hydrolysis product was extracted with ethyl acetate which was washed with base and sodium chloride solution. The ethyl acetate solution was dried. Upon concentration of the solution 3.95 g. of 3α,11β,17α,21-tetrahydroxyallopregnane-20-one (Va), m.p. 238–242°, crystallized. Recrystallization from ethanol-chloroform afforded 2.47 g. of Va, m.p. 242–246° dec.; $[\alpha]_D^{27}$ + 72.2° (ethanol); $\nu_{max}^{KBr}$ 3600, 3410, and 1713 cm.$^{-1}$; reported,[13] m.p. 276°, and[8] 244–245°; $[\alpha]_D^{21}$ + 59.7° (methanol). The mother liquor (3.15 g.) contained unhydrolyzed IVa. Further hydrolysis with 50% aqueous acetic acid yielded an additional 1.01 g. of Va, m.p. 234–240°.

Acetylation of Va with acetic anhydride and pyridine afforded 3α,21-diacetoxy-11β,17α-dihydroxyallopregnane-20-one (Vb), m.p. 197–200°; $[\alpha]_D^{26}$ +62.4°; $\nu_{max}^{CHCl_3}$ 3640, 1742(Sh), and 1726 cm.$^{-1}$; reported[13] m.p. 204–205°; $[\alpha]_D$ + 73.8° (dioxane), and[8] 188–190°; $[\alpha]_D^{19}$ + 65.3° (methanol). The infrared spectrum in chloroform was identical with that of an authentic sample[15] in the regions 4000–2750 cm.$^{-1}$, 1800–1600 cm.$^{-1}$ and 1150–800 cm.$^{-1}$.

*17,20;20,21-Bismethylenedioxyallopregnane-3β,11β-diol 11-methoxymethyl ether* (VI). To a solution of 1.0 g. of 11β-hydroxy-17,20;20,21-bismethylenedioxy-Δ$^4$-pregnene-3-one (II) in 30 ml. of tetrahydrofuran, 30 ml. of ethanol, and 240 ml. of liquid ammonia was added 2.2 g. of lithium ribbon in small portions until the blue color persisted. The reaction mixture was stirred for an additional 25 min. and worked up as before. Recrystallizations of the reduction product from ethyl acetate gave 139 mg. of 17,20;20,21-bismethylenedioxyallopregnane-3β,11β-diol 11-methoxymethyl ether (VI), m.p. 140–142°; $[\alpha]_D^{30}$ −58.1°; $\nu_{max}^{CS_2}$ 3610 and 2755 (BMD) cm.$^{-1}$

*Anal.* Calcd. for $C_{25}H_{40}O_7$: C, 66.34; H, 8.91. Found: C, 66.32; H, 8.85.

A solution of 116 mg. of VI in 50 ml. of 50% aqueous acetic acid was heated on a steam bath for 35 min. The hydrolysis product was worked up in the usual manner and chromatographed on 2 g. of Florisil. Elution with 1% ethanol in chloroform yielded 65 mg. of Reichstein's Substance V. Recrystallized from ethyl acetate, it melted at 211–215°; the infrared spectrum of the diacetate in chloroform was identical with that of an authentic sample[15] in the region 4000–2750 cm.$^{-1}$, 1800–1600 cm.$^{-1}$, 1500–1280 cm.$^{-1}$ and 1150–800 cm.$^{-1}$

*11β,17α,21-Trihydroxyallopregnane-3,20-dione* (VII). A solution of 15 g. of hydrocortisone in 600 ml. of chloroform was shaken for 48 hr. with a solution of 150 ml. of concd. hydrochloric acid and 150 ml. of formalin. The crude reaction product containing a mixture of bismethylenedioxyhydrocortisone (I) and its 11-methoxymethyl ether (II) was dissolved in 150 ml. of ether and 150 ml. of dioxane and the solution was added to 1500 ml. of liquid ammonia. To this solution was added 1.5 g. of lithium ribbon in small portions until the blue color persisted. Seventy five grams of ammonium chloride was added to the reduction mixture and the ammonia allowed to evaporate. Ethyl acetate was added and the organic layer washed with sodium chloride solution. The ethyl acetate solution was dried and the solvent evaporated.

The crude reduction product was dissolved in 400 ml. of 60% formic acid and heated on a steam bath for 25 min. Ethyl acetate was added to the hydrolysis mixture and the extract was washed with base and sodium chloride solution. The hydrolysis product was chromatographed on 500 g. of silica gel containing 200 ml. of ethanol. Elution with 7% ethanol in methylene chloride yielded 2.40 g. of 11β,17α,21-trihydroxyallopregnane-3,20-dione (VII), m.p. 212–222° (dec.). Recrystallization from acetone yielded 1.85 g. of VII, m.p. 234–240° dec.; $\nu_{max}^{KBr}$ 3640, 2400, and 1705 (broad) cm.$^{-1}$; m.p. 230–240° dec.[20] Acetylation with pyridine and acetic anhydride afforded 21-acetoxy-11β,17α-dihydroxyallopregnane-3,20-dione, m.p. 212–215°, reported[21] m.p. 210–212° and[20] 222–226°, the acetate of which depressed the melting point of the unacetylated starting material.

*Acknowledgment.* The authors gratefully acknowledge the support and interest of Dr. T. F. Gallagher throughout this investigation. We wish to express our appreciation to Mrs. Beatrice S. Gallagher for the determination and interpretation of the infrared spectra and to Mr. Jose Bravo for technical assistance.

NEW YORK, N. Y.

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

# Experiments with Furochromones and -coumarins. Synthesis of α-Pyronochromone Derivatives from Visnagin and α-Pyronocoumarin from Bergapten

AHMED MUSTAFA, NICOLAS A. STARKOVSKY, AND (MISS) EKRAM ZAKI

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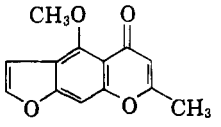
The synthesis of α-pyronochromone derivatives (VIIa-c) from 6-formyl-7-hydroxy-5-methoxy-2-methylchromone (IIIa), readily obtained *via* oxidation of visnagin (I) with chromic acid, and α-pyronocoumarin (X) from 6-formyl-7-hydroxy-5-methoxycoumarin (apoxanthoxyletin) (IV), an oxidation product of bergapten (II) with chromic acid, are described.

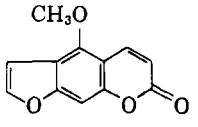
Oxidation of VIIc with alkaline hydrogen peroxide leads to the formation of 7-hydroxy-5-methoxycoumarin-3,6-dicarboxylic acid (IX). Treatment of VIIc with sodium hydroxide solution effects opening of the γ-pyrone ring to give 6-aceto-7-hydroxy-5-methoxycoumarin (VII).

Visnagin[1] (I) and Bergapten[2] (II), which can be extracted together with the medically important antispasmodic khellin, and the photodynamically active xanthotoxin from the Egyptian Ammi visnaga (L.) and Ammi majus (L.), respectively, now have been used as starting materials in the

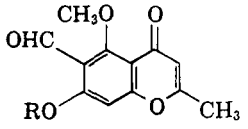
synthesis of other products which may be useful as medicinals or in further synthesis. In these syntheses, use of the 6-formyl-7-hydroxy-5-methoxy-2-methylchromone, the oxidation product of the natural furochromone[3a] (I) and its derivatives (III), and 6-formyl-7-hydroxy-5-methoxycoumarin (apoxanthoxyletin) (IV), the oxidation product of the furocoumarin[3b] (II), allowed the replacement of the furan ring in I and II by an $\alpha$-pyrone ring.



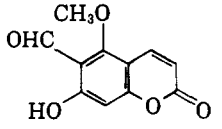
I



II

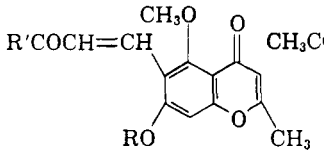


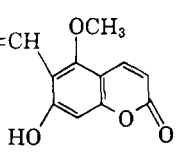
IIIa. R = H
b. R = $OCH_3$



IV

Schönberg, *et al.*,[3a,4] have described the ready formation of chalcones *via* the condensation of visnaginone and khellinone with benzaldehyde. We now have found that the styryl derivatives Va-c and VI are similarly obtained by the condensation of III and IV with ketones in alkaline medium.[5,6]





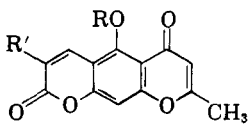
Va. R = H; R′ = $CH_3$
b. R = H; R′ = $C_6H_5$
c. R = H; R′ = $p$-$CH_3C_6H_4$
d. R = $OCH_3$; R′ = $CH_3$

VI

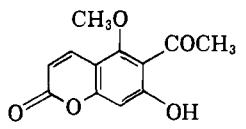
The styryl derivatives (Va-c) are soluble in alkali solution and react readily with the common reagents for carbonyl and hydroxyl groups, thus simulating *o*-hydroxychalcones, *e.g.*, *o*-hydroxybenzylideneacetone[7] and *o*-hydroxybenzylideneacetophenone,[8] in their properties. Attempts to effect the condensation of IIIa with acetone in an acid medium did not lead to the separation of the pyrylium salt.[9]

Whereas, Vd now has been readily obtained by the condensation of IIIb with acetone in the presence of alkali, we have been unable to effect its formation by treatment of Va with methyl iodide and potassium carbonate. Vd is relatively highly soluble in water.

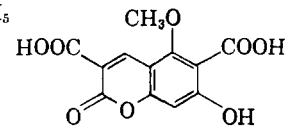
*Synthesis of* (a) *α-Pyronochromone derivatives* (VIIa-c). Condensation of IIIa with ethyl malonate in the presence of piperidine gave the ester derivative (VIIb), which upon hydrolysis yielded the corresponding acid (VIIc). The latter underwent decarboxylation when heated with copper bronze in quinoline to give VIIa. VIIa, a hybrid between I and II, now has also been obtained conveniently *via* treatment of IIIa with acetic anhydride and fused sodium acetate. Alkali treatment of VIIa led to the formation of VIII[10]; and its oxidation with alkaline hydrogen peroxide gave IX.[3a] VIIa and VIIc were readily demethylated[11] by the action of hydrochloric acid to give VIIe and VIId respectively.



VIIa. R = $CH_3$; R′ = H
b. R = $CH_3$; R′ = $COOC_2H_5$
c. R = $CH_3$; R′ = COOH
d. R = H; R′ = COOH
e. R = H; R′ = H

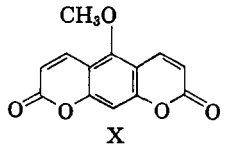


VIII



IX

(b) *α-Pyronocoumarin* (X). Treatment of apoxanthoxyletin (IV) with acetic anhydride and fused sodium acetate led to the formation of X.



X

Both VIIa and X bear a close relationship to the photodynamically active furocoumarin II. However, they both failed to produce the slightest

(1) *Cf.* C. P. Huttrer and E. Dale, *Chem. Reviews*, **48**, 543 (1951) and H. Schmid, *Fortschr. Chem. org. Naturstoffe*, **11**, 124 (1954).

(2) H. Kuske, *Arch. Dermatol. u Syphilis*, **178**, 112 (1938); L. Masajo, G. Rodighiero, and J. Caporale, *Bull. Soc. chim. biol.*, **36**, 1213 (1954).

(3)(a) A. Schönberg, N. Badran, and N. A. Starkovsky, *J. Am. Chem. Soc.*, **75**, 4992 (1953); Ger. Patent **952,900**, Oct. 22, 1954. (b) *J. Am. Chem. Soc.*, **77**, 1019 (1955); Brit. Patent **760,701**, Oct. 31, 1956.

(4) A. Schönberg and A. Sina, *J. Am. Chem. Soc.*, **72**, 1611 (1950); **72**, 3396 (1950).

(5) Condensation of *o*-hydroxyaromatic aldehydes with ketones may lead either to the formation of the corresponding styryl derivatives, or to the corresponding $\alpha$-chromenol derivatives; the formation of the former is favored by alkalies, and the latter by acids [*cf. Heterocyclic Compounds*, R. C. Elderfield (Ed.), Vol. 2, John Wiley and Sons, Inc., New York, pp. 286–287 (1950)].

(6) We were unable to detect the formation of chromene derivatives (*cf.* the formation of the chromene derivative, and not the corresponding styryl derivative, when 2-naphthol-1-aldehyde was condensed with acetone in the presence of alkali [R. Dickinson and I. M. Heilbron, *J. Chem. Soc.*, 14 (1927)].

(7) F. Tiemann and A. Kees, *Ber.*, **18**, 1955 (1885).

(8) A. McGookin and D. J. Sinclair, *J. Chem. Soc.*, 1170 (1928).

(9) H. Decker and Th. von Fellenberg, *Ber.*, **40**, 3815 (1907).

(10) E. Späth and W. Gruber, *Ber.*, **71**, 106 (1938).

(11) *Cf.* A. Mustafa, N. A. Starkovsky, and E. Zaki, *J. Org. Chem.*, **25**, 794 (1960).

skin irritation under the conditions which provoked erythema with xanthotonix or II.[2]

## EXPERIMENTAL[12]

*6-(β-Acetoethenyl)-7-hydroxy-5-methoxy-2-methylchromone* (Va). A solution of 2 g. of IIIa in 20 ml. of 4% aqueous sodium hydroxide solution was treated with 20 ml. of acetone. The reaction mixture was kept aside at room temperature (25°) for 1 hr.; it was then acidified with dilute hydrochloric acid, and the precipitated Va (1.92 g.) was washed thoroughly with water. It was crystallized from acetone or water in colorless crystals, m.p. 238–240° dec.

*Anal.* Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.14; —$OCH_3$, 11.3. Found: C, 65.40; H, 5.25; —$OCH_3$, 11.4.

Va is soluble in ethanol and chloroform, dissolves in aqueous dilute sodium hydroxide solution with a deep yellow color, and in concd. sulfuric acid with an orange color. It does not develop a color when treated with ferric chloride.

*Oxidation of* Va. To a stirred solution of 2 g. of Va in 60 ml. of glacial acetic acid was added slowly during 10 min. a solution of 2 g. of ammonium dichromate in a mixture of 30 ml. of acetic acid and 10 ml. of sulfuric acid (25%). The reaction mixture was poured into 250 ml. of water, extracted with chloroform, and the solvent was evaporated to dryness. The residue was crystallized from ethanol to give 400 mg. of IIIa, m.p. 189° (m.p. and mixed m.p.[3a]).

*Acetyl derivative of* Va. One gram of Va was refluxed for 2 hr. with a mixture of 10 ml. of acetic anhydride and 1 g. of fused sodium acetate. The reaction mixture was worked up in the conventional manner. *7-Acetoxy-6-(β-acetoethenyl)-5-methoxy-2-methylchromone* was obtained as silky needles from ethanol (*ca.* 1.0 g.) m.p. 171°. It is difficultly soluble in water, but is easily soluble in alcohol, and gives no color reaction with ferric chloride.

*Anal.* Calcd. for $C_{17}H_{16}O_6$: C, 64.56; H, 5.06. Found: C, 64.56; H, 5.13.

*Benzoyl derivative of* Va was obtained after the Schotten-Baumann procedure as colorless crystals from ethanol, m.p. 189–192°.

*Anal.* Calcd. for $C_{22}H_{18}O_6$: C, 69.84; H, 4.76. Found: C, 69.54; H, 4.96.

*Condensation product*[13] *of* Va *with:* (a) *hydroxylamine.* A solution of 0.5 g. of Va in a hot (80°) solution of 0.5 g. of hydroxylamine hydrochloride in dry pyridine was allowed to stand at room temperature for 6 hr. The reaction mixture was poured into 100 ml. of water and the precipitated solid was crystallized from acetone in colorless crystals (*ca.* 0.4 g.), m.p. 236–237° dec., soluble in aqueous alkali solution.

*Anal.* Calcd. for $C_{15}H_{15}NO_5$: C, 62.35; H, 5.19; N, 4.85. Found: C, 62.57; H, 5.19; N, 5.07.

(b) *Semicarbazide.* A solution of 0.5 g. of Va in 20 ml. of warm ethanol was treated with a solution of 0.25 g. of semicarbazide hydrochloride in 2 ml. of water, and the reaction mixture was kept at room temperature overnight. The yellow crystals (*ca.* 0.5 g.) so obtained, were collected, washed with hot acetone, and crystallized from glacial acetic acid, m.p. 234° (dark melt). The substance is soluble in aqueous alkali solution.

*Anal.* Calcd. for $C_{16}H_{17}N_3O_5$: C, 58.00; H, 5.13; N, 12.68. Found: C, 58.38; H, 5.10; N, 12.45.

(c) *2,4-Dinitrophenylhydrazine.* Treatment of a solution of 100 mg. of Va in 10 ml. of ethanol with an equivalent amount of 2,4-dinitrophenylhydrazine in 5% alcoholic sulfuric acid gave an almost quantitative yield of a scarlet precipitate, which upon filtration and washing with hot alcohol, melted at 284–286°.

*Anal.* Calcd. for $C_{21}H_{18}N_4O_8$: N, 9.55. Found: N, 9.42.

*6-(β-Benzoylethenyl)-7-hydroxy-5-methoxy-2-methylchromone* (Vb). Similarly obtained upon treatment of a solution of 1 g. of IIIa in aqueous sodium hydroxide solution (4%) with a solution of 2 ml. of acetophenone in 7 ml. of ethanol at room temperature for 6 hr., as described in the case of Va. It crystallized from ethanol in colorless needles (*ca.* 1.22 g.), m.p. 244°.

*Anal.* Calcd. for $C_{20}H_{16}O_5$: C, 71.43; H, 4.76. Found: C, 71.86; H, 4.81.

Vb is soluble in ethanol, dissolves in aqueous sodium hydroxide solution with a yellow color, and gives a negative ferric chloride reaction.

*Acetyl derivative of* Vb. As described for Va, 7-acetoxy-6-(β-benzoylethenyl)-5-methoxy-2-methylchromone was obtained as colorless needles from ethanol, m.p. 156–157°.

*Anal.* Calcd. for $C_{22}H_{18}O_6$: C, 69.84; H, 4.76. Found: C, 69.50; H, 4.81.

*6-(β-p-Toluoylethenyl)-7-hydroxy-5-methoxy-2-methylchromone* (Vc) was obtained from IIIa and *p*-methylacetophenone after the procedure described for Vb. Vc was crystallized from ethanol as yellow plates, m.p. 247–249°. It was soluble in aqueous sodium hydroxide solution with a yellow color.

*Anal.* Calcd. for $C_{21}H_{18}O_5$: C, 72.00; H, 5.15. Found: C, 72.43; H, 5.56.

*6-(β-Acetoethenyl)-5,7-dimethoxy-2-methylchromone* (Vd). To a warm solution (40°) of 1 g. of 5,7-dimethoxy-6-formyl-2-methylchromone[3a] in 15 ml. of acetone was added 5 ml. of aqueous sodium hydroxide solution (4%). The reaction mixture was shaken for 1.5 hr., diluted with 400 ml. of water, acidified with acetic acid, and distilled to 200 ml. The collected colorless crystals of Vd, obtained upon cooling, were crystallized from water, m.p. 146–148°; yield, *ca.* 0.5 g.

*Anal.* Calcd. for $C_{16}H_{16}O_5 \cdot H_2O$: C, 62.74; H, 5.88. Found: C, 62.55; H, 5.68.

It is soluble in hot water, easily soluble in acetone, and does not dissolve in cold aqueous sodium hydroxide solution. It gives a canary yellow color slowly changing to red with sodium hydroxide pellets[4] moistened with ethanol.

*6-(β-Acetoethenyl)-7-hydroxy-5-methoxycoumarin* (VI). One gram of 6-formyl-7-hydroxy-5-methoxycoumarin (apoxanthoxyletin) (IV)[3b] was condensed with acetone, as described for Vd, to give 0.6 g. of buff crystals of VI from dilute ethanol, m.p. 198–200°.

*Anal.* Calcd. for $C_{14}H_{12}O_5$: C, 64.62; H, 4.62. Found: C, 64.39; H, 4.27.

It is soluble in hot water and in alcoholic sodium hydroxide solution with a yellow color and gives a pale violet color with ferric chloride.

*3'-Carbethoxy-5-methoxy-2-methyl-α-pyrone-5',6',6,7-chromone* (VIIb). A mixture of 2.34 g. of IIIa (0.01 mole), 1.75 ml. of ethylmalonate (0.011 mole), 25 ml. of absolute ethanol, 0.1 ml. of piperidine and 1 drop of acetic acid was refluxed for 8 hr. (water bath). Ethanol (200 ml.) was then added, the mixture boiled and filtered while hot. The precipitated curdy VIIb, upon cooling, was collected, and crystallized from ethanol in colorless crystals (*ca.* 2.0 g.), m.p. 212°.

*Anal.* Calcd. for $C_{17}H_{14}O_7$: C, 61.82; H, 4.25. Found: C, 61.52; H, 4.23.

It is insoluble in cold dilute aqueous sodium hydroxide solution, but is soluble on heating with a yellow solution. Its ferric chloride reaction is negative.

*5-Methoxy-2-methyl-α-pyrono-5',6',6,7-chromone-3'-carboxylic acid* (VIIc). VIIb (4 g.) was refluxed with a mixture

(12) All melting points are uncorrected; the ferric chloride reactions were carried out by adding a drop of aqueous ferric chloride to an alcoholic solution of the substance. Elementary analyses were carried out by Drs. Weiler and Strauss, Oxford.

(13) Exclusion of the formation of five-membered heterocyclic ring is not beyond complete doubt; this is under further investigation [*comp.* K. v. Auwers and J. Hügel, *J. prakt. Chem.*, **143**, 157 (1935); P. L. Viguier, *Ann. Chim.*, **28**, 433 (1913); A. Schönberg and M. M. Sidki, *J. Am. Chem. Soc.*, **75**, 5128 (1953)].

of 60 ml. of acetic acid, 60 ml. of water, and 6 ml. of sulfuric acid for 1.5 hr. The reaction mixture solution was then diluted with an equal volume of ethanol, boiled, filtered while hot, and cooled. The separated crystals were recrystallized from ethanol in colorless crystals (3.1 g.), m.p. 235–236°.

*Anal.* Calcd. for $C_{15}H_{10}O_7$: C, 59.60; H, 3.31. Found: C, 59.35; H, 3.45.

VIIc is soluble in sodium bicarbonate solution with effervescence, and in aqueous sodium hydroxide (2%) with a yellow color. Its ferric chloride reaction is negative.

*Demethylation of* VIIc. A solution of 0.5 g. of VIIc in 45 ml. of hydrochloric acid was treated, while being heated, with 15 ml. of water, and was then refluxed for 1.5 hr. The reaction mixture was diluted with water to 250 ml., filtered, and kept aside in the ice chest overnight. The yellow crystals, so obtained, were recrystallized from glacial acetic acid (*ca.* 350 mg.) m.p. 280° dec.

*Anal.* Calcd. for $C_{14}H_8O_7$: C, 58.33; H, 2.78. Found: C, 58.13; H, 2.88.

*5-Hydroxy-2-methyl-α-pyrono-5′,6′,6,7-chromone-3′-carboxylic acid* (VIId) gives a violet-brown ferric chloride reaction. It is insoluble in water, very sparingly soluble in ethanol, and soluble in sodium bicarbonate solution with yellow color.

*Oxidation of* VIIc *with alkaline hydrogen peroxide.* To a cooled mixture of 2 g. of VIIc in 50 ml. of aqueous sodium hydroxide (5%) at 0° was added 6 ml. of hydrogen peroxide solution (30%). After half an hour, the reaction mixture was acidified to give yellow crystals of 7-hydroxy-5-methoxycoumarin-3,6-dicarboxylic acid (IX), which upon recrystallization from dilute ethanol, melted at 218–220° dec.; yield, *ca.* 0.8 g.

*Anal.* Calcd. for $C_{12}H_8O_8$: C, 51.43; H, 2.85. Found: C, 51.63; H, 2.86.

IX is soluble in ethanol with a yellow-blue fluorescence, and in aqueous sodium bicarbonate solution with a strong blue fluorescence. It gives a deep wine-red color with ferric chloride.

*5-Methoxy-2-methyl-5′,6′,6,7-α-pyronochromone* (VIIa). (a) *From* VIIc. A mixture of 0.8 g. of VIIc, 1 g. of copper bronze, and 4 ml. of quinoline was gently boiled (oil bath) for 10 min. The cooled reaction mixture was acidified with dilute hydrochloric acid, extracted several times with chloroform, and evaporated. The residue was crystallized from ethanol or water to give 40 mg. of VIIa, m.p. 225–228° (dark melt).

*Anal.* Calcd. for $C_{14}H_{10}O_6$: C, 65.01; H, 3.88. Found: C, 65.09; H, 3.92.

VIIa is insoluble in aqueous sodium hydroxide (4%), but is soluble in alcoholic sodium hydroxide solution with a yellow color. Its ferric chloride reaction is negative. With potassium hydroxide pellets moistened with ethanol, it gives a yellow color.

(b) *From* IIIa. Five grams of IIIa, 10 g. of freshly fused sodium acetate, and 75 ml. of acetic anhydride were refluxed for 5 hr. The reaction mixture was poured into iced water and the brown precipitate was washed with a cold aqueous sodium hydroxide solution (1%). It was then crystallized from dilute ethanol to give VIIa, m.p. 228° (dark melt) (identified by melting point and mixed melting point); yield, *ca.* 2 g.

*Demethylation of* VIIa. Refluxing a mixture of 200 mg. of VIIa with 40 ml. of dilute hydrochloric acid (50%) for 1 hr., followed by cooling gave 150 mg. of yellow crystals of 5-hydroxy-2-methyl-5′,6′,6,7-α-pyronochromone (VIIe) (from ethanol), m.p. 228–230°. It gives a violet-red color with ferric chloride and a yellow complex soluble in chloroform, with uranyl acetate.[11]

*Anal.* Calcd. for $C_{13}H_8O_6$: C, 63.93; H, 3.28. Found: C, 63.86; H, 3.35.

*Action of alkali on* VIIa. *6-Aceto-7-hydroxy-5-methoxycoumarin* (VIII) (70 mg.) was obtained as colorless crystals, m.p. 223–225 dec., upon refluxing 200 mg. of VIIa with 40 ml. of aqueous sodium hydroxide (10%) for 1 hr., followed by acidification. It gives a green color with ferric chloride.

*Anal.* Calcd. for $C_{12}H_{10}O_5,H_2O$: C, 57.14; H, 4.76. Found: C, 57.16; H, 4.82.

*5-Methoxy-α-pyrono-5′,6′,6,7-coumarin* (X). A mixture of 1.5 g. of IV,[3b] 20 ml. of acetic anhydride, and 3 g. of fused sodium acetate was refluxed for 5 hr. It was then cooled, poured into iced water, and the separated solid (0.8 g.) was crystallized from ethanol in colorless crystals m.p. 270–272°.

*Anal.* Calcd. for $C_{13}H_8O_6$: C, 63.93; H, 3.27. Found: C, 63.96; H, 3.20.

X is almost insoluble in water, sparingly soluble in ethanol, and gives a yellow solution with alcoholic sodium hydroxide solution.

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[CONTRIBUTION FROM THE DIVISION OF NUCLEOPROTEIN CHEMISTRY, SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH; SLOAN-KETTERING DIVISION OF CORNELL UNIVERSITY MEDICAL COLLEGE]

# Nucleosides. VIII. Synthesis of 5-Nitrocytidine and Related Nucleosides[1]

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The mercuri reaction for pyrimidine nucleoside synthesis was extended to 5-nitrocytosine. Condensation of di(5-nitrocytosine)mercury with poly-*O*-acylglycosyl halides yielded nucleosides in which the sugar moiety was linked to the pyrimidine at position 1. Reduction of the 5-nitro group of these nucleosides (*e.g.*, 5-nitrocytidine) afforded 5-amino analogs which were ring-closed to 1-β-D-glycosyl-2-oxypurines or their corresponding 8-aza analogs. Modifications are given for the synthesis of 1-methyl- and 9-methyl-2-oxypurine and some of the intermediates used in their preparation. 2-Oxy-8-azapurine was synthesized by treatment of 5-aminocytosine with nitrous acid.

Ultraviolet absorption spectra and spectrally-determined $pK_a$ values for key compounds in the above syntheses are given.

In a previous report[2] the synthesis of 5-nitrouridine was accomplished by direct nitration of suitably-acylated uridine followed by removal of the protecting groups. Attempts to apply these procedures to the synthesis of 5-nitrocytidine have thus far been unsuccessful.[3] It was of interest to prepare the 5-nitro analog of cytidine for testing as a potential chemotherapeutic agent, for examination as