solution was maintained at 5° while a mixture of sulfuric acid (5 ml.) and concd. nitric acid (5 ml.) was added dropwise. When the addition was complete, the solution was poured into water, the precipitate filtered and washed free of acid. There was obtained 1.1 g. (92%), m.p. 185–190°, of a mononitro derivative[13] which melted at 208–209° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{15}H_{18}O_3N_2$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.32; H, 6.62; N, 10.63.

By this same procedure *trans*-lactam IV (1 g.) yielded 1.0 g. (90%) of a nitration product, m.p. 230–240°, which melted at 241–243° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{15}H_{18}O_3N_2$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.58; H, 6.36; N, 10.66.

***cis*-2-Methyl-2-carboxycyclohexanacetic Acid.**—*cis*-Lactam IV a (5 g.) was heated at 200° with 2.5 *N* sodium hydroxide solution (200 ml.) in a glass-lined autoclave for 15 hours. The cold hydrolysis solution was extracted with ether to yield 2.7 g. (54%) of unhydrolyzed lactam.

The lactams also can be hydrolyzed by refluxing for 15 hours with potassium hydroxide in ethylene glycol. The salts could not be separated efficiently from the ethylene glycol which interfered with the oxidation step. Acidification of the basic solution immediately regenerated the lactams even at room temperature.

The first oxidation carried out by refluxing the salts with potassium permanganate solution for one hour yielded none of the desired acidic products. A synthetic sample of *cis*-acid VIa was 68% destroyed under these conditions. However, when this acid was stirred with basic permanganate solution at room temperature for 12 hours, 77% was recovered unchanged

The basic hydrolysis solution, after removal of unchanged lactam, was diluted to a total volume of 250 ml. and a 50-ml. aliquot, which contained 0.002 mole of the sodium salt Va, was treated with potassium permanganate (2.73 g.) in water (50 ml.) at room temperature for one hour. The solution was acidified carefully with 4 *N* hydrochloric acid (50 ml.) and the solution stirred for an additional hour before excess sodium bisulfite solution was added to stop the reaction.

The organic products were extracted with ethyl acetate (300 ml.) and the ethyl acetate solution concentrated to 50 ml. and extracted with 5% sodium bicarbonate solution (150 ml.). Acidification of the sodium bicarbonate extract followed by extraction with ethyl acetate and evaporation of this solvent yielded an oil. The pure acid was obtained by dissolving the oil in petroleum ether–acetone (5:3 parts by volume) and passing this solution through a column of silica gel. The effluent from the column yielded 95 mg. of a crystalline fraction containing some oil. Recrystallization of this fraction from ethyl acetate yielded 66 mg. (15%) of acid which melted at 163.5–164.5°.

Anal. calcd. for $C_{10}H_{16}O_5$: C, 59.98; H, 8.05. Found: C, 60.21; H, 7.97.

The melting point of a mixture of this acid with an authentic sample of the *cis* isomer prepared by the procedure of Bachmann and Kushner[9] was 164–165°; the infrared spectra of the two samples were identical. Also, the infrared spectrum of the crude oily oxidation product indicated the presence of only the *cis* isomer of acid VI.

***trans*-2-Methyl-2-carboxycyclohexaneacetic Acid.**—When the hydrolysis of *trans* lactam IV (5 g.) was carried out as for the *cis* isomer only 0.5 g. (10%) of unhydrolyzed lactam was recovered. The oxidation was carried out as previously described to yield, from an aliquot (containing 0.002 mole) of the hydrolysis solution, an oily acid which crystallized on trituration with petroleum ether. The crystalline product, 71 mg. (17%), melted at 165–175° but after the recrystallization from ethyl acetate the melting point was 174–178°.

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 59.98; H, 8.05. Found: C, 59.89; H, 7.86.

The melting point of a mixture of this sample with an authentic sample of the *trans* isomer of VI prepared by the method of Bachmann and Kushner[9] was 176–178°. The infrared spectra of the two samples were identical.

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(13) The nitro group probably entered the ring *para* to the acylamino group, to yield 2-keto-5-methyl-7-nitro-4,5-cyclohexano-6,7-benzazepine-1.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, CAIRO UNIVERSITY, AND THE LABORATORIES OF THE MEMPHIS CHEMICAL COMPANY, CAIRO]

Furo-chromones and -Coumarins. XII. Synthesis of Fraxinol from Bergapten and of Baicalein from Visnagin

BY ALEXANDER SCHÖNBERG, NASRY BADRAN AND NICOLAS A. STARKOWSKY

RECEIVED APRIL 18, 1955

The syntheses of fraxinol (IV) from bergapten (I) by a 3-step procedure and of baicalein (XIII) from visnagin (VII) by a 6-step procedure are given, the latter comprising three successive oxidation reactions, using selenium dioxide, chromic acid and hydrogen peroxide.

Bergapten (I) and visnagin (VII), which can be extracted together with the medically important xanthotoxin and khellin from the Egyptian plants *Ammi majus* (L.) and *Ammi visnaga* (L.), respectively, have now been used as starting materials in the synthesis of other products, namely, of some coumarins of the fraxinol group and some flavones of the baicalein group. In these syntheses, the key reaction was the easy oxidation of the furan ring of visnagin (VII)[1a] and bergapten (I)[1b] with chromic acid. This oxidation, which leads to derivatives of salicylaldehyde, now has been extended also to a furoflavone (X) prepared from visnagin.

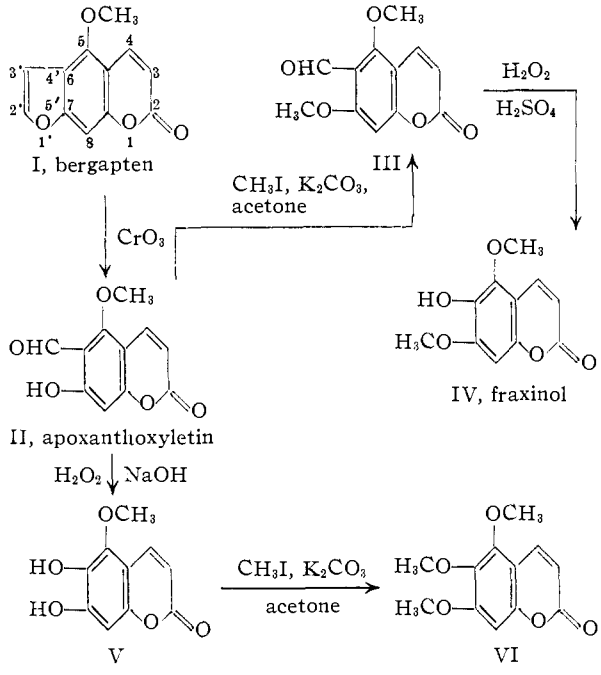
Synthesis of Fraxinol (IV).—The methylation of apoxanthoxyletin (II), obtained by the oxidation of bergapten (I),[1b] with methyl iodide and potassium carbonate in acetone, led to 5,7-dimethoxy-6-formylcoumarin (III). Replacement of the formyl group by a hydroxyl group by means of oxidation with hydrogen peroxide in sulfuric acid medium afforded 5,7-dimethoxy-6-hydroxycoumarin (fraxinol) (IV) in good yield. This substance has been synthesized previously on different lines.[2,3]

The oxidation of apoxanthoxyletin (II) itself with alkaline hydrogen peroxide led to 6,7-dihydroxy-5-methoxycoumarin (V), which has then been methylated to 5,6,7-trimethoxycoumarin (VI).

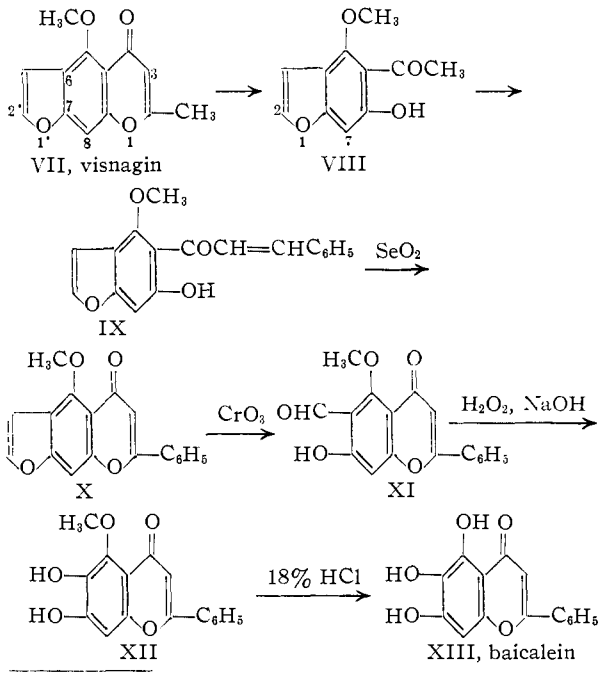
(1) (a) A. Schönberg, N. Badran and N. A. Starkowsky, THIS JOURNAL, **75**, 4992 (1953); (b) **77**, 1019 (1955).

(2) E. Späth and Z. Jerzmanowska-Sienkiewiczowa, *Ber.*, **70**, 698 (1937).

(3) V. J. Dalvi, R. B. Desai and S. Sethna, *J. Indian Chem. Soc.*, **28**, 366 (1951).



Synthesis of Baicalein (XIII).—5-Cinnamoyl-4-methoxy-6-hydroxybenzofuran (IX), the preparation of which from visnagin (VII) through the intermediate visnaginone (VIII) already has been reported,[1a] has now been converted into 5-methoxy-furo-4′,5′,6,7-flavone (X)[3a] using Mahal, Rai and Venkataraman's flavone synthesis.[4] X then has been oxidized with chromic acid to 6-formyl-7-hydroxy-5-methoxyflavone (XI). The formyl group of the latter then was replaced by a hydroxyl group under the conditions of a Dakin's reaction and the 6,7-dihydroxy-5-methoxyflavone (XII) thus obtained was demethylated to 5,6,7-trihydroxyflavone (XIII) (baicalein), which was isolated previously from natural sources and also has been synthesized on different lines.[5]



(3a) As X has the same molecular formula and a similar m.p. as a flavone of unknown constitution of m.p. 176–177°, isolated from *Pongamia pinnata* (L.) by Ramachandra Row, *Australian J. Sci. Res.*, **5A**, 754 (1952), a sample was sent to Dr. Ramachandra Row who kindly confirmed the identity of these two substances and to whom we wish to express our gratitude.

(4) H. S. Mahal, H. S. Rai and K. Venkataraman, *J. Chem. Soc.*, 866 (1935).

Experimental[6]

Methylation of Apoxanthoxyletin (II).—One-half gram of II was refluxed for 24 hr. with anhydrous potassium carbonate (5 g.), methyl iodide (5 ml.) and acetone (50 ml.). The hot mixture then was filtered and the filtrate evaporated to dryness. A crystalline residue was obtained which crystallized from alcohol as colorless needles of **5,7-dimethoxy-6-formylcoumarin (III)**, m.p. 192°, yield 0.4 g.; III was insoluble in 4% sodium hydroxide solution, did not give a ferric chloride reaction and produced a yellow color with *p*-phenylenediamine in alcoholic solution.

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.5; H, 4.3. Found: C, 62.0; H, 4.7.

5,7-Dimethoxy-6-hydroxycoumarin (Fraxinol) (IV).—To a solution of 500 mg. of III in 50 ml. of glacial acetic acid at 0° was added an ice-cold mixture of 30% hydrogen peroxide solution (7.5 ml.) and 25 ml. of 50% sulfuric acid. After standing in the refrigerator for 16 hr., the solution was diluted with water to 500 ml. and neutralized with sodium carbonate. The almost colorless needles of IV which separated out were filtered off and washed with water, m.p. 170–172° (reported m.p. for fraxinol, 171–172°[2]), yield 350 mg.; IV dissolved in dilute sodium hydroxide solution with an intense yellow color.

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59.5; H, 4.5. Found: C, 59.3; H, 4.7.

The acetyl derivative of IV, prepared by the usual acetic anhydride–sodium acetate method, crystallized from dilute alcohol as colorless needles, m.p. 140° (reported m.p. 140–141°[2]).

6,7-Dihydroxy-5-methoxycoumarin (V).—One gram of apoxanthoxyletin (II), dissolved in 13.6 ml. of 4% sodium hydroxide solution at 0° was treated with 3.5 ml. of 30% hydrogen peroxide solution. The brownish mixture thus obtained was stirred with cooling for a few minutes and then kept in the refrigerator for 3 hr. The resulting yellowish solution was acidified with acetic acid and the almost colorless precipitate of V which thus was obtained was filtered off and crystallized from water as pale yellow prisms, m.p. 234–235°, yield 0.65 g. V gave a green-black ferric chloride reaction turning red-brown on addition of one drop of dilute sodium hydroxide solution, and dissolved in 4% sodium hydroxide solution with an intense yellow color. An alcoholic solution of V gave a yellow solution or precipitate, according to concentration, with a drop of aqueous lead acetate solution and reduced ammoniacal silver nitrate solution in the cold.

Anal. Calcd. for $C_{10}H_8O_5$: C, 57.7; H, 3.8. Found: C, 57.7; H, 4.1.

The methylation of V, carried out as described for II, afforded 5,6,7-trimethoxycoumarin (VI), which crystallized from petroleum ether or 20% ethanol as colorless needles, m.p. 74° (reported m.p. 76–77°), yield 0.4 g. VI gave a negative ferric chloride reaction and did not dissolve in cold aqueous 4% sodium hydroxide solution.

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.0; H, 5.1. Found: C, 61.0; H, 5.3.

Oxidation of 5-Cinnamoyl-4-methoxy-6-hydroxybenzofuran (IX) with Selenium Dioxide.—A solution of IX (2 g.) and selenium dioxide (2 g.) in 30 ml. of *n*-butyl alcohol was refluxed for 24 hr. and then filtered and concentrated to a small volume by distillation. On cooling, yellow needles of 5-methoxy-furo-4′,5′,6,7-flavone (X) separated out, m.p.

(5) V. D. N. Sastri and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **23A**, 262 (1946).

(6) All melting points are uncorrected. The ferric chloride reactions were carried out by dissolving the substances in 95% ethanol and adding a drop of an aqueous solution of ferric chloride. Elemental microanalyses were carried out by Drs. Weiler and Strauss, Oxford.

after recrystallization from ethanol, 180°; yield 1.7 g. X gave no ferric chloride reaction and on treatment, in alcoholic solution, with magnesium and hydrochloric acid gave an orange-red color at room temperature.[7]

Anal. Calcd. for $C_{18}H_{12}O_4$: C, 74.0; H, 4.1. Found: C, 73.6; H, 4.1.

6-Formyl-7-hydroxy-5-methoxyflavone (XI).—To 1 g. of X dissolved in a warm (50°) mixture of glacial acetic acid (10 ml.) and 25% sulfuric acid (20 ml.) was added 6.7 ml. of a 30% sodium dichromate solution. The reaction, which started at once, proceeded with elevation of temperature and evolution of carbon dioxide; after a few minutes, colorless XI began to separate out. The mixture then was left to cool at room temperature and was diluted to 100 ml. with water and filtered. After recrystallization from ethanol, the colorless needles of XI had m.p. 207°, yield 0.8 g. XI dissolved in dilute sodium hydroxide solution with a yellow color and gave a red ferric chloride reaction. An orange color was obtained when an alcoholic solution of *p*-phenylenediamine was mixed with a concentrated alcoholic solution of XI. The test with magnesium and hydrochloric acid, carried out as for X, gave a yellow color.

Anal. Calcd. for $C_{17}H_{12}O_5$: C, 68.9; H, 4.0. Found: C, 68.6; H, 4.3.

Oxime of XI.—To 200 mg. of XI in 5 ml. of a 5% sodium hydroxide solution was added a solution of 200 mg. of hydroxylamine hydrochloride in 5 ml. of water. The solution was left to stand for 6 hr. It was then acidified with acetic acid and the precipitated oxime was filtered off and crystallized from a mixture of methanol and acetone as colorless needles, m.p. 266°.

Anal. Calcd. for $C_{17}H_{13}O_5N$: C, 65.6; H, 4.2; N, 4.5. Found: C, 65.7; H, 4.3; N, 4.6.

6,7-Dihydroxy-5-methoxyflavone (XII).—To a solution of XI (0.5 g.) in 5 ml. of 4% sodium hydroxide solution cooled to 0° was added 1.25 ml. of a 30% hydrogen peroxide solution and the reaction mixture was kept in the refrigerator overnight. It was then acidified and the precipitate thus obtained was collected and crystallized from dilute ethanol as yellowish needles, m.p. 223–224° (darkens), yield 300 mg.; XII was soluble in dilute sodium hydroxide solution with a yellow-orange color and had an intense green-black ferric chloride reaction turning red-brown on addition of dilute sodium bicarbonate solution. With a drop of lead acetate solution in alcohol, XII gave a yellow color or precipitate. The test with magnesium and hydrochloric acid carried out as for X gave a deep red color.

Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.6; H, 4.2. Found: C, 67.3; H, 4.3.

Demethylation of XII to 5,6,7-Trihydroxyflavone (XIII) (Baicalein).—One-half gram of XII was refluxed for 3 hr. with 100 ml. of 18% hydrochloric acid. The original substance dissolved in a few minutes and, after a half-hour, yellow XIII began to separate out. After the reaction was over, the precipitate was collected by filtration and recrystallized from dilute acetic acid, m.p. 263–264° undepressed by an authentic sample of baicalein, yield 300 mg. The yellow prisms of XIII were soluble in 4% sodium hydroxide solution with a green color and gave a greenish-brown ferric chloride reaction.

Anal. Calcd. for $C_{15}H_{10}O_5$: C, 66.7; H, 3.7. Found: C, 66.5; H, 4.0.

The trimethyl ether of XIII which was prepared by the procedure described for the methylation of II, crystallized from alcohol as colorless needles, m.p. 165–167° (reported m.p. 165–166°[5]) giving a yellow color with concentrated sulfuric acid. The trimethyl ether of XIII also was obtained by the methylation of XII under similar conditions (m.p. and mixed m.p.).

Physiological Tests.—Although bergapten (I) is known to be photodynamically active, all the coumarins II–VI synthesized from this substance were found to be inactive when tested under the conditions described by Musajo, Rodighiero and Caporale.[8]

Acknowledgment.—We are indebted to Professor T. R. Seshadri for carrying out the mixed m.p. determination of XIII with an authentic sample of baicalein.

(7) For references to the reactions of flavones with magnesium and hydrochloric acid, see T. A. Geissman and R. O. Clinton, THIS JOURNAL, **68**, 700 (1946).

(8) L. Musajo, G. Rodighiero and G. Caporale, *Bull. soc. chim. biol.*, **36**, 1213 (1954).

CAIRO, EGYPT

[CONTRIBUTION FROM THE IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Isomerization of Saturated Hydrocarbons. XIV.[1] Isomerization of Methyl-C^{14}-cyclohexane in the Presence of Aluminum Bromide

BY HERMAN PINES AND R. W. MYERHOLTZ, JR.[2]

RECEIVED FEBRUARY 3, 1955

Although no isomerization takes place when methylcyclohexane is treated with aluminum halide in a batch reaction, a new species of methylcyclohexane was formed when methyl-C^{14}-cyclohexane is treated with aluminum bromide, hydrogen bromide and small amounts of *sec*-butyl bromide. About 31% of the radioactive carbon appears in the cyclohexyl ring. In the absence of *sec*-butyl bromide, only 2% of the radioactive carbon is found in the ring. A chain mechanism for the isomerization is discussed. The synthesis of methyl-C^{14}-cyclohexane and methods of analysis are described.

It has been reported previously that little if any apparent reaction occurred when methylcyclohexane was treated with aluminum bromide or aluminum chloride, or even aluminum chloride and hydrogen chloride at elevated temperatures.[3]

The apparent lack of isomerization of methylcyclohexane might be due to the unfavorable equilibrium constants. The calculated values of equilibrium constants for isomerization of methylcyclohexane to alkylcyclopentanes, as calculated from the free energy data,[4] are given in Table I.

Definite evidence for the isomerization of methylcyclohexane to dimethylcyclopentanes was accomplished recently[5] by refluxing methylcyclohexane with aluminum chloride in the presence of wa-

(1) For paper XIII of this series see H. Pines, R. W. Myerholtz, Jr., and H. M. Neumann, THIS JOURNAL, **77**, 3399 (1955).

(2) Universal Oil Products Co. Predoctoral Fellow, 1951–1954.

(3) (a) N. D. Zelinsky and M. B. Turova-Pollak, *Ber.*, **62B**, 1658 (1929); (b) R. Stratford, *Ann. Combustibiles Liquides*, **4**, 83, 317 (1929); (c) C. D. Nenitzescu, E. Cioranescu and I. P. Cantuniari, *Ber.*, **70B**, 277 (1937); (d) M. B. Turova-Pollak and Z. Makaeva, *J. Gen. Chem. (U.S.S.R.)*, **9**, 1279 (1939); (e) G. C. A. Schuit, H. Hoog and J. Verheus, *Rec. trav. chim.*, **59**, 793 (1940); (f) N. D. Zelinsky, M. B. Turova-Pollak, N. P. Tsvetkova and E. G. Treschova, *Zhur. Obshchei Khim. (J. Gen. Chem.)*, **21**, 2156 (1951).

(4) F. D. Rossini, K. S. Pitzer, R. L. Arnett, R. M. Braun and G. C. Pimentel, "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds," Carnegie Press, Pittsburgh, Pa., 1953.

(5) R. Van Volkenburgh, K. W. Greenlee and C. E. Boord, Abstracts of Papers, 118th Meeting of the American Chemical Society, Chicago, Illinois, September 3–9, 1950, p. 36-N.