dilute alcohol and then from petrol (90–100°) as colorless needles of (IXf), m. p. 125–126°.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.56; H, 6.42. Found: C, 71.43; H, 6.21.

(d) **Isopropyl Ether.**—Obtained, as described in (c) using 1 g. of isopropyl iodide, in the form of colorless needles, m. p. 135° (from petrol 60–90°).

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.56; H, 6.42. Found: C, 71.50; H, 6.31.

(e) **Allyl Ether.**—Obtained as described in (c) using allyl iodide, in the form of colorless crystals (IXh) from petrol (90–100°), m. p. 92°.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.2; H, 5.5. Found: C, 71.99; H, 5.23.

(f) ***n*-Butyl Ether.**—Obtained as described above using *n*-butyl iodide, in the form of colorless crystals (IXg), m. p. 85° from petrol (60–90°).

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.4; H, 6.8. Found: C, 71.90; H, 6.63.

The methyl, ethyl, *n*-propyl, isopropyl, allyl and *n*-butyl ethers of 2-methyl-7-hydroxychromone gave with sulfuric acid a colorless solution showing bluish-violet fluorescence.

2-Methyl-7,8-dimethoxychromone (IXd).—Was prepared by the action of diazomethane on 2-methyl-7,8-dihydroxychromone, as colorless needles m. p. 102° (from petrol 60–90°). Blumberg and Kostanecki[13] gave m. p. 102°.

The Color Reaction of 2,6-Dimethylpyrone and Some Chromones with Potassium Hydroxide.—Potassium hydroxide pellets were placed in a watch glass and the aqueous solution of the γ-pyrones was poured over them and the mixture left to stand without shaking. The aqueous solutions were prepared by heating the substances with water, cooling and then using for the test immediately. The following colors which develop first in the region close to the pellets, were observed after some minutes:

2,6-Dimethylpyrone, 2,3-dimethylchromone, 2-methyl-7-methoxychromone, 2-methyl-7-ethoxychromone, 2-methyl-7-propoxychromone, khellin (IIIb) (natural and synthetic), visnagin (natural and synthetic)	red-violet
Chromone, 6-methylchromone, norkhellin (IIIa), khellinone(I), ω-acetokhellinone (IIa), 2-phenylnorkhellin(IIId), flavone, α-naphthoflavone	no color reaction
2-Ethylnorkhellin(IIIc), 2-*n*-propylnorkhellin(IIId)	weak brownish-red

Compared with khellin, the intensity of the color developed with 2-ethylnorkhellin and 2-*n*-propylnorkhellin was much less. 2-Phenylnorkhellin did not give the color test even after dissolving first in a little alcohol and then adding boiling water, to increase its solubility.

Summary

Norkhellin (IIIa), its 2-methyl, 2-ethyl, 2-propyl-*n* and 2-phenyl derivatives have been pre-

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(11) Späth and Gruber, *Ber.*, **74**, 1492 (1941).

(12) Kostanecki and Rozycki, *ibid.*, **34**, 102 (1901)

(13) Blumberg and Kostanecki, *ibid.*, **36**, 2191 (1903).

pared. A styryl derivative (IIIf) of khellin (IIIb) and khellin perchlorate are described. A reddish-violet color reaction of potassium hydroxide with khellin and certain other 2-methylchromones is discussed and the importance of the methyl group in position 2 for this reaction is stressed.

The physiological activities of norkhellin and its derivatives and of some simpler chromones and derivatives of khellinone is stated in figures beside the formulas, the activity of khellin being taken as 100. Some styryl derivatives described, show structural similarities to substances showing vitamin P activity.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, QUEEN'S UNIVERSITY]

The Chemistry of N-β-Substituted Ethyl-N'-nitroguanidines

BY A. F. McKAY[1] AND J. E. MILKS

The original purpose of this work was a study of the nitration products of N-β-hydroxyethyl-N'-nitroguanidine I. One of the products, N-β-nitroxyethyl-N'-nitroguanidine, was observed to undergo a change at elevated temperatures or on boiling with water. This observation led to a more extensive investigation of other β-substituted ethylnitroguanidines.

N-β-Hydroxyethyl-, N-β-chloroethyl-, N-β-bromoethyl-, N-β-methoxyethyl- and N-β-hydroxypropylnitroguanidine were prepared by a reaction previously described[2,3] by adding N-methyl-N-nitroso-N'-nitroguanidine to the corresponding amine in water or aqueous ethanol.

$$CH_3N(NO)\text{—}(CNH)\text{—}NHNO_2 + XCH(R)\text{—}CH_2NH_2 \longrightarrow$$
$$XCH(R)\text{—}CH_2\text{—}NH\text{—}C(NH)\text{—}NHCO_2 + N_2\uparrow$$
$$\text{I}$$

Where X = OH, Cl, Br or OCH_3 and R = H or CH_3.

N-β-Hydroxyethyl-N'-nitroguanidine I on treatment with 2.3 mole equivalents of absolute nitric acid in acetic anhydride gave N-β-nitroxyethyl-N'-nitroguanidine IV. This latter compound melted at 107° resolidified at 108–109° and then melted with decomposition at 161. The crude product gave a negative secondary nitramine test[4,5] with dimethylaniline. On refluxing compound IV with water it became more soluble and it was necessary to concentrate the solution in order to obtain a product. The recovered product was more soluble in water and less soluble in organic solvents than the original N-β-nitroxyethyl-N'-nitroguanidine IV. This behavior suggested that a salt was formed which was confirmed by treating its aqueous solution with nitron[6] when an immediate quantitative precipitate of nitron nitrate formed. Compound VI gave a strong secondary nitramine test indicating that N-β-nitroxyethyl-N'-nitroguanidine had cyclized. This assumption was verified when 2,5-dinitro-2,5-diaza-1-cyclopentanone VII was obtained in 84% yield from compound VI on nitration with excess nitric acid in acetic anhydride. Compound VI may have either structure VI(a) or VI(b). In view of its failure to nitrosate structure VI(a) is preferred.

The linear compounds N-β-hydroxyethyl-N'-nitroguanidine I and N-β-nitroxyethyl-N'-nitroguanidine are easily nitrosated. The resulting yellow crystalline nitrosamines on treatment with aniline are converted into phenylnitroguanidine III.

On the careful addition of ammonium hydroxide to 1-nitro-2-amino-2-imidazoline hydrobromide the free base (m. p. 133.5°) is obtained.

Similar reactions were obtained with N-β-hydroxypropyl-N'-nitroguanidine which was converted into β-nitroxypropylnitroguanidine (m. p. 129–129.5°) by nitration. The latter compound was cyclized to 1-nitro-2-amino-5-methyl-2-imidazoline nitrate (m. p. 115–116°). Further proof of this cyclic structure was obtained by nitration to 2,5-dinitro-3-methyl-2,5-diaza-1-cyclopentanone.[7]

When N-β-hydroxyethyl-N'-nitroguanidine is nitrated with six mole equivalents of nitric acid in acetic anhydride a new compound VIII is obtained. This compound gives a strong secondary nitramine test[4] and analytical values in good agreement with N-β-nitroxyethyl-N-nitro-N'-nitroguanidine. This is the first reported[2] instance of the formation of a linear N,N'-dinitroguanidine derivative. Since this is a β-substituted ethylnitroguanidine it would also be expected to undergo cyclization with liberation of nitric acid on heating with water. This was found to be the case. This liberation of nitric acid is followed by hydrolysis and 1,2-dinitraminoethane IX (m. p. 176°) is isolated as the end-product. Compound VIII is also obtained from N-β-nitroxyethyl-N'-nitroguanidine IV on treatment with excess nitric acid in the presence of acetic anhydride,

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(2) A. F. McKay and G. F. Wright, THIS JOURNAL, **69**, 3028 (1947).

(3) A. F. McKay, *ibid.*, **71**, 1968 (1949).

(4) A. P. N. Franchimont, *Rev. trav. chim.*, **16**, 226 (1897).

(5) On attempted purification of this compound some cyclization occurs and the product then gives a weak secondary nitramine test.

(6) E. C. Worden, "Nitrocellulose Industry," D. Van Nostrand Co., New York, N. Y., 1911, Vol. II, p. 768.

(7) A. F. McKay and D. F. Manchester, THIS JOURNAL, **71**, 1970 (1949).