TABLE I

Compound	Yield, %	M. p., °C., cor.	Nitrogen, % Calcd.	Nitrogen, % Found
m-$NO_2C_6H_4CHOHCOOCH_3$	80	66	6.63	6.50
m-$NO_2C_6H_4CHOHCOOC_2H_5$[a]	85	63	...	...
m-$NO_2C_6H_4CHOHCOOC_3H_7$-*n*	63	73	5.85	5.71
m-$NO_2C_6H_4CHOHCOOC_3H_7$-*i*	52	57	5.85	5.73
m-$NO_2C_6H_4CHOHCOOC_4H_9$-*n*	31	65	5.53	5.45
m-$NH_2C_6H_4CHOHCOOCH_3$	54	139	7.73	7.65
m-$NH_2C_6H_4CHOHCOOC_2H_5$	72	55	7.18	7.25
m-$NH_2C_6H_4CHOHCOOC_3H_7$-*n*	31	101	6.69	6.58
m-$NH_2C_6H_4CHOHCOOC_3H_7$-*i*	42	146	6.69	6.57
m-$NH_2C_6H_4CHOHCOOC_4H_9$-*n*	23	110	6.27	6.32
m-$NH_2C_6H_4CHOHCOOC_2H_4N(C_2H_5)_2$	36	...	...	...
m-$NH_2C_6H_4CHOHCOOC_2H_4N$-$(C_2H_5)_2 \cdot HCl$	41	133	9.26	9.30
m-$NO_2C_6H_4CHOHCOOC_2H_4Cl$	63	76	5.39	5.44
m-$NH_2C_6H_4CHOHCOOC_2H_4Cl$	54	91	6.08	5.92

[a] Synthesized by Beyer, *J. prakt. Chem.*, **31**, 391 (1885).

The acid solution was evaporated to dryness in a vacuum desiccator and light brown crystals of the hydrochloride were obtained. The free base was unstable and was not analyzed as such. The physical constants and results of the analysis of the compounds prepared appear in the table.

Summary

The simple alkyl esters and the β-diethylaminoethyl ester of *m*-nitro- and *m*-aminomandelic acid have been synthesized. The local anesthetic activity of the esters with the amino group in the meta position was found to be much less than that of the corresponding para amino derivatives previously prepared.

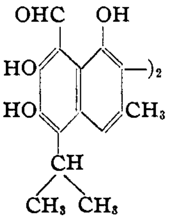
CHICAGO, ILLINOIS RECEIVED JANUARY 20, 1941

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

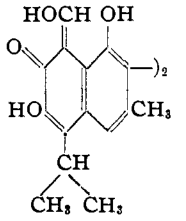
The Reactions of 2,8-Dihydroxynaphthaldehyde

BY ROGER ADAMS AND D. E. BURNEY[1]

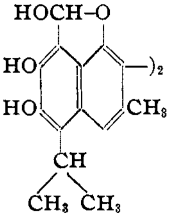
Gossypol has been demonstrated to have structure I.[2] With various reagents it gives derivatives of one of three tautomeric forms (I, II or III).



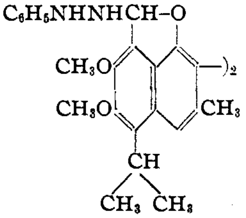
I



II



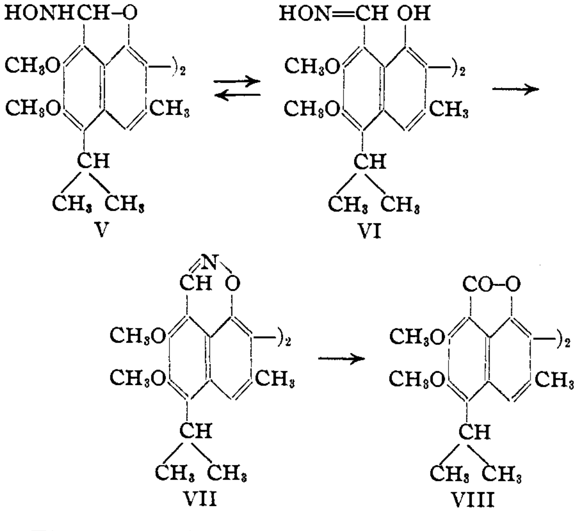
III



IV

Anhydrogossypol is derived from Formula II by loss of water between the peri groups, and gossypol hexamethyl ether has Formula III as its parent nucleus.

Treatment of gossypol hexamethyl ether with phenylhydrazine or hydroxylamine in ethanol solution failed to result in any reaction, but in acetic acid derivatives are obtained in which one methoxyl group in each half of the molecule has been eliminated (IV).[3] In the case of hydroxylamine two molecules of water also are lost with formation of orthoxazine rings; the sequence of the reactions involved is shown in Formulas V–VII.[2] Alkaline hydrolysis of the orthoxazine (VII) followed by treatment with acetic acid resulted in formation of the lactone (VIII); the mechanism of the conversion has been discussed in a previous communication.



V VI VII VIII

The present investigation was undertaken to discover whether the reactions just described were typical of any 2,8-dihydroxynaphthaldehyde or whether they were dependent as well on the pres-

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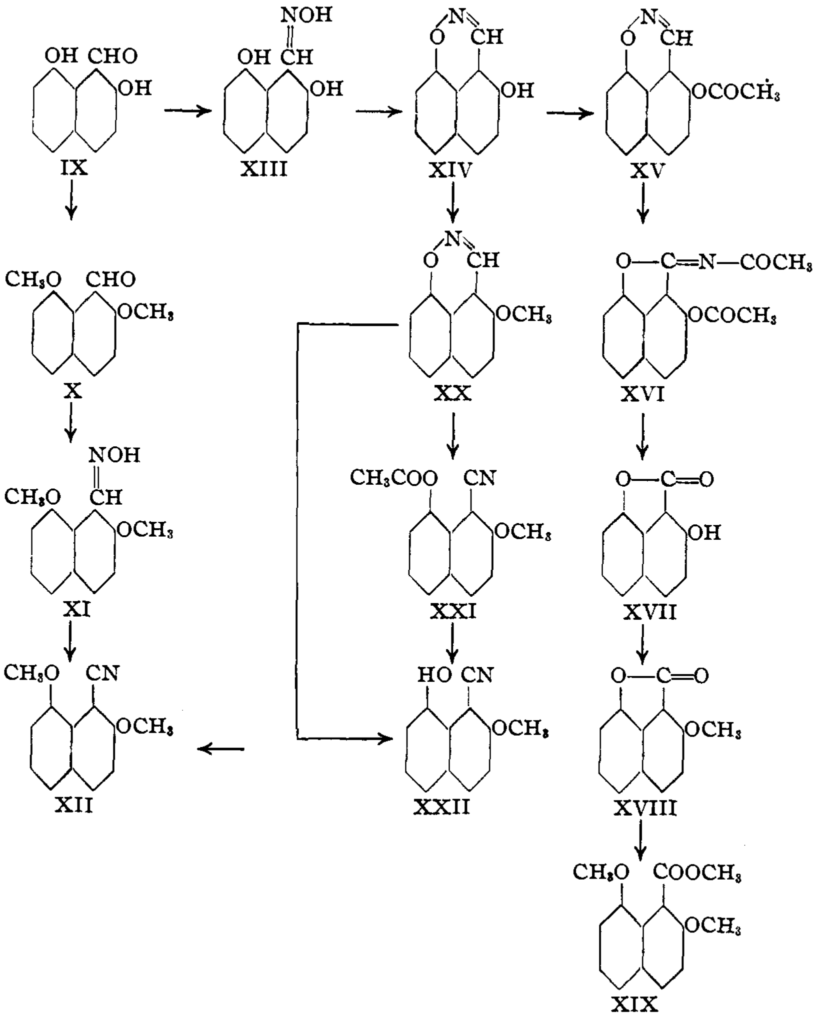
[1] In partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

[2] Adams, Morris, Geissman, Butterbaugh and Kirkpatrick, THIS JOURNAL, **60**, 2193 (1938).

[3] Adams and Geissman, *ibid.*, **60**, 2166 (1938).

ence of one or more other substituents as found in the gossypol molecule.



By the introduction of an aldehyde group into 2,8-dihydroxynaphthalene, one of the products is 2,8-dihydroxynaphthaldehyde (IX) which was used for the present study. This compound does not dehydrate under the conditions used in the formation of anhydrogossypol from gossypol of tautomeric structure III. It methylates readily to a dimethyl ether (X) which reacts with phenylhydrazine in ethanol (thus differing from gossypol hexamethyl ether) or in acetic acid with loss of a molecule of water and formation of a phenylhydrazone. Both methoxyls are retained in the product, thus demonstrating the absence of an acetal methoxyl. Similarly, a normal oxime of the dimethyl ether (XI) is formed from hydroxylamine. This derivative is dehydrated readily to the corresponding nitrile (XII).

2,8-Dihydroxynaphthaldehyde (IX) also gives a normal phenylhydrazone and oxime. The latter (XIII), which was obtained only in a single form, undergoes several interesting reactions. In cold acetic anhydride it dehydrates to the orthoxazine (XIV); upon warming with acetic anhydride acetylation of the hydroxyl occurs next with formation of the orthoxazine acetate (XV); refluxing with acetic anhydride and anhydrous sodium acetate converts this latter product to a diacetate which is postulated as having structure XVI because of its reactions.

By the action of cold concentrated hydrochloric acid compound XVI is hydrolyzed probably through an imido ether to an hydroxy lactone (XVII) identified by acetylation to a monoacetate and by methylation with diazomethane to the monomethyl ether (XVIII) which in turn, by means of alkali and dimethyl sulfate, gives methyl 2,8-dimethoxynaphthoate (XIX).

The hydroxy orthoxazine (XIV) methylates with dimethyl sulfate in acetone and potassium carbonate to the corresponding methyl ether (XX) which, with acetic anhydride and sodium acetate, is transformed to the monoacetate (XXI). The suggested formula for this latter compound is that of a nitrile rather than of an isomeric imido ether similar to XVI as judged by its conversion by means of cold concentrated hydrochloric acid to 2-methoxy-8-hydroxynaphthonitrile (XXII). By means of ethanolic potassium hydroxide followed by acetic acid, compound XX is hydrolyzed directly to compound XXII. The presence of an hydroxyl group in compound XXII is indicated by the color with ferric chloride and by methylation with dimethyl sulfate and potassium carbonate in acetone to 2,8-dimethoxynaphthonitrile previously prepared by an unequivocal method.

Thus, it is probable that compound XXII does not have the tautomeric imido ether stucture and hence obvious that the reactions of the acetoxy orthoxazine (XV–XIX) and of the methoxy orthoxazine (XX–XXII) follow different courses with the same reagents. It appears that the presence of the 2-methoxyl hinders or prevents the tautomerization of the phenolic nitrile to the corresponding imido ether.

Like gossypol, the 2,8-dihydroxynaphthaldehyde may be converted to an orthoxazine ring from which by hydrolysis a peri-lactone is obtained providing the 2-position is not substituted by a methoxyl group. The orthoxazine formation in gossypol and in the naphthaldehyde is best explained on the assumption of the normal form of the hydroxy aldehyde. Those reactions of gossypol which result in derivatives of tautomeric forms (II and III) either did not take place at all with 2,8-dihydroxynaphthaldehyde, or followed a course to be expected of the normal form of the aldehyde. Thus, it may be deduced that merely the presence of the 2-hydroxyl group in 2,8-dihydroxynaphthaldehyde is not effective in causing facile tautomerization of the aldehyde group. It appears likely that an additional hydroxyl in the 3-position as found in gossypol is also necessary for activation of the aldehyde group.

In the initial experiments on 2,8-dihydroxynaphthaldehyde, unusual difficulty was encountered; the yields of products were low, and oily or colored by-products were present. It was not until the discovery was made that unusually mild conditions were necessary that excellent yields of pure derivatives were obtained.

Experimental

2,8-Dihydroxynaphthalene.—This was prepared by the method of Emmert[4] and Morgan and Vining.[5] The yield from crude commercial β-naphthol-8-sulfonic acid was 27–30%.

2,8-Dihydroxynaphthaldehyde.—The Gattermann reaction was used on 2,8-dihydroxynaphthalene.[6] Instead of hydrogen cyanide, zinc cyanide and hydrochloric acid was substituted.[7] The 2,8-dihydroxynaphthaldehyde was extracted from the isomeric by-product 4,6-dihydroxynaphthaldehyde by means of boiling benzene; yield, 34–38%.

2,8-Dihydroxynaphthaldoxime.—In a 200-cc. round-bottomed flask was placed a mixture of 10 g. of 2,8-dihydroxynaphthaldehyde, 10 g. of hydroxylamine hydrochloride, 40 cc. of 10% sodium hydroxide, and 75 cc. of water. It was heated on a steam cone, ethanol was added until solution was complete, and heating the red solution was continued for fifteen minutes. After filtration and cooling in ice the oxime precipitated in golden-yellow needle crystals. It was purified by recrystallization from dilute ethanol, m. p. 161–162° (cor.) with decomposition; yield, 9.5 g. (87%). Only a very small additional amount of product could be obtained from the mother liquors.

Anal. Calcd. for $C_{11}H_9O_3N$: C, 65.00; H, 4.43; N, 6.90. Found: C, 65.08; H, 4.51; N, 7.05.

2-Hydroxy-*peri*-naphthoxazine.—A mixture of 2 g. of 2,8-dihydroxynaphthaldoxime and 20 cc. of acetic anhydride was shaken occasionally and allowed to stand for five hours. The oxime dissolved slowly with formation of a dark solution from which crystals separated. The entire mixture was poured onto 50 g. of ice and stirred until all of the acetic anhydride was decomposed. The brown solid remaining was separated by filtration, and washed with water. It was recrystallized by suspending the solid in 20 cc. of hot water, adding ethanol until solution was complete, decolorizing with Norit, filtering and cooling; white needles separated, m. p. 190–191° (cor.); yield, 1.2 g. (65%).

Anal. Calcd. for $C_{11}H_7O_2N$: C, 71.35; H, 3.78. Found: C, 71.64; H, 4.00.

2-Acetoxy-*peri*-naphthoxazine.—A. A mixture of 2 g. of 2,8-dihydroxynaphthaldoxime and 10 cc. of acetic anhydride was refluxed for one hour and then poured onto 50 g. of ice. After the excess of acetic anhydride had completely hydrolyzed, a brown solid remained. It was extracted twice with boiling petroleum ether (b. p. 60–110°) and if necessary the ether solution was decolorized with Norit. On cooling, white needles separated, m. p. 159–160° (cor.); yield, 1.69 g. (72%).

The material not soluble in the petroleum ether was a small amount of 2-hydroxy-*peri*-naphthoxazine which could be purified from dilute ethanol.

B. The same product could be prepared from 2-hydroxy-*peri*-naphthoxazine by a similar procedure; yield, 80%.

Anal. Calcd. for $C_{13}H_9O_3N$: C, 68.72; H, 3.97; N, 6.17. Found: C, 68.76; H, 3.95; N, 5.90.

2-Acetoxy-N-acetyl-*peri*-naphthoimidolactone.—A. A mixture of 1 g. of 2,8-dihydroxynaphthaldoxime, 1 g. of freshly fused sodium acetate and 10 cc. of acetic anhydride was refluxed for five hours, and then poured onto 50 g. of ice. After stirring until all of the excess acetic anhydride had decomposed a dark-colored solid remained. This product was extracted three times with 50-cc. portions of petroleum ether (b. p. 60–110°), the combined ether extracts decolorized with Norit, filtered and cooled. The very fine white needles which separated had a m. p. 100–101° (cor.); yield, 0.95 g. (75%).

Anal. Calcd. for $C_{15}H_{11}O_4N$: C, 66.91; H, 4.09; N, 5.20. Found: C, 66.94, 66.90; H, 4.08, 4.09; N, 5.25.

B. 2-Hydroxy-*peri*-naphthoxazine and 2-acetoxy-*peri*-naphthoxazine could be converted to this product by a similar procedure.

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[4] Emmert, *Ann.*, **241**, 371 (1887).

[5] Morgan and Vining, *J. Chem. Soc.*, **119**, 1709 (1921).

[6] Morgan and Vining, *ibid.*, **119**, 186 (1921).

[7] Adams and Levine, THIS JOURNAL, **45**, 2373 (1923).

2-Hydroxy-*peri*-naphtholactone.—A suspension of 0.50 g. of 2-acetoxy-N-acetyl-*peri*-naphthoimidolactone in 5 cc. of concentrated hydrochloric acid was allowed to stand for one day. The suspended solid went into solution slowly and dark-colored plates crystallized out. The solid which was probably 2-hydroxy-*peri*-naphthoimidolactone hydrochloride was separated by filtration through asbestos, or the solution could be diluted first and then filtered in the usual way. It was then suspended in 25 cc. of water and heated, after which it went into solution and hydrolyzed to the lactone. The lactone separated. To the hot suspension ethanol was added until solution was complete. It was then decolorized with Norit, filtered, and cooled. After two recrystallizations the product was pure, m. p. 193–194° (cor.); yield, 90%.

Anal. Calcd. for $C_{11}H_6O_3$: C, 70.97; H, 3.23. Found: C, 70.61; H, 3.58.

2-Acetoxy-*peri*-naphtholactone.—A mixture of 0.10 g. of 2-hydroxy-*peri*-naphtholactone, 5 cc. of acetic anhydride and 0.1 g. of freshly fused sodium acetate was refluxed for three hours and then poured onto 25 g. of ice. After all of the acetic anhydride had hydrolyzed, a white solid remained. This product was recrystallized from petroleum ether (b. p. 60–110°); white needles, m. p. 134–135° (cor.); yield, 90%.

Anal. Calcd. for $C_{13}H_8O_4$: C, 68.42; H, 3.51. Found: C, 68.38; H, 3.61.

2-Methoxy-*peri*-naphtholactone.—A. A mixture of 1 g. of 2-hydroxy-*peri*-naphtholactone, 1.0 g. of anhydrous potassium carbonate, 40 cc. of dry acetone, and 3 cc. of dimethyl sulfate was stirred and refluxed for four hours. After this heating, the acetone was removed by distillation and 25 cc. of water was added to dissolve the potassium carbonate and decompose the excess dimethyl sulfate. The solid which remained was filtered and then suspended in 20 cc. of hot water to which 95% ethanol was added until solution was complete. The solution was decolorized by boiling with Norit. The product separated on cooling and was purified by recrystallization from carbon tetrachloride; white crystals, m. p. 128–129° (cor.); yield, 0.8 g. (75%).

B. To an ethereal solution of diazomethane was added 0.80 g. of 2-hydroxynaphtholactone and the mixture allowed to stand for one-half hour. The ether and excess diazomethane were removed by distillation and the brown solid which remained was purified as described; yield, 0.62 g. (72%).

Anal. Calcd. for $C_{12}H_8O_3$: C, 72.00; H, 4.00; Found: C, 71.99; H, 4.02.

Methyl 2,8-Dimethoxynaphthoate.—A solution of 2.1 g. of 2-methoxy-*peri*-naphtholactone in 10 cc. of hot 10% aqueous sodium hydroxide was treated with 1 cc. of dimethyl sulfate and shaken until the dimethyl sulfate was completely hydrolyzed. Another 1 cc. of dimethyl sulfate was added and if the solution was not basic after all of the dimethyl sulfate had hydrolyzed, more 10% aqueous sodium hydroxide was added. The light brown solid which separated was filtered and washed with hot 10% aqueous sodium hydroxide and then with water and recrystallized from petroleum ether (b. p. 60–110°); white crystals, m. p. 131–132° (cor.); yield, 0.22 g. (90%).

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.29; H, 5.69. Found: C, 68.38; H, 5.75.

2-Methoxy-*peri*-naphthoxazine.—A. To an ether solution of excess of diazomethane was added 0.90 g. of 2-hydroxy-*peri*-naphthoxazine and the mixture allowed to stand for three hours. The nitrogen was liberated slowly as the material went into solution. The ether was distilled off and the brown solid which remained was recrystallized from dilute ethanol or petroleum ether (b. p. 60–110°). From the latter solvent the product crystallized as white needles, m. p. 111–112° (cor.); yield, 0.30 g. (30%). The petroleum ether insoluble residue consisted of a small amount of starting material.

B. A mixture of 1.8 g. of 2-hydroxy-*peri*-naphthoxazine, 5 g. of anhydrous potassium carbonate, 3 cc. of dimethyl sulfate and 40 cc. of dry acetone was stirred and refluxed for four hours. The acetone was then removed by distillation and 50 cc. of water added to dissolve the potassium carbonate and decompose the excess dimethyl sulfate. The light-colored solid, which remained, was filtered, washed with water and dried and extracted twice with 25-cc. portions of petroleum ether (b. p. 60–110°). Upon cooling, white crystals deposited, m. p. 111–112° (cor.); yield, 1.4 g. (75%).

The solid which was not soluble in petroleum ether was starting material which could be purified by suspending it in 10 cc. of hot water, and adding ethanol until solution was complete. This solution was decolorized with Norit, filtered, and cooled.

Anal. Calcd. for $C_{12}H_9O_2N$: C, 72.36; H, 4.52. Found: C, 72.17; H, 4.47.

2-Methoxy-8-acetoxynaphthonitrile.—A mixture of 1.25 g. of 2-methoxy-*peri*-naphthoxazine, 1 g. of freshly fused sodium acetate and 15 cc. of acetic anhydride was refluxed for five hours and then poured onto 50 g. of ice. The solid, which remained after the excess acetic anhydride had hydrolyzed, was extracted with three 25-cc. portions of petroleum ether (b. p. 60–110°). The solution was decolorized with Norit, filtered and cooled; white needles, m. p. 94.5–96°; yield, 1.10 g. (72%).

Anal. Calcd. for $C_{14}H_{11}O_3N$: C, 69.71; H, 4.56. Found: C, 69.51; H, 4.54.

2-Methoxy-8-hydroxynaphthonitrile.—A. A suspension of 0.75 g. of 2-methoxy-8-acetoxynaphthonitrile in 10 cc. of concentrated hydrochloric acid was allowed to stand at room temperature for one day. The solid did not go into solution but turned from white to gray in color. The mixture was diluted with 50 cc. of water and the gray solid filtered. It was dissolved in boiling benzene, decolorized with Norit, filtered, and an equal volume of petroleum ether (b. p. 60–110°) added to the filtrate. On cooling, very fine white needles separated, m. p. 194–195° (cor.); yield, 0.50 g. (80%).

B. A solution of 0.30 g. of 2-methoxy-*peri*-naphthoxazine in 10 cc. of 10% methanolic potassium hydroxide was allowed to stand overnight. The methanol was removed under reduced pressure at room temperature and the light brown solid which remained was dissolved in 5 cc. of glacial acetic acid. After standing for two hours, the acetic acid was removed by heating on a steam-bath under reduced pressure, the solid was washed with water and recrystallized from chloroform; white crystals, m. p. 194–195° (cor.); yield, 0.22 g. (73%).

Anal. Calcd. for $C_{12}H_9O_2N$: C, 72.36; H, 4.52; N, 7.04; OCH_3, 15.57. Found: C, 72.52; H, 4.83; N, 7.16, 7.61; OCH_3, 15.4, 15.1.

2,8-Dimethoxynaphthaldehyde.—A mixture of 3.0 g. of 2,8-dihydroxynaphthaldehyde, 5 g. of anhydrous potassium carbonate, 5 cc. of dimethyl sulfate and 50 cc. of anhydrous acetone was stirred and refluxed for five hours. The acetone was then removed by heating on a steam-bath and 100 cc. of water added to decompose excess dimethyl sulfate and dissolve the potassium carbonate. A brown solid remained. It was filtered and dissolved in hot petroleum ether (b. p. 60–110°), decolorized with Norit, filtered, and cooled; white needles, m. p. 90–91° (cor.); yield, 2.4 g. (70%).

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.22; H, 5.56. Found: C, 72.01; H, 5.59.

2,8 - Dimethoxynaphthaldehyde Phenylhydrazone.—A solution of 0.50 g. of 2,8-dimethoxynaphthaldehyde in 20 cc. of ethanol and 1 cc. of phenylhydrazine was warmed on a steam-bath for fifteen minutes and then allowed to cool slowly. The product separated. After filtration, concentration of the mother liquors yielded more product. Purified from ethanol, light yellow plates were obtained, m. p. 126–127° (cor.); yield, 0.62 g. (88%).

Anal. Calcd. for $C_{18}H_{18}O_2N_2$: C, 74.51; H, 5.88; OCH_3, 20.3. Found: C, 74.36; H, 6.08; OCH_3, 20.1, 20.0.

2,8-Dimethoxynaphthaldoxime.—A suspension of 0.50 g. of 2,8-dimethoxynaphthaldehyde in 20 cc. of water containing 0.50 g. of hydroxylamine hydrochloride and 0.50 g. of sodium hydroxide was heated on a steam-bath, ethanol was added until solution was complete and the heating continued for fifteen minutes. After filtration and cooling, 0.37 g. of product separated. Evaporation of part of the ethanol and cooling resulted in the separation of 0.12 g. more of product. Purified from petroleum ether (b. p. 60–110°) it formed white crystals, m. p. 137–139° (cor.); yield, 0.45 g. (85%).

Anal. Calcd. for $C_{13}H_{13}O_3N$: C, 67.53; H, 5.63. Found: C, 67.28, 67.53; H, 5.47, 5.77.

2,8-Dimethoxynaphthonitrile.—A. A mixture of 5 cc. of acetic anhydride and 0.35 g. of 2,8-dimethoxynaphthaldoxime was refluxed for one hour. The light brown solution was poured onto 20 g. of ice, 50 cc. of water added and the mixture stirred until the excess acetic anhydride had decomposed. The solid was recrystallized from petroleum ether (b. p. 60–110°); white needles, m. p. 148–149° (cor.); yield, 0.28 g. (90%).

B. A solution of 0.20 g. of 2-methoxy-8-hydroxynaphthonitrile in 5 cc. of 10% aqueous sodium hydroxide and 1 cc. of dimethyl sulfate was shaken until all of the dimethyl sulfate had been hydrolyzed. The solid which separated was filtered, washed with alkali, then with water and dried. It was purified by recrystallization from petroleum ether (b. p. 60–110°); white crystals, m. p. 148–149° (cor.); yield, 0.17 g. (80%).

It could also be recrystallized from chloroform. A mixed melting point with the material obtained in A showed no depression.

Anal. Calcd. for $C_{13}H_{11}O_2N$: C, 73.24; H, 5.16; N, 6.57. Found: C, 73.50; H, 5.59; N, 6.52.

Summary

1. 2,8-Dihydroxynaphthaldoxime with acetic anhydride yields in the cold 2-hydroxy-*peri*-naphthoxazine, on warming 2-acetoxy-*peri*-naphthoxazine and when heated with acetic anhydride and sodium acetate 2-acetoxy-N-acetyl-*peri*-naphthoimidolactone. This latter product hydrolyzes with hydrochloric acid to 2-hydroxy-*peri*-naphtholactone which can be acetylated and methylated. The methoxy derivative was hydrolyzed and methylated to methyl 2,8-dimethoxynaphthoate.

2. 2-Hydroxy-*peri*-naphthoxazine is methylated to the 2-methoxy derivative which reacts with acetic anhydride and sodium acetate to give 2-methoxy-8-acetoxynaphthonitrile. This last product with hydrochloric acid yields 2-methoxy-8-hydroxynaphthonitrile which can also be obtained directly from 2-methoxy-*peri*-naphthoxazine by the action of alkali. Finally methylation of 2-methoxy-8-hydroxynaphthonitrile yields 2,8-dimethoxynaphthonitrile.

3. 2,8-Dihydroxynaphthaldehyde methylates to 2,8-dimethoxynaphthaldehyde. From this, the oxime is obtained in the usual way and acetic anhydride converts it to 2,8-dimethoxynaphthonitrile. The naphthonitrile thus obtained is identical with that obtained by the series of reactions described in 2.

4. The derivatives of 2,8-dihydroxynaphthaldehyde can be explained best on the basis of the normal aldehyde structure. Attempted reactions to obtain derivatives of tautomeric forms of 2,8-dihydroxynaphthaldehyde were unsuccessful. It may thus be concluded that to obtain such tautomerization as was observed in gossypol, additional substituents are necessary, probably another hydroxyl in the 3-position.

URBANA, ILLINOIS RECEIVED JANUARY 23, 1941