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Novobiocin. VI. Structure of the Coumarin Moiety

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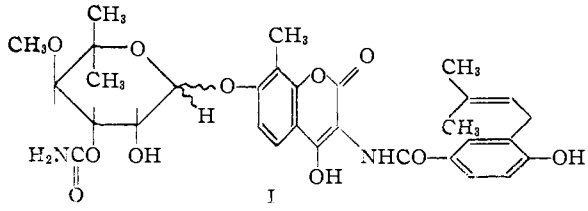
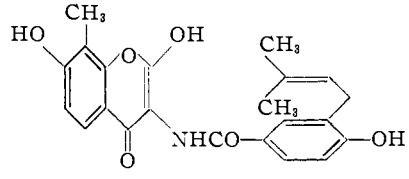
The structure of the coumarin moiety of novobiocin (I) is shown to be 3-amino-4,7-dihydroxy-8-methylcoumarin (VII). Degradation of dihydronovobiocic acid (III) using HBr–HOAc–Ac_2O gave a substituted chromone V, while HCl–HOAc–H_2O gave an amine hydrochloride VIII. Clemmensen reduction of VIII gave 4-ethyl-2-methylresorcinol (X). Thus, the structure of novobiocic acid (II), the aglycon of novobiocin, is 2,7-dihydroxy-3-(4-hydroxy-3-[3-methyl-2-butenyl]-benzamido)-8-methylchromone.

The structure of the antibiotic novobiocin (I) has been reported.[1-3] Alcoholic hydrochloric acid cleaves[1,4] the glycosidic linkage in novobiocin forming the methyl glycoside of 3-O-carbamylnoviose[1,2] and the aglycon, novobiocic acid (II).[4b] Deg-



I

radation of I and II has shown II to be the amide of 4-hydroxy-3-(3-methyl-2-butenyl)-benzoic acid[5,6] and 3-amino-4,7-dihydroxy-8-methylcoumarin.[1,4] This paper describes our chemical studies which led to the elucidation of the structure of the coumarin moiety of II.



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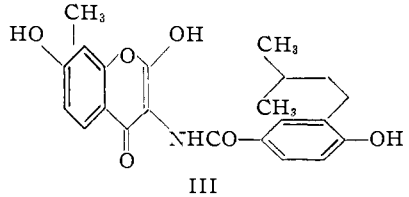


III

Cleavage of dihydronovobiocin[5,6] with alcoholic hydrochloric acid gave the aglycon, dihydronovobiocic acid (III). We used this compound as the starting point for our degradation studies since, in contrast to novobiocic acid, it can be obtained more readily in pure form. When dihydronovobiocic acid (III), $C_{22}H_{23}NO_6$, pK_a' 6.3,[7] was treated with a refluxing mixture of hydrogen bromide–acetic acid–acetic anhydride, two compounds were isolated. One of these was the known[6] 4-acetoxy-3-(3-methylbutyl)-benzoic acid (IV). The other, V, was an acidic compound, $C_{14}H_{13}NO_6$, pK_a' 4.9, containing two acetyl groups. The structural relationship of V to dihydronovobiocic acid (III) was indicated by the similarity of their ultraviolet absorption spectra in aqueous alkali. However, besides showing an enol ester carbonyl band, the infrared spectrum of V like that of novobiocin showed a 5.92 μ carbonyl band not present in the spectrum of III. The absence of this 5.92 μ band in the infrared spectra of the novobiocic acids, II and III, indicated that the carbonyl function in these acids differs in some way from that in novobiocin and in V.

When the acid V was hydrolyzed with aqueous sodium hydroxide, one acetyl group was removed and the product VI, $C_{12}H_{11}NO_5$, pK_a' 5.3 and 11.1, showed no carbonyl absorption in the 5.5–6.0 μ region of its infrared spectrum. The absence of the 5.92 μ band in the infrared spectrum of VI indicated that possibly V and VI have a structural feature capable of tautomerism. That VI could be reacetylated to give V showed that no gross structural change had occurred during the alkaline hydrolysis of V

Acidic hydrolysis of V afforded an amino acid hydrochloride (VIII) which was difficult to purify.[8] Analytical data for VII agreed approximately with the composition $C_{10}H_{10}NO_4Cl$, while potentiometric titration indicated that the amino function was only feebly basic and probably aromatic. A color test[9] using fluorescein chloride confirmed this conclusion. Reacetylation of VII gave V showing that during acid hydrolysis the fundamental structure of V had suffered no rearrangement. Up to this point, the data suggested that V was an acetylated aminodihydroxycoumarin. The rapid loss of *one* acetyl group in alkaline solution made it likely that V was an O,N-diacetyl compound. The acidic function of V was accounted for by assuming a 4-hydroxycoumarin structure. Since low yields of 2,4-dihydroxy-*m*-toluic and 2,4-dihydroxy-*m*-tolylglyoxylic acids had been obtained by alkaline degradation of cyclonovobiocic acid,[1] it ap-

(1) C. H. Shunk, C. H. Stammer, E. A. Kaczka, E. Walton, C. F. Spencer, A. N. Wilson, J. W. Richter, F. W. Holly and K. Folkers, THIS JOURNAL, **78**, 1770 (1956).

(2) H. Hoeksema, E. L. Caron and J. W. Hinman, *ibid.*, **78**, 2019 (1956).

(3) E. Walton, J. O. Rodin, C. H. Stammer, F. W. Holly and K. Folkers, *ibid.*, **78**, 5454 (1956).

(4) (a) J. W. Hinman, H. Hoeksema, E. L. Caron and W. G. Jackson, *ibid.*, **78**, 1072 (1956); (b) J. W. Hinman, E. L. Caron and H. Hoeksema, *ibid.*, **79**, 3789 (1957).

(5) E. A. Kaczka, C. H. Shunk, J. W. Richter, F. J. Wolf, M. M. Gasser and K. Folkers, *ibid.*, **78**, 4125 (1956).

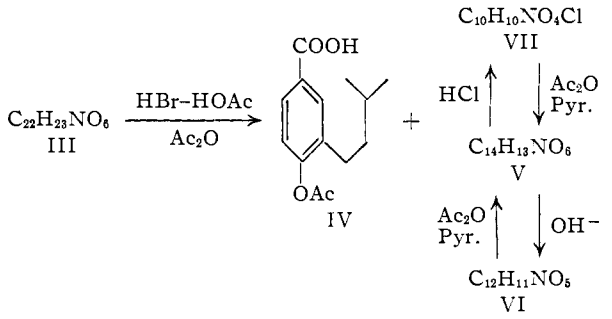
(6) H. Hoeksema, J. L. Johnson and J. W. Hinman, *ibid.*, **77**, 6710 (1955).

(7) The pK'a values given here are actually $pH_{1/2}$ values obtained by potentiometric titration in 70% acetone–water mixture using a hydrogen electrode.

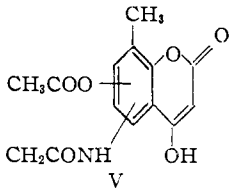
(8) C. F. Huebner and K. P. Link, THIS JOURNAL, **67**, 99 (1945), found it necessary to acetylate 3-amino-4-hydroxycoumarin for purification.

(9) F. Feigl, "Qualitative Analysis by Spot Tests," Elsevier Publ. Co., Inc., Houston, Texas, 3rd Ed., 1946, pp. 373, 375.

peared that a methyl group was in the 8-position and that either the acetoxyl or acetamido group was

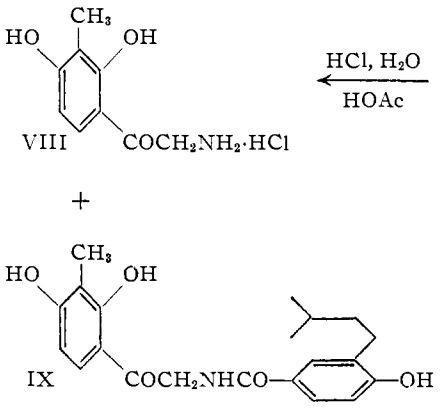


in the 7-position on the coumarin (V). Confirmation of this assignment and a direct determination

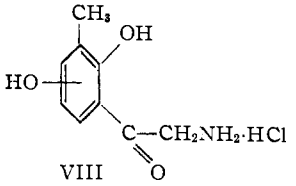


of the structure of the coumarin were accomplished by a different degradation scheme described below.

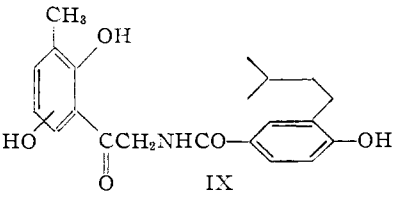
Refluxing concentrated hydrochloric acid–acetic acid solution converted dihydronovobiocic acid



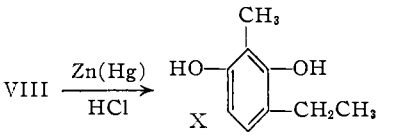
into two new degradation products. One was a water-soluble amine hydrochloride (VIII), $C_9H_{12}NO_3Cl$, pK_a''s 7.6 and 9.6, and the other a weakly acidic compound (IX), $C_{21}H_{25}NO_5$, pK_a''s 9.8 and 11.9. In compound VIII, the magnitude of the first ionization constant, attributable to the amine hydrochloride function, indicated that the amino group was *aliphatic*. Since the hydrogen bromide–acetic acid–acetic anhydride degradation of III led to an *aromatic* amino compound, we were led to the conclusion that the amino group was attached to the pyrone ring of the coumarin (V). Thus our second degradation scheme had destroyed the pyrone ring and VIII must have the structure



The second ionization constant of VIII thus corresponds to a phenolic function. The second product from the hydrochloric acid–acetic acid degradation of III appeared to have structure IX in which the amide link of III was still intact. The attach-



ment of the *p*-hydroxybenzoic acid moiety to the coumarin through an amide link was inferred from the absence of ester carbonyl absorption in the infrared spectra of both III and IX. It remained only to show the relative positions of the substituents on the ring in VIII. This was accomplished by Clemmensen reduction[10] of VIII to the known[11] 2-methyl-4-ethylresorcinol (X). The structures of



dihydronovobiocic acid (III) and all its degradation products can thus be written

Novobiocin (I) and the acetoxycoumarin V each have 5.92 μ absorption bands, which are attributed to the carbonyl group of the unsaturated lactone. Consequently, the coumarin structure rather than the tautomeric chromone form is assigned to I and V. Dihydronovobiocic acid (III) and the hydroxychromone VI, however, show no 5.92 μ band. Undoubtedly, the carbonyl absorption of these compounds is present above 6 μ, but in this region it is masked by the amidic carbonyl absorption. The chromone structure is assigned to III and VI since the carbonyl group in this tautomer would be expected to absorb at a longer wave length than in the coumarin. It should be noted that of these four compounds (I, III, V and VI) only the two having a free 7-hydroxyl group exist as chromones.

(10) J. V. Braun and K. Weisbach, *Ber.*, **62**, 2416 (1935), showed that N,N-dimethylphenacylamine underwent Clemmensen reduction to ethylbenzene.

(11) R. Robinson and R. C. Shah, *J. Chem. Soc.*, 1491 (1934).

The variation in physical properties, including the infrared spectrum, among various samples of the aminocoumarin VII did not allow a definite assignment of structure; consequently, we have drawn it arbitrarily in the coumarin form.

Confirmation of the novobiocic acid structures here deduced is afforded by syntheses[12] which will be fully described in a succeeding paper.

Experimental

Dihydronovobiocic Acid (III) (2,7-Dihydroxy-3-(4-hydroxy-3-[3-methylbutyl]-benzamido)-8-methylchromone).—A solution of 20 g. of novobiocin in 400 ml. of methanol was hydrogenated at room temperature and 40 p.s.i. initial pressure using 0.4 g. of platinum oxide. After 2 hr. the reduction was complete and the catalyst was filtered and washed with methanol. To the filtrate was added 30 ml. of concentrated hydrochloric acid and the solution was refluxed 2.5 hr. After standing overnight at 0–5°, the reaction mixture yielded 7.35 g. of product, m.p. 229–237°. The filtrate was evaporated to about 200 ml. and on standing at 0–5° gave another 4.0 g. of the acid, m.p. 228–235°. The two crops were combined and recrystallized from 125 ml. of isopropyl alcohol. The yield of dihydronovobiocic acid was 7.5 g., m.p. 236–237°; λ_{max}^{Nujol} 6.07 μ (C=O); $\lambda_{max}^{0.1\ N\ NaOH}$ 325 mμ (log ϵ 4.5), 263 mμ (log ϵ 4.2) and 247 mμ (log ϵ 4.3); pK'_a 6.3 in 70% acetone–water. A sample was prepared for analysis by recrystallization from isopropyl alcohol, m.p. 237–238°, and dried at 140° (0.2 mm.) for 2 hr.

Anal. Calcd. for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.53; O, 24.2. Found: C, 66.66; H, 5.68; N, 3.84; O, 23.4.

Degradation of Dihydronovobiocic Acid (III) with 32% Hydrogen Bromide–Acetic Acid and Acetic Anhydride. 3-Acetamido-7-acetoxy-4-hydroxy-8-methylcoumarin (V).—A solution of 2.0 g. of dihydronovobiocic acid in 20 ml. of a 1:1 mixture of 32% hydrogen bromide–acetic acid and acetic anhydride was refluxed for 3 hr. When the solution was cooled in an ice-bath, a solid separated. Filtration gave 257 mg. of product melting at 203–235°. Recrystallization of this material from ethyl acetate gave 105 mg. of solid, m.p. 260–261°. The filtrate from the reaction mixture was diluted to 200 ml. with water. A precipitate weighing 1.55 g., m.p. 115–200°, was collected on a filter. Recrystallization of this material from ethyl acetate gave 248 mg. of solid, m.p. 259–260°. The two crops of product were combined and recrystallized from ethyl acetate giving 253 mg. of 3-acetamido-7-acetoxy-4-hydroxy-8-methylcoumarin (V), m.p. 260–261°; $\lambda_{max}^{0.1\ N\ NaOH}$ 325 mμ (log ϵ 4.4) and 246 mμ (log ϵ 4.4); λ_{max}^{Nujol} 5.69 μ (C=C—O—C=O), 5.92 μ(C=O); pK'_a 4.9 in 70% acetone–water. The sample for analysis was dried at 100° (0.2 mm.) for 3 hrs.

Anal. Calcd. for $C_{14}H_{13}NO_6$: C, 57.72; H, 4.50; N, 4.81; CH_3CO, 29.6. Found: C, 57.72; H, 4.11; N, 4.90; CH_3CO, 24.8.

The filtrate from the second crop of the above product gave 226 mg., m.p. 141–143°, of 4-acetoxy-3-(3-methylbutyl)-benzoic acid.[6] This is a known compound and was deacetylated to the known 4-hydroxy-3-(3-methylbutyl)-benzoic acid[5] as a confirmation of structure.

3-Acetamido-2,7-dihydroxy-8-methylchromone (VI).—A solution of 63 mg. of 3-acetamido-7-acetoxy-4-hydroxy-8-methylcoumarin in 1 ml. of 2.5 *N* sodium hydroxide was allowed to stand at room temperature for 15 hr. The solution was acidified with 2.5 *N* hydrochloric acid, and 79 mg. of product, m.p. 277–284°, was obtained. This product can be sublimed at 190–210° at *ca.* 0.2 mm. or recrystallized from ethanol giving 3-acetamido-4,7-dihydroxy-8-methylcoumarin, m.p. 280–281°; $\lambda_{max}^{0.1\ N\ NaOH}$ 325 mμ (log ϵ 4.4) and 246 mμ (log ϵ 4.3); λ_{max}^{Nujol} 6.09 μ (C=O); pK'_a in 70% acetone–water 5.3 and 11.1. The sample for analysis was dried at 140° (0.2 mm.) for 4 hr.

Anal. Calcd. for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62; CH_3CO, 17.27. Found: C, 57.79; H, 4.71; N, 5.45; CH_3CO, 20.0. Analyses of five different samples were run before the above analysis was obtained.

Acetylation of 3-Acetamido-2,7-dihydroxy-8-methylchromone. 3-Acetamido-7-acetoxy-4-hydroxy-8-methylcoumarin (V).—A solution of 200 mg. of 3-acetamido-2,7-dihydroxy-8-methylchromone in 4 ml. of pyridine containing 0.4 ml. of acetic anhydride was allowed to stand overnight at room temperature. The reaction mixture was poured into about 40 ml. of ice and water and the solution was acidified to congo red with concentrated hydrochloric acid. This solution was continuously extracted with ether for about 3 hr. Some solid which separated from the ether extract was redissolved with a little chloroform and the solution was dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* left a residue weighing 220 mg. Recrystallization of this product from about 30 ml. of ethyl acetate gave 90 mg. of purified material, m.p. 261–262°. The melting point of a mixture of this material with an authentic sample of 3-acetamido-7-acetoxy-4-hydroxy-8-methylcoumarin was 261–262°.

Acid Hydrolysis of 3-Acetamido-7-acetoxy-4-hydroxy-8-methylcoumarin. 3-Amino-4,7-dihydroxy-8-methylcoumarin Hydrochloride (VII).—A slurry of 1.0 g. of 3-acetamido-7-acetoxy-4-hydroxy-8-methylcoumarin in a mixture of 50 ml. of purified dioxane and 50 ml. of 2.5 *N* hydrochloric acid was refluxed for 1 hr. The solid dissolved during the reflux period, and the red solution was concentrated *in vacuo* until most of the dioxane had been removed. The orchid colored precipitate was collected on a filter and weighed 660 mg., m.p. 300°. A solution of this solid in 50 ml. of absolute ethanol was treated with Darco and after addition of 50–60 ml. of ether was diluted with 300–400 ml. of petroleum ether (b.p. 40–60°) giving a cloudy solution. Again orchid colored, 570 mg. of the product separated. Another recrystallization from ethanol–petroleum ether gave 400 mg. of a pink solid melting above 330°; $\lambda_{max}^{0.1N\ HCl}$ 296 mμ (log ϵ 4.1); $\lambda_{max}^{0.1\ N\ NaOH}$ 252 mμ (log ϵ 3.8) and 343 mμ (log ϵ 4.4); λ_{max}^{Nujol} 5.86 μ (C=O); pK'_a's in 70% acetone–water 2.9, 8.4 and 11.5. This compound gave a red color with ferric chloride, a positive halogen test with silver nitrate and reduced ammoniacal silver nitrate to metallic silver.

Anal. Calcd. for $C_{10}H_{10}NO_4Cl$: C, 49.29; H, 4.14; N, 5.75; Cl, 14.55. Found: C, 48.77; H, 5.24; N, 5.30; Cl, 10.0.

Acetylation of Amine Hydrochloride (VII). 3-Acetamido-7-acetoxy-4-hydroxy-8-methylcoumarin (V).—A solution of 200 mg. of the amine hydrochloride VII in 4 ml. of pyridine containing 0.6 ml. of acetic anhydride was allowed to stand at room temperature overnight. The reaction mixture was poured into about 40 ml. of ice and water and the solution was acidified with concentrated hydrochloric acid. The resulting yellow solution was extracted continuously with ether for 3 hr. A solid, 100 mg., m.p. 260–261°, separated from the ether extract. The melting point of a mixture of this material and 3-acetamido-7-acetoxy-4-hydroxy-8-methylcoumarin was 259–261°. The ether solution after drying over anhydrous sodium sulfate was evaporated to dryness giving another 130 mg. of product. This was recrystallized from about 15 ml. of ethyl acetate giving 60 mg. of the diacetyl compound V, m.p. 260–262°.

Degradation of Dihydronovobiocic Acid with Concentrated Hydrochloric Acid–Acetic Acid. 2-Amino-2′,4′-dihydroxy-3′-methylacetophenone (VIII) and N-(2′,4′-Dihydroxy-3′-methylphenacyl)-4-hydroxy-3-(3-methylbutyl)-benzamide (IX).—A solution of 10 g. of dihydronovobiocic acid in a mixture of 125 ml. of concentrated hydrochloric acid and 250 ml. of glacial acetic acid was refluxed for 16 hr. The solution was evaporated to dryness *in vacuo* and extracted with three 100-ml. portions of boiling ether. The ether insolubles were then extracted with two 50-ml. portions of boiling ethyl acetate. The ethyl acetate-insoluble solid weighed 3.0 g., m.p. 256–266° dec., and was water soluble. It gave a strong halogen test with silver nitrate and reduced ammoniacal silver nitrate to metallic silver. A 2.4-g. sample of this product was dissolved in 200 ml. of hot 95% ethanol containing 5 ml. of water; 200 ml. of purified dioxane was added and the solution was allowed to stand overnight at 3–5°. The crystalline 2-amino-2′,4′-dihydroxy-3′-methylacetophenone (VIII), 1.55 g., m.p. 255–263° dec., was collected on a filter. Evaporation of the filtrate to 50 ml., followed by addition of 50 ml. of dioxane gave a second crop, 1.05 g., m.p. 248–258° dec. A sample

(12) C. F. Spencer, C. H. Stammer, J. O. Rodin, E. Walton, F. W. Holly and K. Folkers, THIS JOURNAL, **78**, 2655 (1956); C. F. Spencer, C. H. Stammer, J. O. Rodin, E. Walton, F. W. Holly and K. Folkers, *ibid.*, in press.

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.

Acknowledgment.—The authors wish to thank Mr. J. J. Wittick, Mr. H. Murphy, Jr., and Mr. F. A. Bacher for potentiometric titrations and ultraviolet absorption spectra, and Mr. R. N. Boos and his associates for the microanalyses.

(13) R. Robinson and R. C. Shah, *J. Chem. Soc.*, 1491 (1934), report m.p. 88–90°.

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

BY CLAUDE F. SPENCER, JOHN O. RODIN, EDWARD WALTON, FREDERICK W. HOLLY AND KARL FOLKERS

RECEIVED AUGUST 23, 1957

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]

(1) J. W. Hinman, H. Hoeksema, E. L. Caron and W. G. Jackson, THIS JOURNAL, **78**, 1072 (1956).

(2) C. H. Shunk, C. H. Stammer, E. A. Kaczka, E. Walton, C. F. Spencer, A. N. Wilson, J. W. Richter, F. W. Holly and K. Folkers, *ibid.*, **78**, 1770 (1956).

(3) H. Hoeksema, E. L. Caron and J. W. Hinman, *ibid.*, **78**, 2019 (1956).

(4) J. W. Hinman, E. L. Caron and H. Hoeksema, *ibid.*, **79**, 3789 (1957).

(5) C. H. Stammer, E. Walton, A. N. Wilson, R. W. Walker, N. R. Trenner, F. W. Holly and K. Folkers, *ibid.*, **80**, 137 (1958).

(6) E. A. Kaczka, C. H. Shunk, J. W. Richter, F. J. Wolf, M. M. Gasser and K. Folkers, *ibid.*, **78**, 4125 (1956).

(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.