pentol 20,21-diacetate (XIVa) was accomplished in the usual manner with 1.2 g. of *p*-toluenesulfonyl chloride in 14 ml. of pyridine. Recrystallization from acetone afforded 1.20 g. of the 3β-tosylate XIVc, m.p. 136–154° dec.; $[\alpha]_D^{26}$ −30.7°; $\nu_{max}^{CHCl_3}$ 3640 (sh), 3605 and 1740 (broad) cm.$^{-1}$

Anal. Calcd. for $C_{32}H_{46}O_8$: C, 63.34; H, 7.64. Found: C, 63.23; H, 7.66.

The 3β-tosylate (1.2 g., XIVc) was solvolyzed as above for the 11-keto analog (XIIb) with 2.4 g. of freshly fused potassium acetate in 38 ml. of glacial acetic acid for 3 hr. The epimerized product (903 mg.) was saponified with methanolic potassium hydroxide to give 690 mg. of oily material. The saponification product was chromatographed on 100 g. of silica gel containing 40 ml. of ethanol. Elution with 9% ethanol in chloroform afforded 152 mg. of allocortol. Recrystallization from methanol–ethyl acetate gave *allocortol* (XVI); m.p. 226–228°; $[\alpha]_D^{30}$ +19.5 (ethanol); ν_{max}^{KBr} 3440 (broad).

Anal. Calcd. for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.61; H, 10.01.

The triacetate was prepared in the usual manner but could not be crystallized. Its infrared spectrum was consistent with the structure of the compound. Oxidation of allocortol (5 mg.) with sodium bismuthate gave 3α,11β-dihydroxyandrostane-17-one, m.p. 180–190°. The infrared spectrum in carbon disulfide and mobility on paper in the system *isooctane:toluene:methanol:water* (1:3:3:1) were identical to that of an authentic sample.

A less polar material (300 mg.) was eluted from the partition column with 5% ethanol in chloroform. Recrystallization from methanol–ethyl acetate gave a product which had an analysis corresponding to *Δ⁵-allopregnene-11β,17α,-20α,21-tetrol* (XVII), m.p. 217–219°.

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.97; H, 9.78. Found: C, 71.67; H, 9.88.

Reichstein's Substance U diacetate. 3,3-Ethylenedioxy-17α-hydroxy-21-acetoxy-Δ⁵-pregnene-11,20-dione (VII, 460 mg.) in 100 ml. of ethyl acetate and 100 ml. of ethyl alcohol was hydrogenated in the presence of Adam's catalyst until the absorption of hydrogen ceased. The reduction product XVIII was hydrolyzed with 50% acetic acid at 90° for 1 hr. and then acetylated with pyridine and acetic anhydride to give 428 mg. of crude Reichstein's Substance U diacetate, $\lambda_{max}^{C_2H_5OH}$ 237 mμ, $\epsilon_{1cm}^{1\%}$ 342. Chromatography on silica gel and elution with 50% ethyl acetate in benzene gave 50 mg. of the 20α-acetoxy epimer as judged by its infrared spectrum and mobility on paper. Further elution with the same solvent gave 330 mg. of Reichstein's Substance U diacetate. Recrystallizations from acetone gave 160 mg., m.p. 234–237°. Its infrared spectrum was identical with that of an authentic sample.[9]

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(9) The authors thank Professor T. Reichstein for this compound.

[CONTRIBUTION FROM THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

Synthesis of Reichstein's Substance C and Related Compounds[1]

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The synthesis of Reichstein's Substance C, 3α,11β,17α,21-tetrahydroxyallopregnane-20-one, its 3β-hydroxy epimer and 11β,17α,21-trihydroxyallopregnane-3,20-dione from bismethylenedioxyhydrocortisone are described. A side product formed in the preparation of bismethylenedioxyhydrocortisone from hydrocortisone and formalin has been characterized as the 11-methoxymethyl ether of bismethylenedioxyhydrocortisone.

3α,11β,17α,21 - Tetrahydroxyallopregnane - 20-one, Reichstein's Substance C (Va), was first isolated from beef adrenal glands[2–4] and has recently been isolated from human urine.[5,6] This metabolite was found to represent 7–13% of the radioactivity present in the neutral steroid extract of the urine following administration of hydrocortisone-4-C^{14} to normal men.[7] The synthesis of Reichstein's Substance C was desirable in order to obtain sufficient amounts for carrier purposes in radioactive tracer studies and for investigation of its biological properties.

Reichstein's Substance C, commonly called "allotetrahydro F," was recently synthesized by hydrogenation of hydrocortisone with rhodium on alumina as the catalyst.[8] Although obtained in fair yield it was one of four isomeric reduction products with attendant separation problem. A novel method of protecting the dihydroxyacteone side-chain of hydrocortisone and similar steroids by the formation of bismethylenedioxy (BMD) derivatives was recently reported by Beyler and co-workers.[9] This blocking group made the reduction of the α,β-unsaturated ketone in ring A to the 3β-hydroxyallopregnane derivative feasible with lithium, ammonia, and ethanol without destruction of the

(1) This investigation was supported in part by a grant from the American Cancer Society and a research grant (CY-3207) from the National Cancer Institute of the National Institutes of Health, United States Public Health Service.

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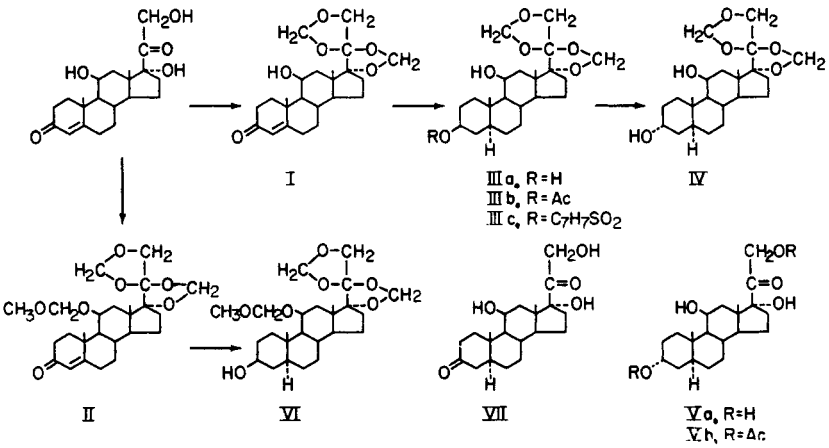

dihydroxyacetone side-chain group. Rearrangement of the 3β-hydroxyl group to the desired 3α-hydroxy epimer was then possible with the protecting group intact.

The reaction of formalin and hydrocortisone by the method of Beyler and co-workers gave not only the bismethylenedioxy derivative of hydrocortisone (I) in about 40% yield but a less polar product II in about equal amount. The characterization of II is discussed later. The α,β-unsaturated ketone of 11β-hydroxy-17,20;20,21-bismethylenedioxy-Δ⁴-pregnene-3-one (I) was smoothly reduced with lithium, ammonia, and ethanol to the 3β-hydroxyallopregnane derivative IIIa further characterized as the monoacetate IIIb. The expected steric course of the reduction[10,11] was verified by the hydrolysis of IIIa with 60% formic acid to Reichstein's Substance V, 3β,11β,17α,21-tetrahydroxyallopregnane-20-one.

The 3β-hydroxy group of 17,20;20,21-bismethylenedioxyallopregnane-3β,11β-diol (IIIa) was epimerized to the desired 3α-hydroxy group by the formation of the 3-monotosylate IIIc and treatment with *N,N*-dimethylformamide.[12] The reaction product was hydrolyzed with base and chromatographed on silica gel. The epimer 17,20;20,21-bismethylenedioxyallopregnane-3α,11β-diol (IV) was the principal product and only a small amount of an elimination product was obtained. Hydrolysis of IV with 50% acetic acid afforded a good yield of Reichstein's Substance C (VIa). The physical constants[8,13] and the mobility on paper chromatography were the same as that of an authentic sample.[14] The infrared spectrum of the 3,21-diacetate was identical with that of an authentic sample.[15]

The other product (II) obtained from the reaction of formalin with hydrocortisone had a greater mobility on paper or column chromatography than bismethylenedioxyhydrocortisone (I). The presence of the α,β-unsaturated ketone was shown by ultraviolet and infrared spectrometry. II was stable to chromic acid indicating the loss of the 11β-hydroxyl group either by elimination or reaction with formalin. The absence of the hydroxyl group was further substantiated by infrared spectrometry which also showed no unsaturation other than that of the Δ⁴-3-ketone. The unknown compound had an analysis corresponding to $C_{25}H_{36}O_7$ which suggested a substance that was a derivative of bismethylenedioxyhydrocortisone with two additional carbons and one oxygen atom.The unknown compound yielded three moles of formaldehyde on hydrolysis whereas bismethylenedioxyhydrocortisone (I) released but two moles. Analysis of II demonstrated the presence of a mole of methoxyl group. All these results were in accord with the structure, 11β-hydroxy-17,20;20,21-bismethylenedioxy-Δ⁴-pregnene-3-one 11-methoxymethyl ether (II), assigned for this compound. The methoxymethyl ether of I is the result of the mixed acetal formation of formaldehyde with the 11β-hydroxyl group of bismethylenedioxyhydrocortisone and methanol. The latter is present in commercial formalin which was used without purification. Such formation of methoxymethyl ether can be utilized in protecting the 11β-hydroxyl group as well as any other hydroxyl groups. The effect of the 11-methoxymethyl ether on the reduction of the α,β-unsaturated ketone in II with lithium, ammonia and ethanol was studied. The reduction proceeded as expected to give the 3β-hydroxyallopregnane derivative VI which was characterized by hydrolysis to Reichstein's Substance V.

Another possible metabolite of hydrocortisone, 11β,17α,21-trihydroxyallopregnane-3,20-dione ("allodihydro F," VII), was prepared from hydrocortisone without isolation of the intermediate products. Hydrocortisone was reacted with formalin and

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(14) The authors are grateful to Dr. Harold Levy of the Worcester Foundation for Experimental Biology for this compound.

(15) The authors thank Professor T. Reichstein for this compound.

hydrochloric acid. The mixture of bismethylenedioxyhydrocortisone (I) and its methoxymethyl ether (II) was reduced directly with lithium and ammonia without ethanol[16] to give the 3-ketoallopregnane derivative. Hydrolysis of the reduction product and chromatography on silica gel afforded a 16% yield of "allodihydro F" (VII).

EXPERIMENTAL[17]

11β-Hydroxy-17,20;20,21-bismethylenedioxy-Δ⁴-pregnene-3-one (I) *and its 11-methoxymethyl ether* (II). A solution of 1.0 g. of hydrocortisone in 40 ml. of chloroform was shaken with a solution of 10 ml. of formalin[18] and 10 ml. of concd. hydrochloric acid for 48 hr. at room temperature as described by Beyler and co-workers.[9] The reaction product, 1.15 g., was chromatographed on 100 g. of acid washed alumina. Elution with benzene–petroleum ether mixtures afforded 444 mg. of crystalline material (II), m.p. 154–160°. Further elution with ethyl acetate–benzene mixtures yielded 454 mg. of 11β-hydroxy-17,20;20,21-bismethylenedioxy-Δ⁴-pregnene-3-one (I), m.p. 180–221°. Recrystallizations from ethyl acetate gave 215 mg. of bismethylenedioxyhydrocortisone (I), m.p. 222–227°; $[\alpha]_D^{25}$ + 25.4°; $\nu_{max}^{CHCl_3}$ 3620, 2765 (BMD), 1663 and 1617 cm.$^{-1}$; reported[9] m.p. 217–222°; $[\alpha]_D$ + 26°.

The less polar material, m.p. 154–160°; from the alumina column was recrystallized from ethyl acetate to give 11β-hydroxy-17,20;20,21-bismethylenedioxy-Δ⁴-pregnene-3-one 11-methoxymethyl ether (II), m.p. 160–162°; $[\alpha]_D^{25}$ + 31.6°; $\lambda_{max}^{C_2H_5OH}$ 241 mμ, ε 16,000; $\nu_{max}^{CS_2}$ 2750 (BMD), 1677 and 1619 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09; OCH_3, 6.92; HCHO, 20.2. Found: C, 66.79; H, 8.01; OCH_3, 6.63; HCHO,[19] 20.8.

The compound was recovered unchanged after treatment with chromic acid in acetic acid at room temperature for 1 hr. Hydrolysis of II (300 mg.) with 10 ml. of 60% formic acid on a steam bath for 30 min. yielded 169 mg. of crude hydrocortisone, m.p. 188–194°, which after purification by chromatography on Florisil and recrystallization from ethyl acetate had m.p. 198–203°. Acetylation with pyridine afforded hydrocortisone acetate, m.p. 212–216°; infrared spectrum was identical with that of the standard reference sample.

17,20;20,21-Bismethylenedioxyallopregnane-3β,11β-diol (IIIa). A solution of 15.9 g. of bismethylenedioxyhydrocortisone (I) in 330 ml. of tetrahydrofuran and 330 ml. of ethanol was added to 3 l. of liquid ammonia. To this mixture was added 38.5 g. of lithium ribbon in small portions until the blue color persisted. The reaction mixture was stirred for another hour at the end of which time the blue color had disappeared. Ethanol was cautiously added and the ammonia evaporated by gentle warming on the steam bath. When about a liter of solution remained, 3 l. of ether was added and the mixture was heated under reflux until ammonia ceased to evolve. Water and ethyl acetate were added and the organic layer separated. The ethyl acetate–ether extract was washed with sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent evaporated to give 15.8 g. of crystalline product. Recrystallizations from ethyl acetate–methanol yielded 8.6 g. of reduction product melting at 230–238°. An additional 3.0 g. of product with slightly lower melting points were obtained on chromatography of the mother liquors on alumina. The analytical sample of 17,20;20,21-bismethylenedioxyallopregnane-3β,11β-diol (IIIa) had m.p. 238–241°; $[\alpha]_D^{27}$ −73.4°; $\nu_{max}^{CHCl_3}$ 3640 (Sh), 3615 and 2760 (BMD) cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.53; H, 8.94.

Hydrolysis of IIIa with formic acid on a steam bath and chromatography on Florisil afforded 3β,11β,17α,21-tetrahydroxyallopregnane-20-one (Reichstein's Substance V), m.p. 208–210°. The diacetate had an infrared spectrum in chloroform 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.$^{-1}$.

Acetylation of IIIa with pyridine and acetic anhydride gave 17,20;20,21-bismethylenedioxyallopregnane-3β,11β-diol 3-monoacetate (IIIb), m.p. 202–204°; $[\alpha]_D^{27}$ −68.3°; $\nu_{max}^{CS_2}$ 3610, 2755 (BMD), 1735 and 1243 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.43; H, 8.46.

17,20;20,21-Bismethylenedioxyallopregnane-3β,11β-diol 3-p-toluenesulfonate (IIIc). A cold solution of 100 mg. of *p*-toluenesulfonyl chloride in pyridine was added to a cold solution of 100 mg. of 17,20;20,21-bismethylenedioxyallopregnane-3β,11β-diol (IIIa) in pyridine. The mixture was stored overnight at room temperature and excess reagent was destroyed with ice and water. The reaction product was extracted with ethyl acetate and washed with dilute acid, base, and water. The ethyl acetate solution was dried and the solvent evaporated. The oily product was crystallized from cyclohexane-acetone yielding 128 mg. of the 17,20;20,21-bismethylenedioxyallopregnane-3β,11β-diol 3-*p*-toluenesulfonate (IIIc), m.p. 170–172° dec.; $[\alpha]_D^{27}$ −51.3°; $\nu_{max}^{CS_2}$ 3615 and 2755 (BMD) cm.$^{-1}$

Anal. Calcd. for $C_{30}H_{43}O_8S$: C, 64.03; H, 7.52. Found: C, 64.13; H, 7.57.

17,20;20,21-Bismethylenedioxyallopregnane-3α,11β-diol (IV). A solution of 14.8 g. of 17,20;20,21-bismethylenedioxyallopregnane-3β,11β-diol 3-*p*-toluenesulfonate (IIIc) in 600 ml. of *N,N*-dimethylformamide (unpurified)[12] was heated at 80–82° for 72 hr. The solution was poured onto ice and water and extracted with chloroform. The chloroform extract was washed with water, dried, and the solvent was evaporated. The oily residue was saponified with 1.5 l. of 5% methanolic potassium hydroxide solution at room temperature for 4 hr. Most of the methanol was removed and the product was extracted with ethyl acetate. The ethyl acetate solution was washed with sodium chloride solution, dried and the solvent evaporated. Recrystallizations from ethyl acetate–methanol yielded 4.6 g. of IV, m.p. 231–234° and 1.66 g. of second crop, m.p. 224–228°. The analytical sample of 17,20;20,21-bismethylenedioxyallopregnane-3α,11β-diol (IV) melted at 232–236°; $[\alpha]_D^{27}$ −74.9°; $\nu_{max}^{CHCl_3}$ 3640 (Sh), 3620 and 2760 (BMD) cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.53; H, 8.82.

Chromatography of the mother liquors of IV on 220 g. of acid washed alumina and elution with ethyl acetate–benzene afforded an additional 1.84 g. of IV, m.p. 226–232°. Less polar material eluted with benzene (1.4 g.) was assigned the structure 17,20;20,21-bismethylenedioxy-Δ²-allopregnene-11β-ol, m.p. 170–173° $[\alpha]_D^{30}$ −53.2°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.85; H, 8.49.

3α,11β,17α,21-Tetrahydroxyallopregnane-20-one, Reichstein's Substance C (Va). A solution of 6.95 g. of 17,20;20,21-bismethylenedioxyallopregnane-3α,11β-diol (IV) in 500 ml. of 50% aqueous acetic acid was refluxed for 30 min. The

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(17) Melting points were determined on a micro hot stage and are corrected. Optical rotations were taken in chloroform unless otherwise specified. Infrared spectra were determined in the medium specified on a Model 21 Perkin-Elmer spectrophotometer using sodium chloride and calcium fluoride prisms, Sh = shoulder.

(18) Commercial 37% aqueous formaldehyde was used without purification.

(19) Formaldehyde content was determined with chromotropic acid by the method of V. P. Hollander, S. DiMauro, and O. H. Pearson, *Endocrinol.*, 49, 617 (1951), and A. A. Henly and M. Potter, *Lancet*, I, 697 (1952).

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); ν_{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.; ν_{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.

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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

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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