of the first crop was dried at 100° (0.2 mm.) for analysis and showed $\lambda_{max}^{0.1\ N\ HCl}$ 288 mμ (log ε 3.1); $\lambda_{max}^{0.1\ N\ NaOH}$ 331 mμ (log ε 4.3) and 234 mμ (log ε 3.9); λ_{max}^{Nujol} 6.08 μ (C=O); pK'_a's in 70% acetone–water 7.1 and 9.2.

Anal. Calcd. for $C_9H_{12}NO_3Cl$: C, 49.64; H, 5.56; N, 6.43; Cl, 16.30. Found: C, 49.74; H, 5.76; N, 6.32; Cl, 16.45.

When the ethyl acetate extract of the ether insolubles was evaporated to dryness, a solid weighing 2.16 g., m.p. 200–225°, was obtained. A sample of this product was recrystallized twice from 5:3 ethanol–water giving N-(2′,4′-dihydroxy-3′-methylphenacyl)-4-hydroxy-3-(3-methylbutyl)-benzamide (IX), m.p. 217–220°; $\lambda_{max}^{0.1\ N\ NaOH}$ 304 mμ (log ε 4.4); λ_{max}^{Nujol} 6.1 μ (C=O); pK'_a's in 70% acetone 9.8 and 11.9. The sample for analysis was dried 3 hr. at 100° (0.2 mm.).

Anal. Calcd. for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 68.15; H, 6.26; N, 3.92.

Triacetyl Derivative of 2,4-Dihydroxy-3-methylphenacylamine (VIII).—A solution of 487 mg. of 2,4-dihydroxy-3-methylphenacylamine hydrochloride in 5 ml. of pyridine was cooled in an ice-bath; 0.8 g. of acetic anhydride was added and the solution was allowed to stand overnight at room temperature. The solution was evaporated to 2 ml. under a stream of nitrogen, 5 ml. of water was added and the solution was acidified to *p*H 5 with 2.5 *N* hydrochloric acid. The resulting precipitate was centrifuged and washed five times with water giving 314 mg. of the crude triacetyl derivative, m.p. 147–157°. This product was recrystallized twice from ethyl acetate yielding 217 mg. of the triacetyl derivative of 2,4-dihydroxy-3-methylphenacylamine, m.p. 152–156°. The sample for analysis was dried 3 hr. at 52° (0.2 mm.).

Anal. Calcd. for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56; CH_3CO, 42.0. Found: C, 58.66; H, 5.58; N, 4.83; CH_3CO, 44.4.

Reduction of 2,4-Dihydroxy-3-methylphenacylamine Hydrochloride (VIII) to 4-Ethyl-2-methylresorcinol.—A slurry of 4.0 g. of zinc dust in a solution of 0.2 g. of mercuric chloride in 5 ml. of water was stirred for 0.5 hour. The supernatant liquid was decanted and the zinc was washed several times with water. A solution of 1.0 g. of 2,4-dihydroxy-3-methylphenacylamine hydrochloride in 5 ml. of hot water was added to the zinc. Then 5 ml. of concentrated hydrochloric acid was added and the mixture was refluxed 2.5 hr. The cooled mixture was filtered and the filtrate was extracted with three 40-ml. portions of ether. These extracts were dried over anhydrous sodium sulfate and evaporated to dryness leaving a brown oil which partially crystallized. The oil was extracted with 40 ml. of boiling petroleum ether (b.p. 40–60°). The extract was treated with Darco and allowed to stand at room temperature. Crude 4-ethyl-2-methylresorcinol, 161 mg., m.p. 70–77°, separated as an oil which crystallized on standing. It was recrystallized twice from Skellysolve B giving 52 mg. of the dialkylresorcinol which melted at 91–92°,[13] with a transition occurring at 80–85°. A small sample was sublimed at 50–55° (0.2 mm.) for analysis.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.01; H, 7.95. Found: C, 70.74; H, 8.04.

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RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC.]

Novobiocin. VII. Synthesis of Novobiocic Acid, Dihydronovobiocic Acid and Cyclonovobiocic Acid

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The structure of the aglycon of novobiocin has been confirmed by synthesis. Syntheses of novobiocic acid (X), dihydronovobiocic acid (VIII) and cyclonovobiocic acid (VI) are described. These acids were prepared by acylation of 3-amino-2,7-dihydroxy-8-methylchromone (IV) with the appropriate benzoyl chlorides. Preparation of novobiocic acid (X), the aglycon of novobiocin, by degradation of novobiocin is also described.

The structure of novobiocic acid (X), the aglycon of novobiocin, has been elucidated by degradative studies.[1–5] The isomeric cyclonovobiocic acid (VI) and dihydronovobiocic acid (VIII) have also been described[1,2,6] and a preliminary account of their synthesis has been reported.[7] A synthesis of novobiocic acid is described in this paper, together with details of the syntheses of VI and VIII.

For synthesis of each of the acids X, VI and VIII the appropriate substituted benzoyl chloride was allowed to react with 3-amino-2,7-dihydroxy-8-methylchromone hydrochloride (IV) in pyridine solution. This aminochromone was prepared from 2-methylresorcinol by a four-step synthesis. Condensation of 2-methylresorcinol with ethyl cyanoacetate formed 2,7-dihydroxy-4-imino-8-methylbenzopyran (I). Hydrolysis of the iminobenzopyran (I) in 50% sulfuric acid gave 2,7-dihydroxy-8-methylchromone (II),[8,9] which was nitrosated with sodium nitrite in dilute acetic acid, giving 2,7-dihydroxy-8-methyl-3-nitrosochromone (III). The nitrosochromone III was unstable; consequently, the crude product was hydrogenated over a palladium–Darco catalyst in ethanol containing a small amount of hydrochloric acid. The reduction product was 3-amino-2,7-dihydroxy-8-methylchromone hydrochloride (IV).[1,5]

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(7) C. F. Spencer, C. H. Stammer, J. O. Rodin, E. Walton, F. W. Holly and K. Folkers, *ibid.*, **78**, 2655 (1956).

(8) A. Sonn, *Ber.*, **50**, 1292 (1917), describes a preparation of 4,7-dihydroxycoumarin or 2,7-dihydroxychromone.

(9) For a discussion of the coumarin–chromone tautomerism in these compounds, see ref. 5.

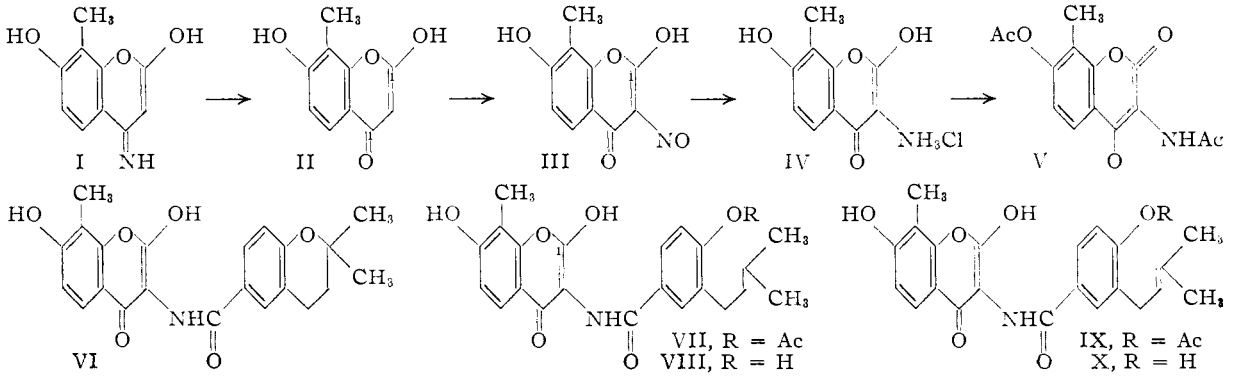
Acetylation of the aminochromone IV with acetic anhydride in pyridine gave 3-acetamido-7-acetoxy-4-hydroxy-8-methylcoumarin (V). The melting point and infrared absorption spectrum of this synthetic product were identical with those of the diacetylcoumarin[2] obtained by degradation of novobiocin.

2,2-Dimethylchroman-6-carboxylic acid[6,10] was converted with thionyl chloride into 2,2-dimethylchroman-6-carbonyl chloride. The amine hydrochloride IV was then treated with this acid chloride in pyridine, giving cyclonovobiocic acid (VI). The melting point of this product was the same as that of VI obtained by degradation of novobiocin, and the melting point of a mixture of the two was not depressed. The infrared absorption spectra of the two also were identical.

4-Acetoxy-3-(3-methylbutyl)-benzoic acid[10] was converted with thionyl chloride into 4-acetoxy-3-(3-methylbutyl)-benzoyl chloride. This acid chloride, an oil, was characterized as its anilide. Treatment of the amine hydrochloride IV with this acid chloride yielded monoacetyldihydronovobiocic acid (VII). Alkaline hydrolysis of VII gave dihydronovobiocic acid (VIII). The melting point of synthetic VIII was the same as that of VIII obtained by degradation of dihydronovobiocin, and the melting point of a mixture of the two was not depressed. The infrared absorption spectra of the two were identical.

4-Acetoxy-3-(3-methyl-2-butenyl)-benzoic acid[10] was converted with oxalyl chloride into 4-acetoxy-3-(3-methyl-2-butenyl)-benzoyl chloride, characterized as its anilide. Treatment of the amine hydrochloride IV with this acid chloride gave monoacetylnovobiocic acid (IX), which, upon alkaline hydrolysis, yielded novobiocic acid (X). For comparison with this synthetic novobiocic acid, novobiocin was treated with sulfuric acid in dioxane at room temperature. The product had the same melting point and infrared absorption spectrum as synthetic novobiocic acid.

3-Acetamido-7-acetoxy-4-hydroxycoumarin, an analog of the diacetylcoumarin V, also was synthesized. Treatment of 2,7-dihydroxychromone[8] with nitrous acid yielded 2,7-dihydroxy-3-nitrosochromone. Hydrogenation of this nitrosochromone over a palladium–Darco catalyst in ethanol containing a small amount of hydrochloric acid yielded 3-amino-2,7-dihydroxychromone hydrochloride. Acetylation of this amine with acetic anhydride in pyridine afforded 3-acetamido-7-acetoxy-4-hydroxycoumarin.



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Experimental

2,7-Dihydroxy-4-imino-8-methylbenzopyran (I).—A solution of 8.5 g. of 2-methylresorcinol and 7.7 g. of ethyl cyanoacetate in 85 ml. of dry ether was cooled in an ice-bath; 5 g. of anhydrous zinc chloride was added. Dry hydrogen chloride was passed into the stirred, cooled mixture for 2 hours. The mixture was kept at room temperature for 3 days. The solid product was filtered, washed with ether, slurried with water, filtered, washed with cold water and dried in a vacuum desiccator over phosphorus pentoxide; 8.6 g. (66%) of 2,7-dihydroxy-4-imino-8-methylbenzopyran was obtained. A sample recrystallized from dimethylformamide–water melted above 350°, $\lambda_{max}^{CCl_4}$ 6.1–6.4 μ.[9]

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.67; H, 4.51; N, 7.33.

2,7-Dihydroxy-8-methylchromone (II).—A suspension of 1.0 g. of 2,7-dihydroxy-4-imino-8-methylbenzopyran in 20 ml. of 50% sulfuric acid was heated on a steam-bath for 24 hours. The mixture was cooled in an ice-bath and the product was filtered, washed with cold water and recrystallized from water; 0.5 g. of 2,7-dihydroxy-8-methylchromone, m.p. 270–280° dec.; λ_{max}^{Nujol} 6.0–6.1, 6.23 and 6.38 μ, was obtained.

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.87; H, 4.12.

After sodium fusion the product gave a negative test for nitrogen, distinguishing it from I.

2,7-Dihydroxy-8-methyl-3-nitrosochromone (III).—A solution of 0.18 g. of sodium nitrite in 10 ml. of water was added to a suspension of 0.50 g. of 2,7-dihydroxy-8-methylchromone in 100 ml. of water at room temperature. The mixture was acidified with a few drops of acetic acid. After about 1 hour most of the chromone had dissolved. The solution was filtered and the filtrate was extracted with eight 75-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate and evaporated to dryness under reduced pressure. The solid residue, 0.27 g., was hydrogenated without purification because attempts to crystallize a previous preparation had resulted in decomposition.

3-Amino-2,7-dihydroxy-8-methylchromone Hydrochloride (IV).—A solution of 265 mg. of 2,7-dihydroxy-8-methyl-3-nitrosochromone in 10 ml. of ethanol was added to a suspension of 1 g. of a prereduced palladium–Darco (10%) catalyst in 100 ml. of ethanol containing 2.7 ml. of 2.5 *N* hydrochloric acid. The mixture was shaken with hydrogen at room temperature and atmospheric pressure. Absorption of hydrogen stopped after 6 hours. The catalyst was filtered and the filtrate was evaporated to dryness under reduced pressure under nitrogen. The solid residue, 3-amino-2,7-dihydroxy-8-methylchromone hydrochloride, was acylated without purification.

3-Acetamido-7-acetoxy-4-hydroxy-8-methylcoumarin (V).—The 3-amino-2,7-dihydroxy-8-methylchromone hydrochloride prepared above was dissolved in 10 ml. of pyridine. The solution was filtered to remove a small amount of insoluble material, cooled in an ice-bath and 2 ml. of acetic

anhydride was added. After standing overnight at room temperature, the solution was poured into 100 ml. of ice-water, acidified with hydrochloric acid and extracted with four 50-ml. portions of chloroform. The combined chloroform extracts were dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue was crystallized from ethyl acetate, yielding 122 mg. of 3-acetamido-7-acetoxy-4-hydroxy-8-methylcoumarin, m.p. 260–262°. After sublimation at 190° (0.01 mm.), the product melted at 263–265°; $\lambda_{max}^{CHCl_3}$ 5.69, 5.92, 6.05, 6.20 and 6.50 μ.

Anal. Calcd. for $C_{14}H_{13}NO_6$: C, 57.73; H, 4.50; N, 4.81. Found: C, 57.45; H, 4.12; N, 5.10.

2,2-Dimethylchroman-6-carbonyl Chloride.—A solution of 6 g. of 2,2-dimethylchroman-6-carboxylic acid[6,10] in 25 ml. of thionyl chloride was heated under reflux for 70 minutes and then concentrated to dryness under reduced pressure. The resulting solid residue was crystallized from 200 ml. of petroleum ether, yielding 4.7 g. of 2,2-dimethylchroman-6-carbonyl chloride, m.p. 90–93°. Recrystallization from petroleum ether raised the melting point to 95–97°.

Anal. Calcd. for $C_{12}H_{13}O_2Cl$: C, 64.14; H, 5.83; Cl, 15.8. Found: C, 64.43; H, 5.59; Cl, 14.8.

3-(2,2-Dimethylchroman-6-carboxamido)-2,7-dihydroxy-8-methylchromone (Cyclonovobiocic Acid, VI).—2,2-Dimethylchroman-6-carbonyl chloride (4.1 g.) was added in small portions to a suspension of 2.0 g. of 3-amino-2,7-dihydroxy-8-methylchromone hydrochloride in 16 ml. of anhydrous pyridine cooled in ice–salt-bath. The mixture was stirred at room temperature overnight during which time the chromone dissolved and a different white solid appeared. This solid dissolved upon the addition of a few ml. of water; 50 ml. more water was added causing a gum to separate. The mixture was acidified with hydrochloric acid and extracted with chloroform. The chloroform solution was dried over magnesium sulfate and evaporated under reduced pressure to a white glass which was leached with petroleum ether to yield 5.4 g. of white powder. This powder was digested with 150 ml. of ethanol and the insolubles were filtered (1.1 g.). The filtrate was concentrated under reduced pressure and the residue was crystallized from 50 ml. of 95% ethanol; 0.6 g. of cyclonovobiocic acid, m.p. 270–280°, was obtained. The melting point was raised to 280–284° by two recrystallizations from 95% ethanol; $\lambda_{max}^{0.1\ N\ NaOH}$ 250 mμ ($E_{1\ cm}^{1\%}$ 364), 326 mμ ($E_{1\ cm}^{1\%}$ 300); λ_{max}^{Nujol} 6.05, 6.12, 6.28, 6.50 and 6.67 μ.

Anal. Calcd. for $C_{22}H_{21}NO_6$: C, 66.82; H, 5.35; N, 3.54. Found: C, 66.63; H, 5.29; N, 3.24.

4-Acetoxy-3-(3-methylbutyl)-benzoic Acid.—A mixture of 9 g. of 3-(3-methylbutyl)-4-hydroxybenzoic acid, 25 ml. of pyridine and 10 ml. of acetic anhydride was kept at room temperature overnight. It was added to a mixture of 26 ml. of concentrated hydrochloric acid and 100 g. of ice. The oil which separated slowly crystallized. After being air-dried the solid was recrystallized twice from about 200 ml. of Skellysolve C yielding 8 g. of 4-acetoxy-3-(3-methylbutyl)-benzoic acid, m.p. 147–149°.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.36; H, 7.26.

4-Acetoxy-3-(3-methylbutyl)-benzoyl Chloride.—A solution of 0.5 g. of 4-acetoxy-3-(3-methylbutyl)-benzoic acid in 5 ml. of thionyl chloride was heated under reflux for 70 minutes and then concentrated under reduced pressure. The resulting clear oil was dissolved in benzene and the solution was again concentrated. This procedure was twice repeated using petroleum ether instead of benzene. The 4-acetoxy-3-(3-methylbutyl)-benzoyl chloride was characterized by the preparation of its anilide.

4-Acetoxy-3-(3-methylbutyl)-benzanilide.—A solution of 0.31 g. of aniline in 5 ml. of chloroform was added to a solution of 0.5 g. of 4-acetoxy-3-(3-methylbutyl)-benzoyl chloride in 5 ml. of chloroform. Heat was evolved and a precipitate formed immediately. The mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was triturated with water and crystallized from 35 ml. of Skellysolve C, yielding 0.55 g. of 4-acetoxy-3-(3-methylbutyl)-benzanilide, m.p. 133–136°. Recrystallization raised the melting point to 135–137°.

Anal. Calcd. for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.31. Found: C, 73.62; H, 6.88; N, 4.48.

2,7-Dihydroxy-3-[4-acetoxy-3-(3-methylbutyl)-benzamido]-8-methylchromone (Monoacetyldihydronovobiocic Acid, VII).—4-Acetoxy-3-(3-methylbutyl)-benzoyl chloride (4.7 g.) was added in small portions to a suspension of 2.0 g. of 3-amino-2,7-dihydroxy-8-methylchromone hydrochloride in 30 ml. of anhydrous pyridine cooled in an ice-bath. The mixture was stirred at room temperature overnight. A precipitate (0.4 g.) was filtered, 100 ml. of chloroform and 100 ml. of water were added to the filtrate, and the mixture was acidified slowly with hydrochloric acid. A yellow solid precipitated in the chloroform phase. The aqueous phase was extracted with chloroform, and the combined chloroform extracts were cooled and filtered, giving 2.1 g. of monoacetyldihydronovobiocic acid, m.p. 206–209°. A sample was recrystallized twice from chloroform, m.p. 207–209°.

Anal. Calcd. for $C_{24}H_{25}NO_7$: C, 65.59; H, 5.73; N, 3.19. Found: C, 64.23, 64.62; H, 5.74, 5.60; N, 3.45.

2,7-Dihydroxy-3-[4-hydroxy-3-(3-methylbutyl)-benzamido]-8-methylchromone (Dihydronovobiocic Acid, VIII).—A solution of 0.44 g. of monoacetyldihydronovobiocic acid in 10 ml. of 10% sodium hydroxide was kept at room temperature for 1 hour, cooled and acidified with 3 *N* hydrochloric acid. The precipitate was filtered, washed with water and dried, yielding 0.4 g. of dihydronovobiocic acid, m.p. 230–237°. A sample was recrystallized twice from isopropyl alcohol and dried at 150° (0.01 mm.) for 3 hours. The melting point (236–239°) was not depressed when mixed with a sample of dihydronovobiocic acid obtained by degradation[2] of dihydronovobiocin; $\lambda_{max}^{0.1\ N\ NaOH}$ 247 mμ ($E_{1\ cm}^{1\%}$ 514), 263 mμ ($E_{1cm}^{1\%}$ 387), 325 mμ ($E_{1cm}^{1\%}$ 845); λ_{max}^{Nujol} 6.0, 6.09, 6.22, 6.32, 6.45 and 6.63 μ.

Anal. Calcd. for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.48; H, 5.94; N, 3.72.

4-Acetoxy-3-(3-methyl-2-butenyl)-benzoyl Chloride.—To a solution of 6.5 g. of 4-acetoxy-3-(3-methyl-2-butenyl)-benzoic acid in 65 ml. of methanol was added 26.1 ml. of 1 *N* sodium hydroxide solution. Most of the methanol was distilled under reduced pressure at 0–5° and the aqueous solution was lyophilized. The white solid residue was triturated twice with dry benzene. Benzene (90 ml.) was added to the residue, and a small volume was distilled to remove traces of water. The suspension was cooled to 5°, 4.1 g. of oxalyl chloride was added, and the mixture was brought to room temperature. Gas was evolved. The cloudy yellow solution was refluxed for 2 hours, cooled to room temperature and filtered. The filtrate was evaporated under reduced pressure and the yellow oily residue was distilled in a von Braun flask, giving 4.9 g. (71%) of 4-acetoxy-3-(3-methyl-2-butenyl)-benzoyl chloride, b.p. 131–134° (0.7 mm.), $n^{25}D$ 1.5367.

4-Acetoxy-3-(3-methyl-2-butenyl)-benzanilide.—A solution of 0.33 g. of aniline in 5 ml. of chloroform was added to a solution of 0.47 g. of 4-acetoxy-3-(3-methyl-2-butenyl)-benzoyl chloride in 5 ml. of chloroform. The mixture was filtered after 0.5 hour, and the yellow filtrate was concentrated under reduced pressure. The yellow oil was dissolved in 25 ml. of ether, and a small amount of insoluble material was filtered. To the filtrate was added 100 ml. of Skellysolve C. The ether was boiled off, the solution was cooled, and precipitation of oily white crystals was initiated by scratching. The crystals were collected and dried, giving 0.40 g. of 4-acetoxy-3-(3-methyl-2-butenyl)-benzanilide, m.p. 105–115°. Two recrystallizations from Skellysolve C raised the melting point to 113–116°, with softening at 95°.

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.34. Found: C, 74.08; H, 6.90; N, 4.68.

2,7-Dihydroxy-3-[4-acetoxy-3-(3-methyl-2-butenyl)-benzamido]-8-methylchromone (Monoacetylnovobiobic Acid, IX).—3-Amino-4,7-dihydroxy-8-methylcoumarin hydrochloride (1.9 g.) was added to a solution of 4.2 g. of 4-acetoxy-3-(3-methyl-2-butenyl)-benzoyl chloride in 25 ml. of anhydrous pyridine at 0°. The solution was allowed to stand at room temperature overnight. Chloroform (150 ml.) and water (150 ml.) were added, and the mixture was acidified with 25 ml. of hydrochloric acid. The yellow crystals of monoacetylnovobiocic acid which separated were filtered and dried in a vacuum desiccator; 1.6 g. (47%), m.p. 225–245°. Three recrystallizations from dimethylformamide–methanol followed by drying at 150° (0.01 mm.) for 2 hours raised the melting point to 243–249°.

Anal. Calcd. for $C_{24}H_{23}NO_7$: C, 65.89; H, 5.30; N, 3.20; $COCH_3$, 9.84. Found: C, 66.78; H, 5.75; N, 3.42; $COCH_3$, 11.46.

2,7-Dihydroxy-3-[4-hydroxy-3-(3-methyl-2-butenyl)-benzamido]-8-methylchromone (Novobiocic Acid, X).—A solution of 0.44 g. of monoacetylnovobiocic acid in 10 ml. of 2.5 *N* sodium hydroxide solution was allowed to stand at room temperature for 2 hours, cooled, and acidified with 10 ml. of 3 *N* hydrochloric acid. The yellow crystals were filtered, washed with water and dried, giving 0.4 g. of crude novobiocic acid. Four recrystallizations from dimethylformamide–water followed by drying at 150° (0.01 mm.) overnight yielded novobiocic acid, m.p. 218–234°; λ_{max}^{Nujol} 6.1, 6.10, 6.20, 6.30, 6.45 and 6.62 μ. The melting point was not depressed by novobiocic acid obtained by degradation of novobiocin.

Anal. Calcd. for $C_{22}H_{21}NO_6$: C, 66.82; H, 5.35; N, 3.54. Found: C, 66.86; H, 5.43; N, 3.76.

Novobiocin Acid by Degradation of Novobiocin.—A solution of 6.25 g. of novobiocin and 20 g. of concentrated sulfuric acid in 1 l. of purified dioxane was kept at room temperature for 22 hours. A solution of 17 g. of sodium hydroxide in 500 ml. of methanol and 100 ml. of water was added. The precipitated sodium sulfate was filtered and the filtrate was concentrated under reduced pressure to 200–300 ml. The product was precipitated by the addition of about 1 l. of water. The precipitate was filtered, washed with cold water and dried in a vacuum desiccator; 5.15 g. of crude novobiocic acid was obtained.

To purify this material, 4.69 g. of it was dissolved in 500 ml. of chloroform. After filtration to remove a small amount of insoluble material, the solution was placed on a column containing 350 g. of acid-washed alumina. Elution with chloroform removed practically nothing from the column. Elution with acetone gave 1.61 g. of residue after evaporation of the acetone. This residue was crystallized from ethanol–water, giving 1.0 g. of novobiocic acid, m.p. 217–232°; $\lambda_{max}^{0.1\ N\ NaOH}$ 247 mμ ($E_{1cm}^{1\%}$ 496), 264 mμ ($E_{1cm}^{1\%}$ 365), 325 mμ ($E_{1cm}^{1\%}$ 787); λ_{max}^{Nujol} 6.02, 6.12, 6.21, 6.31, 6.49 and 6.63 μ.

2,7-Dihydroxychromone[3] was prepared in the same manner as described above for 2,7-dihydroxy-8-methylchromone, using resorcinol in place of 2-methylresorcinol. The yield of 2,7-dihydroxychromone from 44 g. of resorcinol, 34 g. of ethyl cyanoacetate and 20 g. of zinc chloride was 14 g., m.p. 274–277° dec. after two recrystallizations from water; λ_{max}^{Nujol} 6.0, 6.1, 6.2 and 6.35 μ.

Anal. Calcd. for $C_9H_6O_4$: C, 60.68; H, 3.40. Found: C, 60.88; H, 3.53.

2,7-Dihydroxy-3-nitrosochromone.—A solution of 202 mg. of 2,7-dihydroxychromone in 11.3 ml. of 0.1 *N* sodium hydroxide was cooled in an ice-bath and 82 mg. of sodium nitrite was added. The solution was kept at room temperature for 2 hours and then acidified with acetic acid. The yellow crystalline precipitate was filtered, washed with a little cold water and dried in a vacuum desiccator over phosphorus pentoxide; 183 mg. (78%) of 2,7-dihydroxy-3-nitrosochromone, m.p. 210–220° dec., was obtained. After sublimation at 150° (5 μ) a sample melted at 221–226° dec.

Anal. Calcd. for $C_9H_5NO_5$: C, 52.18; H, 2.43; N, 6.76. Found: C, 52.68; H, 2.12; N, 6.38.

3-Amino-2,7-dihydroxychromone Hydrochloride.—A solution of 97 mg. of 2,7-dihydroxy-3-nitrosochromone in 20 ml. of ethanol was added to a suspension of 0.5 g. of a prereduced palladium–Darco (10%) catalyst in 20 ml. of ethanol containing 0.6 ml. of 2.5 *N* hydrochloric acid. The mixture was shaken with hydrogen at room temperature and atmospheric pressure. Absorption of hydrogen stopped after 3 hours. The catalyst was filtered and the filtrate was evaporated to dryness under reduced pressure under nitrogen. Attempts to crystallize the residue did not succeed and it was acetylated without purification.

3-Acetamido-7-acetoxy-4-hydroxycoumarin.—The 3-amino-2,7-dihydroxychromone hydrochloride prepared above was dissolved in 4 ml. of pyridine. The solution was cooled in an ice-bath and 0.3 ml. of acetic anhydride was added. After standing overnight at room temperature the solution was poured into 20 ml. of ice-water. The mixture was acidified with hydrochloric acid and extracted with four 25-ml. portions of chloroform. The combined chloroform extracts were dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue was crystallized from ethyl acetate, yielding 46 mg. of 3-acetamido-7-acetoxy-4-hydroxycoumarin, m.p. 249–255°. The compound was recrystallized from ethyl acetate and sublimed at 200° (0.01 mm.), m.p. 256–260°; λ_{max}^{Nujol} 5.70, 5.93, 6.10, 6.20, 6.30 and 6.45 μ.

Anal. Calcd. for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05. Found: C, 56.27; H, 3.90; N, 5.03.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Cyclohepta[klm]benz[e]indene. Further Considerations on the Stability of Complex Polynuclear Systems

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The synthesis of cyclohepta[klm]benz[e]indene (III) has been effected by application of the hydrogen-transfer reaction, using chloranil, to either the hexahydro derivative V or the tetrahydro derivative XV. This method similarly permitted the direct conversion of acepleiadane (IV) to acepleiadylene (II). The preparation of V, a necessary intermediate for this work, permitted the isolation of a second series of racemates, isomeric with that previously obtained. Calculations of resonance energy increments have been made, by an approximate L.C.M.O. method, for conversions leading to I, II and III, and these values correlated with the yields of conversion. The results are consistent with the yield–stability relation previously proposed, and this is shown to have some theoretical justification.

The observation that pleiadiene (I)[1,2] is less stable than acepleiadylene (II)[1] although a logical extension of the Hückel rule would suggest the converse for C_{14}- and C_{16}-cyclic polyenes, prompted the investigation of related systems. The present report is concerned with the synthesis and some of the properties of cyclohepta[klm]benz[e]indene (III). Substance III is a particularly useful choice for comparison with I and II since II and III are isomeric and contain the same total number of π-electrons as well as the same number of peripheral π-electrons. Moreover, a comparison of yields in the preparation of II and III from their hexahydro derivatives IV and V by an aromatization reaction would be interesting as it would bear

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