[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF UTAH]

Study of 2-Naphthol–Hexamethylenetetramine Condensation Products

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Evidence is presented regarding the structure of products from the condensation of 2-naphthol with hexamethylenetetramine and their possible relationship. N,N-Bis-(2-naphthoxymethyl)-amine (III) was found to rearrange to N,N-bis-(2-hydroxy-1-naphthylmethyl)-amine (II) by heating in the presence of acids. The amide IV corresponding to III is shown to undergo an analogous rearrangement.

The reaction of phenolic compounds with hexamethylenetetramine has served as an attractive source of synthetic intermediates. Such condensations also have been used in model studies directed toward the determination of structure of phenol–formaldehyde polymers from novolacs and hexamethylenetetramine. The type of product obtained has been shown to depend upon the temperature employed, nature of the phenolic compound and particularly on the reaction medium. Duff and Bills[2] reported that 2-naphthol reacted with hexamethylenetetramine in hot glacial acetic acid to form a Schiff base, I. Under similar conditions except that the solvent was equal parts of ethanol and acetic acid, use of 1-naphthol resulted in a compound assigned the structure bis-(1-naphthoxymethyl)-amine. When 2-naphthol was heated with hexamethylenetetramine in aqueous ethanol, the only product isolated was bis-(2-hydroxy-1-naphthyl)-methane. In contrast Betti[3] found that condensation of 2-naphthol with formaldehyde and alcoholic ammonia yielded tris-(2-hydroxy-1-naphthylmethyl)-amine. An attractive general synthesis of hydroxy-aromatic aldehydes devised by Duff[4] involved the reaction of phenols with hexamethylenetetramine at 150–160° in anhydrous glycerol containing glyceroboric acid. Later work[5] showed that reaction of 2-naphthol with hexamethylenetetramine in 2-ethoxyethanol containing boric acid gave bis-(2-hydroxy-1-naphthylmethyl)-amine (II). Analogous *o*-hydroxyarylmethylamines resulted with several other phenolic compounds, but 1-naphthol was an exception in that a *p*-hydroxy derivative, bis-(1-hydroxy-4-naphthylmethyl)-amine, was obtained. Related work by Zinke,[6a] Zigeuner,[6b] and Hultzsch[6c] showed that condensation of 2,4-disubstituted phenols with hexamethylenetetramine gave bis- or tris-(3,5-disubstituted-2-hydroxybenzyl)-amines or bis-(3,5-disubstituted-2-hydroxyphenyl)-methanes, depending upon reaction conditions.

Galimberti[7] reported that 2-naphthol condensed with hexamethylenetetramine in ethanol to form bis-(2-naphthoxymethyl)-amine (III). This result was of interest in view of work in this Laboratory[8] which showed that condensation of primary amines and formaldehyde under similar conditions yielded bis-(2-hydroxy-1-naphthylmethyl)-alkylamines. A related compound, α,α-bis-(1-naphthylethyl)-amine, was obtained indirectly in a study of the condensation of 2-naphthol with acetaldehyde ammonia.[9]

In view of these results and in connection with a study of phenol–formaldehyde polymers, the present work was undertaken to investigate the relationship of the nitrogen containing products from 2-naphthol and hexamethylenetetramine. Galimberti[7] assigned the structure III on the basis that the product was not soluble in aqueous sodium hydroxide and formed only a monoacetyl derivative. However, Burckhalter[10] showed that certain *o*-dialkylaminomethylphenols were insoluble in 5% aqueous sodium hydroxide while the corresponding isomeric *p*-dialkylaminomethylphenols were soluble. Since alkali insolubility is not a good criterion for the absence of a free hydroxyl group in such compounds, our attention was directed to the acetylation of the product from the condensation of 2-naphthol with hexamethylenetetramine in refluxing ethanol. Treatment of this compound with acetic anhydride in pyridine yielded either of two products depending upon the method of isolation. Dilution of the reaction mixture with petroleum ether yielded a monoacetyl derivative melting at 150–151° (IV). Use of water in place of petroleum ether resulted in a monoacetyl derivative V, which melted at 194–196°. In both instances high yields were obtained. Galimberti[7] reported a melting point of 164° for a product assigned the structure IV and obtained by reaction of III with acetic anhydride followed by quenching of the reaction mixture in water. Investigation of IV showed that while it was stable in boiling toluene, it could very readily be rearranged to V by heating either in pyridine or in an ethanol solution containing acetic acid or a trace of hydrochloric acid. It would appear from this that the product (m.p. 164°) obtained by Galimberti[7] may be a mixture of IV and V. The fact that a mixture of the two had a melting point intermediate between the values for the pure compounds lends support to this conjecture.

The presence of two free hydroxyl groups in V was shown through the preparation of the diacetate, VI. Upon treatment with a dilute aqueous methanol solution of sodium hydroxide, VI was deacetylated to V. Further evidence regarding the structure of V was obtained through an independent synthesis. Duff and Bills[2] showed that the Schiff base

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(1) (a) University of Utah Research Committee Fellow; (b) Atomic Energy Commission Fellow.

(2) J. C. Duff and E. J. Bills, *J. Chem. Soc.*, 1305 (1934).

(3) M. Betti, *Gazz. chim. ital.*, [I] **34**, 212 (1904); *J. Chem. Soc.*, **86**, 581 (1904).

(4) J. C. Duff, *ibid.*, 547 (1941).

(5) J. C. Duff and V. I. Furness, *ibid.*, 1512 (1951).

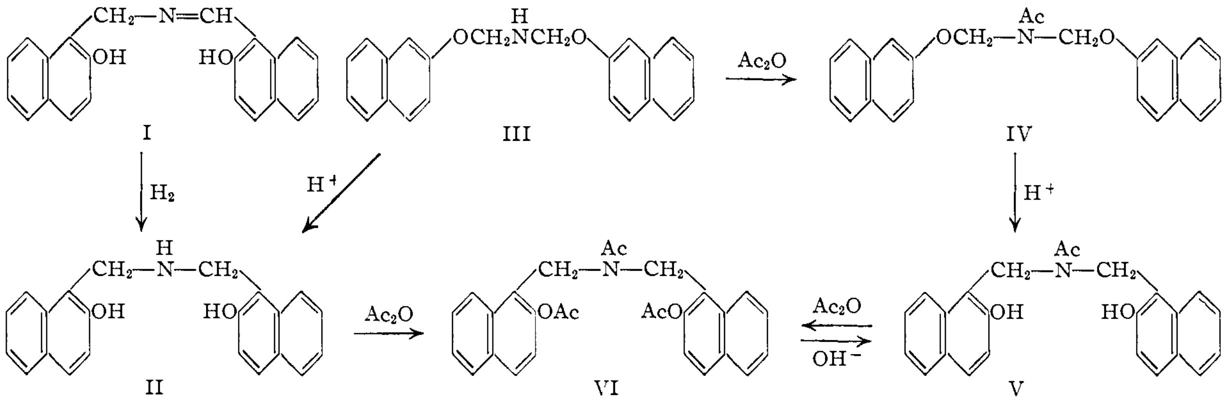
(6) (a) A. Zinke and St. Pucker, *Monatsh.*, **79**, 26 (1948); (b) G. Zigeuner and Th. Volker, *ibid.*, **83**, 100 (1952); (c) K. Hultzsch, *Ber.*, **82**, 16 (1949).

(7) P. Galimberti and C. Erba, *Gazz. chim. ital.*, **77**, 375 (1947).

(8) W. J. Burke, M. J. Kolbezen and C. W. Stephens, THIS JOURNAL, **74**, 3601 (1952).

(9) W. J. Burke and R. J. Reynolds, *ibid.*, **76**, 1291 (1954).

(10) J. H. Burckhalter, F. H. Tendick, E. M. Jones, W. F. Holcomb and A. L. Rawlins, *ibid.*, **68**, 1894 (1946).

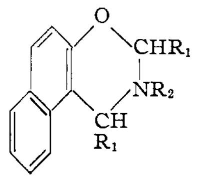


from the condensation 2-naphthol with hexamethylenetetramine in hot acetic acid gave 2-hydroxy-1-naphthaldehyde on hydrolysis but did not establish the structure of the amine obtained simultaneously. Reaction of the latter with piperidine resulted in the formation of 1-piperidinomethyl-2-naphthol[11] in an amine exchange reaction. This indicated that the aminomethyl group in the basic product from the hydrolysis of I was in the 1-position of 2-naphthol. Condensation of 1-aminomethyl-2-naphthol with 2-hydroxy-1-naphthaldehyde gave the Schiff base I, which was identical with that obtained from 2-naphthol and hexamethylenetetramine. Reduction of I with hydrogen in the presence of platinum oxide and hydrogen chloride resulted in the hydrochloride of II. Reaction of II with acetic anhydride in pyridine gave VI, which was identical with the product obtained by the acetylation of V.

The diacetate VI prepared from II gave V upon hydrolysis in dilute alcoholic sodium hydroxide at room temperature. The product prepared by Duff[5] from 2-naphthol and hexamethylenetetramine in 2-ethoxyethanol containing boric acid and assigned the structure II melted over a wide range (170–178°). Study of this product showed that the melting point range varied considerably with the purification procedure employed. However, the assigned structure was confirmed by conversion to VI, identical with that obtained from V and from the reduction product of I. Acetylation of I followed by catalytic hydrogenation gave the amide, V, the reduction being accompanied by a shift of acetyl from oxygen to nitrogen. An attempted direct preparation of V by reaction of 2-naphthol with formaldehyde and acetamide resulted in a 68% yield of bis-(2-hydroxynaphthyl)-methane.

Duff and Bills[2] reported that bis-(1-naphthoxymethyl)-amine from 1-naphthol and hexamethylenetetramine was hydrolyzed with dilute sulfuric acid to yield formaldehyde, ammonia and a resinous product. In view of this and the ease with which IV was rearranged to V, it was of interest to study the stability of III. Reaction of III with boiling methanol containing concentrated hydrochloric acid gave an almost quantitative yield of a hydrochloride. Treatment of the latter with pyridine in methanol resulted in the regeneration of III. However, heating of III in 2-ethoxyethanol containing boric acid resulted in rearrangement to II. Refluxing in butanol-1 containing concentrated hydrochloric acid also converted III to II. These results suggest the possibility that III may be an intermediate in the preparation of I and II, which have been isolated as the major products of the condensation of hexamethylenetetramine with 2-naphthol under selected conditions. Duff[5] showed that II could be obtained directly in refluxing 2-ethoxyethanol containing boric acid and that II upon reaction with hexamethylenetetramine in acetic acid gave I.

In comparison with related compounds having an –O–C–N– linkage, III resembled VIIa, from 2-naphthol and acetaldehyde ammonia,[9] more than VIIb, from 2-naphthol, formaldehyde and methylamine[8] with regard to stability to acids. III was recovered unchanged after treatment with hot aqueous sodium hydroxide.



VIIa, $R_1 = CH_3$; $R_2 = H$
VIIb, $R_1 = H$; $R_2 = CH_3$

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Experimental

Bis-(2-naphthoxymethyl)-amine (III).—This compound prepared from 2-naphthol and hexamethylenetetramine in refluxing 95% ethanol as described by Galimberti,[7] melted at 161–162° after repeated recrystallization from hot ethyl acetate or after recrystallization from N,N-dimethylformamide–methanol at room temperature; lit.[7] m.p. 168°.

Anal. Calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81. Found: C, 79.98; H, 5.80.

The **hydrochloride** was prepared in essentially quantitative yield by addition of concentrated hydrochloric acid to a suspension of III in boiling methanol; m.p. 205–208°, after recrystallization from boiling methanol.

Anal. Calcd. for $C_{22}H_{20}ClNO_2$: Cl, 9.69. Found: Cl, 9.68.

To a solution of 4.3 g. of the hydrochloride in 25 ml. of warm pyridine was added 75 ml. of methanol. The resulting free base (3.2 g.) melted at 160–162° and did not depress the m.p. of III prepared directly from 2-naphthol and hexamethylenetetramine.

N,N-Bis-(2-naphthoxymethyl)-acetamide (IV).—Bis-(2-naphthoxymethyl)-amine (III, 5 g., 0.015 mole) was treated with 30 ml. of pyridine containing 10 ml. of acetic anhydride. After four days at room temperature, 100 ml. of

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(11) W. T. Caldwell and T. R. Thompson, This Journal, **61**, 2354 (1939).

petroleum ether (b.p. 30–60°) was added. The resulting crystalline product (4.2 g.) was removed by filtration and washed with petroleum ether; m.p. 148–150°; yield 75%. The compound was insoluble in aqueous alkali and melted at 150–151° after recrystallization from benzene–petroleum ether (3:1 by volume).

Anal. Calcd. for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.93; H, 5.46; N, 3.70.

Galimberti[7] reported a m.p. of 164° for a product assigned the structure IV. A mixture of approximately equal amounts of IV and V (m.p. 194–196°) melted at 178–181°.

Synthesis of V from III.—N,N-Bis-(2-naphthoxymethyl)-amine (III, 14 g.) was treated with 20 ml. of acetic anhydride in 100 ml. of pyridine for two days. Methanol (20 ml.) was added and after 30 minutes 300 ml. of water was added. The white solid (15.6 g.) which separated was washed with water and recrystallized from methanol; m.p. 193–197°; yield 99%. The product was soluble in dilute aqueous alkali and did not depress the m.p. of V, prepared by the rearrangement of IV as described below.

Rearrangement of IV to V.—A solution of 2.0 g. of N,N-bis-(2-naphthoxymethyl)-acetamide in 275 ml. of 95% ethanol containing 3 ml. of acetic acid was heated under reflux for 25 minutes. Water was added to the cooled reaction mixture until crystals began to separate. The product (1.8 g., 90% yield) melted at 194–196° after recrystallization from methanol.

Anal. Calcd. for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.10; H, 6.18; N, 3.81.

IV was also rearranged to V when 0.1 g. of IV was boiled for 15 minutes in 5 ml. of ethanol containing one drop of concentrated hydrochloric acid. Treatment of IV with boiling pyridine for 15 minutes also caused rearrangement but IV was recovered unchanged when treated with boiling toluene.

N,N-Bis-(2-acetoxy-1-naphthylmethyl)-acetamide (VI).—Acetic anhydride (7 ml.) was added to 0.75 g. of N,N-bis-(2-hydroxy-1-naphthylmethyl)-acetamide (V) dissolved in 15 ml. of pyridine. After 25 hours at room temperature, the reaction mixture was diluted with 25 ml. of water and solid sodium bicarbonate was added until effervescence ceased. The solid (0.62 g.) which separated upon addition of 100 ml. of water and cooling melted at 140–142° after recrystallization from methanol-water; yield 67%.

Anal. Calcd. for $C_{28}H_{25}NO_5$: C, 73.83; H, 5.53; N, 3.08. Found: C, 73.53; H, 5.55; N, 3.06.

Deacetylation of VI to V.—One gram of N,N-bis-(2-acetoxy-1-naphthylmethyl)-acetamide (VI), prepared by acetylation of V, was dissolved in a solution of 2 g. of sodium hydroxide in 25 ml. each of methanol and water. After two hours the mixture was acidified with 5 ml. of concentrated hydrochloric acid and neutralized with sodium bicarbonate. The solid (0.62 g., 76% yield) which separated on addition of the reaction mixture to a large volume of water was recrystallized from N,N-dimethylformamide–methanol and then from ethyl acetate; m.p. 195–196°. The product did not depress the m.p. (194–196°) of V prepared by rearrangement of IV.

1-Piperidinomethyl-2-naphthol.—The amine hydrochloride (0.48 g.) obtained by the hydrolysis of the Schiff base I according to Duff and Bills[2] was dissolved in 25 ml. of piperidine and the solution heated under reflux for two hours. The volume of the reaction mixture was reduced to 10 ml. and 10 ml. of ethanol was added. The solid (0.17 g.) which separated upon cooling melted at 94–96°, after recrystallization from methanol. An additional 0.26 g. of product was obtained from the mother liquor; yield 69%. The m.p. was not depressed when the product was mixed with 1-piperidinomethyl-2-naphthol (m.p. 94–96°).[11]

Synthesis of I from 1-Aminomethyl-2-naphthol.—Addition of 3.0 g. of 2-hydroxy-1-naphthaldehyde (0.0174 mole) to an ether solution of 3.0 g. of 1-aminomethyl-2-naphthol (0.0174 mole) resulted in an immediate yellow precipitate. Benzene was added and water was removed by azeotropic distillation. The mixture was cooled and the product (1.55 g., 47% yield) separated by filtration; m.p. 221° dec.[12] The m.p. was not depressed by admixture with the product (m.p. 220 dec.) prepared from 2-naphthol and hexamethylenetetramine according to Duff and Bills.[2]

The yellow **hydrochloride** melted at 208–210° dec. after recrystallization from acetone–methanol.

Anal. Calcd. for $C_{22}H_{18}ClNO_2$: Cl, 9.74. Found: Cl, 9.53.

Reduction of I to II.—A mixture of 5 g. of the Schiff base I, 200 ml. of methanol, 7.5 ml. of concentrated hydrochloric acid and 250 mg. of Adams catalyst was shaken for three hours under an initial hydrogen pressure of 2.7 atm. The catalyst was removed by filtration and the filtrate concentrated to a volume of 20 ml. The solid (4.2 g.) which separated on cooling was recrystallized from a methanol-benzene solution which was saturated with hydrogen chloride; m.p. 207–209° dec., yield 83%.

Anal. Calcd. for $C_{22}H_{20}ClNO_2$: Cl, 9.69. Found: Cl, 9.62, 9.73.

The free base was obtained by addition of pyridine to a methanol solution of the hydrochloride; m.p. 145° dec. after several recrystallizations from dimethylformamide-methanol and drying at room temperature. After drying at 78° (0.1 mm.), the compound began to discolor at 150° and melted[13] at 162–167°; lit.[5] m.p. 170–178°.

Anal. Calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81. Found: C, 80.48; H, 6.39.

Acetylation of II.—To a suspension of 1.9 g. of bis-(2-hydroxy-1-naphthylmethyl)-amine (II, m.p. 145°, prepared from I) in 25 ml. of pyridine was added 5 ml. of acetic anhydride. The solid dissolved slowly and after two days at room temperature the reaction mixture was neutralized with aqueous sodium bicarbonate. The resulting precipitate (2.6 g., 99% yield) was removed by filtration and washed with water; m.p. 140° after recrystallization from methanol-water. The m.p. was not depressed when the product was mixed with VI prepared from V as described above.

The product (1.3 g.) was treated at room temperature for two hours with potassium hydroxide in aqueous methanol. The reaction mixture was acidified with hydrochloric acid, neutralized with sodium bicarbonate and diluted with water. The solid (1.0 g., 94% yield) which separated melted at 195–196° after recrystallization from ethyl acetate and did not depress the m.p. of V prepared by rearrangement of IV.

Acetylation of II (m.p. 165–175°; lit.[5,13] m.p. 170–178°), prepared according to Duff and Furness,[5] by the above procedure gave a product (m.p. 140–142°) which did not depress the m.p. of VI prepared from V.

Acetylation of I.—Acetic anhydride (6.4 ml.) was added to a warm mixture containing 10 g. of N-(2-hydroxy-1-naphthylmethylene)-1-aminomethyl-2-naphthol (I), 2.5 g. of sodium hydroxide, 30 ml. of dioxane and 10 ml. of water. The reaction mixture was extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate and concentrated to a volume of 25 ml. Benzene was then added and the solvent removed under reduced pressure. The yellow diacetate (9.2 g., 73% yield) melted at 143–145° after recrystallization from benzene.

Anal. Calcd. for $C_{26}H_{21}NO_4$: C, 75.90; H, 5.15. Found: C, 75.84; H, 5.68.

Conversion of I Diacetate to V.—A solution of 7 g. of N-(2-acetoxy-1-naphthylmethylene)-1-aminomethyl-2-naphthyl acetate in 100 ml. of ethyl acetate and 500 mg. of Adams catalyst was shaken for 45 minutes under an initial hydrogen pressure of 2.7 atm. The precipitated product and catalyst were removed by filtration and the organic material separated by extraction with a mixture of acetone and N,N-dimethylformamide. Most of the solvent in the filtrate was removed by evaporation in a stream of cold air. A solid product (6.25 g., 98% yield) was obtained by adding the residue to water; m.p. 193–195°, after recrystallization from methanol-water. The product did not depress the m.p. of V (m.p. 194–196°), prepared by rearrangement of IV.

Anal. Calcd. for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70. Found: C, 77.13; H, 5.93.

Reaction of 2-Naphthol with Formaldehyde and Acetamide.—A methanol (120 ml.) solution containing 14.4 g. of 2-naphthol (0.10 mole), 7.5 ml. of 37% aqueous formaldehyde (0.10 mole) and 3 g. of acetamide (0.05 mole) was heated under reflux for six hours. The product (12.4 g.)

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[12] Duff and Bills[2] did not record a m.p. for their product.

[13] The m.p. of this compound was found to vary considerably with the solvent used for recrystallization and the drying conditions employed.

which separated on cooling melted at 200° after recrystallization from methanol. The m.p. was not depressed by mixing with a specimen of bis-(2-hydroxy-1-naphthyl)-methane (lit.[14] m.p. 200°); yield 84%.

Rearrangement of III to II. Procedure A.—A solution of 2 g. of N,N-bis-(2-naphthoxymethyl)-amine (III) in 40 ml. of 2-ethoxyethanol containing 4 g. of boric acid was heated under reflux for two hours. The cooled reaction mixture was poured slowly into 150 ml. of cold water and the resulting precipitate (1.67 g., 83%) removed by filtration; m.p. 178–190°, after recrystallization from acetone-water.[13]

Acetylation of the product at room temperature with acetic anhydride gave a derivative melting at 139–141° after recrystallization from methanol–water. The m.p. was not depressed when the derivative was mixed with an authentic specimen of VI.

Treatment of the acetyl derivative (m.p. 139–141°) with sodium hydroxide in methanol at room temperature followed by acidification gave a solid (69% yield) melting at 194–196° after recrystallization from methanol–water. The m.p. was not depressed when the product was mixed with an authentic specimen of V.

Procedure B.—A solution of 2 g. of N,N-bis-(2-naphthoxymethyl)-amine (III) in 50 ml. of butanol-1 containing 5 ml. of concentrated hydrochloric acid was heated under reflux for three hours. The crystalline product obtained by concentration and cooling of the reaction mixture was removed by filtration and washed with acetone and ether; m.p. 197–204°; yield 1.5 g. (68%). A solution of the product (0.85 g.) in 25 ml. of methanol and 10 ml. of pyridine was added to 150 ml. of water. The resulting solid (0.55 g.) was removed by filtration and washed successively with water, ethanol, and ether in that order; m.p. 141–145°.[13] The m.p. was not depressed when the product was mixed with a sample of N,N-bis-(2-hydroxy-1-naphthylmethyl)-amine (II) prepared by reduction of I.

Treatment of the product with acetic anhydride in pyridine gave a solid (m.p. 139–141°) which did not depress the m.p. of VI.

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[14] K. Fries and H. Hubner, *Ber.*, **39**, 439 (1906).

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Erythromycin. VII. The Structure of Cladinose[1]

BY PAUL F. WILEY AND OLLIDENE WEAVER

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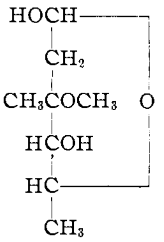
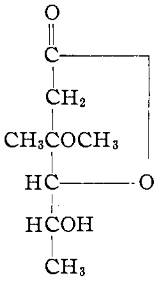
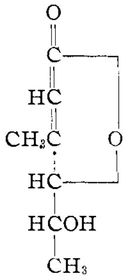
Cladinose, the nitrogen-free sugar from erythromycin, has been degraded to acetaldehyde and β-formylcrotonic acid, thus showing cladinose to have structure I.



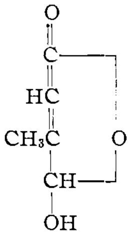
I



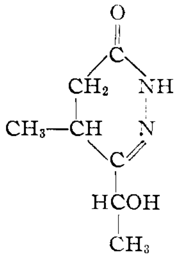
II



III



IV



V

The isolation of cladinose from erythromycin has been reported previously.[2,3] Cladinose was shown to have the composition $C_8H_{16}O_4$ and to contain two C–CH_3 groups, two hydroxyl groups and one methoxyl group. Evidence was presented which showed the presence of a hemiacetal grouping and the moiety CH_3CHO– with participation of this oxygen in the hemiacetal ring. These facts and material presented in this paper prove that cladinose has structure I.[4]

Oxidation of cladinose with aqueous bromine gave rise to a lactone II. This compound was never obtained pure as it lost the methoxyl group on distillation. However, the infrared spectrum of II showed absorption at 2.90 and 5.65 μ with a shoulder at 5.81 μ which is consistent with a hydroxy-γ-lactone having a smaller amount of a δ-lactone present. The lactone was characterized as its 3,5-dinitrobenzoate which was a derivative of a γ-lactone (absorption at 5.63 μ in the infrared).

Treatment of II with 5% sodium hydroxide solution followed by neutralization eliminated the methoxyl group and formed an unsaturated lactone III. This lactone was not completely purified due to decomposition on distillation nor was a completely unambiguous derivative formed, but there is considerable evidence to indicate structure III. The impure product had absorption in the ultraviolet at 212 mμ, ϵ 10,000, consistent with an α,β-unsaturated lactone. The infrared absorption curve showed hydroxyl absorption at 3.0 μ, mixed γ- and δ- lactone absorption at 5.6–5.8 μ and $>C{=}C<$ absorption at 6.1 μ. Methoxyl analysis indicated the absence of such a group. Reaction of the unsaturated lactone with hydrazine formed a crystalline derivative which has the composition $C_7H_{12}N_2O_2$. It was concluded that this product has structure V because of its analysis and the great similarity of its ultraviolet spectrum to that of 4,5-dihydro-6-methyl-3(2H)-pyridazone. Both compounds absorbed at 242 mμ with V having ϵ 7520

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[1] A preliminary report of this work was published as a Communication to the Editor: see P. F. Wiley and O. Weaver, THIS JOURNAL, **77**, 3422 (1955).

[2] E. H. Flynn, M. V. Sigal, Jr., P. F. Wiley and K. Gerzon, *ibid.*, **76**, 3121 (1954).

[3] R. B. Hasbrouck and F. C. Garven, *Antibiotics & Chemotherapy*, **3**, 1040 (1953).

[4] No indication of absolute or relative configurations is intended in the formulas.