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The Preparation and Properties of Various Naphthylglyoxylic Acids[1]

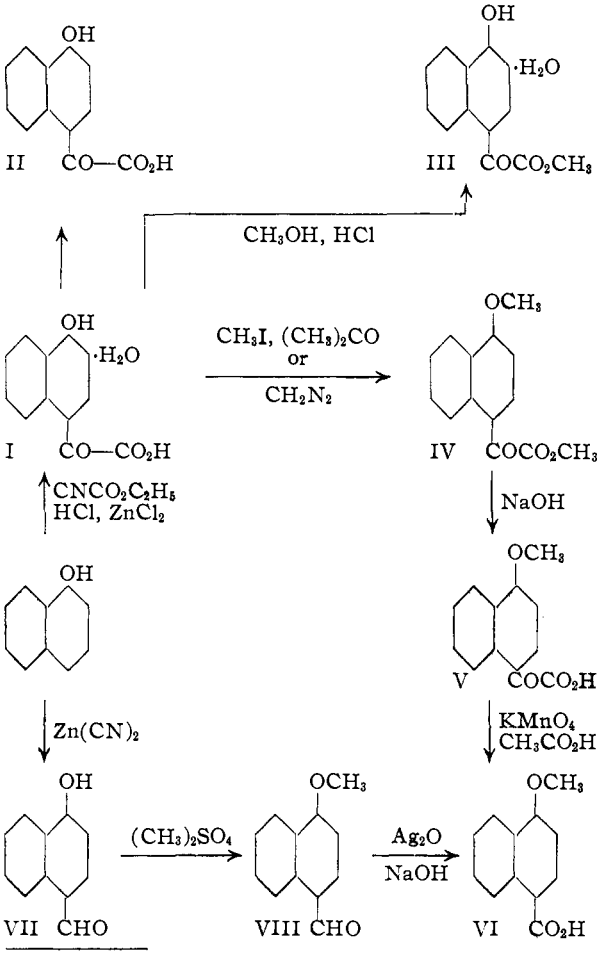
BY ALEXANDER B. NEILL[2] AND E. D. AMSTUTZ

The new synthetic approach to hydroxyarylglyoxylic acids, involving the use of ethyl cyanoformate, has been extended to the preparation of several new hydroxynaphthylglyoxylic acids. These acids were derived from α-naphthol, β-naphthol, 1,5-dihydroxynaphthalene and 2,7-dihydroxynaphthalene. The position of the glyoxylic acid group in the lactones of 4,8-dihydroxynaphthylglyoxylic acid and 2,7-dihydroxynaphthylglyoxylic acid has been proven.

In a previous paper[3] various substituted hydroxyphenylglyoxylic acids were prepared by condensing alkylresorcinols with ethyl cyanoformate in the presence of anhydrous hydrogen chloride and zinc chloride. In this paper is reported the synthesis of a number of naphthylglyoxylic acids using this same procedure. These glyoxylic acids were desired in order to study their chemical and antibacterial properties.

When the ethyl cyanoformate condensation was applied to α-naphthol, 4-hydroxynaphthylglyoxylic acid monohydrate (I) was obtained. The anhydrous acid (II) was obtained from the monohydrate (I) by drying over phosphorus pentoxide.

α-NAPHTHOL SERIES



The methyl ester, after recrystallization from aqueous ethanol, was likewise obtained as the monohydrate.

In the preparation of methyl 4-methoxynaphthylglyoxylate (IV) from the acid (I), two methods were used, both giving almost the same yield. Methyl iodide afforded a 74.9% yield of the methoxy ester while diazomethane gave a 79.5% yield. On hydrolysis of the ester 4-methoxynaphthylglyoxylic acid (V) was formed.

Both the methyl 4-methoxynaphthylglyoxylate and the 4-methoxynaphthylglyoxylic acid had been prepared previously[4] by the Friedel–Crafts reaction of α-naphthol methyl ether and oxalyl chloride but the position of the entering glyoxylic acid group was not definitely proven. This investigation has indicated that the glyoxylic acid group went into position four in the hydroxynaphthalene nucleus. To prove this point, 4-methoxynaphthylglyoxylic acid was oxidized with potassium permanganate in 50% acetic acid to form the known 4-methoxynaphthoic acid (VI). Our melting point for this acid was 241.8–242.8° while the melting point as reported by Gattermann[5] was 232°. In order to secure additional confirmation of this point, the 4-methoxynaphthoic acid was synthesized from 4-hydroxynaphthaldehyde (VII),[6] by methylating this aldehyde with dimethyl sulfate and then oxidizing the resulting 4-methoxynaphthaldehyde (VIII) with silver oxide[7] to form the 4-methoxynaphthoic acid (VI). This acid was, in every respect, the same as that acid prepared from the oxidation of 4-methoxynaphthylglyoxylic acid (V). Thus, the position of the entering glyoxylic acid group was established.[8]

The condensation of ethyl cyanoformate with β-naphthol yielded the lactone of 2-hydroxynaphthylglyoxylic acid (IX). This lactone had been prepared previously by a number of other investigators.[9,10a,b,11]

The position of the glyoxylic acid group had been determined by Passerini[10b] by oxidation of the lactone (IX) to form the known 2-hydroxynaphthoic acid.

It is interesting to note that the free acid could not be prepared; only the lactone was obtained. This tendency to form lactones in compounds

(1) Taken in part from a dissertation submitted by Alexander B. Neill in partial fulfillment of the requirements for the degree of Doctor of Philosophy, October, 1949.

(2) Lehigh Student Chemistry Foundation Fellow, 1946–1948.

(3) I. M. Hunsberger and E. D. Amstutz, THIS JOURNAL, 70, 671 (1948).

(4) L. Rousset, *Bull. soc. chim.*, 17, 305 (1897).

(5) L. Gattermann, *Ann.*, 244, 73 (1888).

(6) R. Adams and I. Levine, THIS JOURNAL, 45, 2373 (1923).

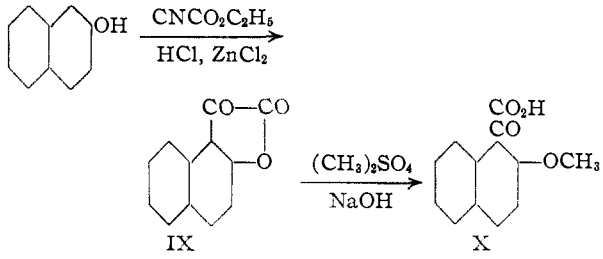
(7) I. A. Pearl, *ibid.*, 68, 429 (1946).

(8) No absolute proof of orientation has been offered for these compounds. The circumstantial evidence is excellent, however, and is felt to be strengthened by present evidence.

(9) K. Fries and R. Frellstedt, *Ber.*, 54, 715 (1921).

(10) (a) M. Giua and V. de Franciscia, *Gazz. chim. ital.*, 47, I, 51 (1917); (b) M. Passerini, *ibid.*, 54, I, 184 (1924).

(11) H. Staudinger, B. Sehlenker and H. Goldstein, *Helv. Chim. Acta*, 4, 334 (1921).



containing a hydroxyl group ortho to a glyoxylic acid has been found in other compounds in the naphthalene series, not only in the work reported here, but also in that reported by other investigators.[9,12,13,14] In all the various hydroxynaphthylglyoxylic acids which have a hydroxy group ortho to the glyoxylic acid group, a lactone was formed except in the case of the 1-hydroxynaphthyl-2-glyoxylic acid.[9] In this case, only the free acid was formed.

On methylation of the 2-hydroxynaphthylglyoxylic acid lactone (IX) with dimethyl sulfate, the 2-methoxynaphthylglyoxylic acid (X) was formed. Staudinger, Schlenker and Goldstein[11] reported that 2-methoxynaphthylglyoxylic acid could not be prepared by this method.

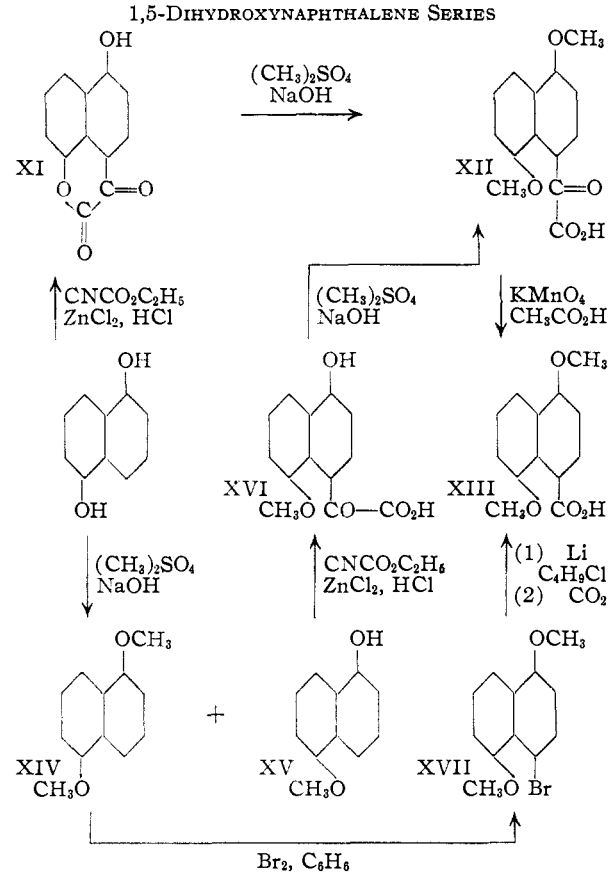
On condensing ethyl cyanoformate with 1,5-dihydroxynaphthalene, a brick-red compound was obtained which, after repeated fractional crystallizations, yielded a compound which was identified as the 4,8-dihydroxynaphthylglyoxylic acid lactone (XI). Apparently, some of the other isomer, 1,5-dihydroxynaphthyl-2-glyoxylic acid lactone was formed, for the impure red material analyzed correctly for the lactone (XI), even though it melted over a range, 284–295° (dec.). The pure lactone (XI) melted at 294–296° (dec.).

Knobloch and Schraufstaetter[14] reported a melting point of 272° for a brick-red compound which they obtained from the reaction of cyanogen and 1,5-dihydroxynaphthalene. They were not sure whether they had the 1,5-dihydroxynaphthyl-2 or 4-glyoxylic acid lactone. From the work reported in this paper, it appears that they had the 1,5-dihydroxynaphthyl-2-glyoxylic acid lactone since in this investigation, the lactone obtained was shown to be the 4,8-dihydroxynaphthylglyoxylic acid lactone (XI).

The position of the glyoxylic acid group on the ring of the lactone (XI) was determined by conversion to the dimethoxy acid (XII) with dimethyl sulfate and then this acid was oxidized by the use of potassium permanganate in 50% acetic acid to the known 4,8-dimethoxynaphthoic acid. A sample of this known acid was prepared from 1,5-dimethoxynaphthalene (XIV) by the same method Adams and co-workers[15] used in preparing 2,7-dimethoxynaphthoic acid (XX). A mixed melting point of this acid with that obtained from the 4,8-dimethoxynaphthylglyoxylic (XII) showed no depression. Since the position of the carboxyl group in the 4,8-dimethoxynaphthoic acid (XIII) is

(12) K. Fries and W. Pfaffendorf, *Ber.*, **45**, 154 (1912).
(13) K. Fries and E. Pusch, *Ann.*, **442**, 272 (1925).
(14) K. Knobloch and E. Schraufstaetter, *Ber.*, **81**, 224 (1948).
(15) R. Adams, M. W. Miller, F. C. McGrew and A. W. Anderson, THIS JOURNAL, **64**, 1795 (1942).

1,5-DIHYDROXYNAPHTHALENE SERIES



known,[16] it follows that the structures of all the compounds prepared in this series are also known.[8]

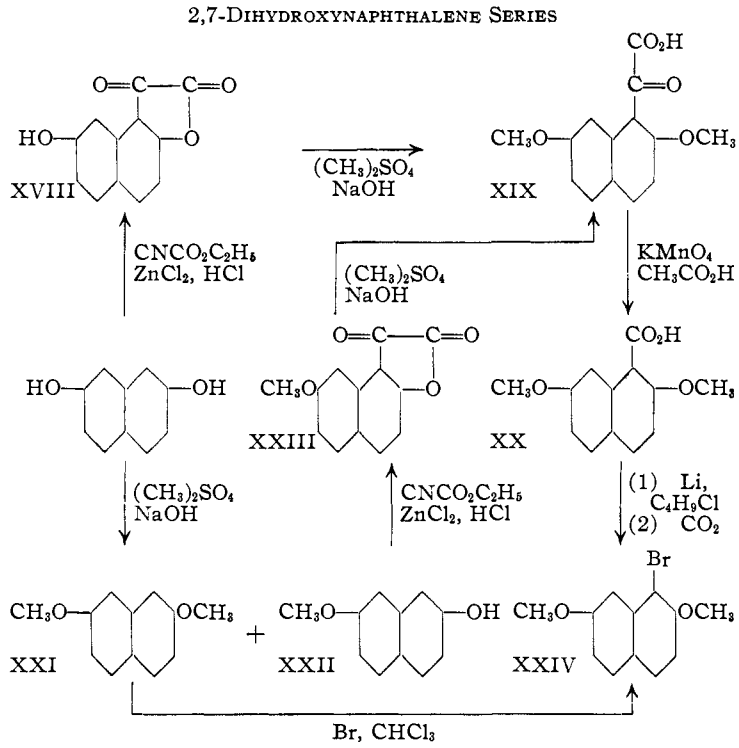
On condensation of ethyl cyanoformate with 5-methoxy-1-naphthol, 4-hydroxy-8-methoxynaphthylglyoxylic acid (XVI) was formed. The position of the glyoxylic acid group on the ring was indicated by the fact that the compound did not form a lactone and was converted by methylation into (XII).

On condensing ethyl cyanoformate with 2,7-dihydroxynaphthalene, 2,7-dihydroxynaphthylglyoxylic acid lactone (XVIII) compound was formed. This lactone, which melted at 280–282° (dec.) had the same melting point as the lactone prepared by Passerini[10b] from the reaction of phenyl isonitrile on 2,7-dihydroxynaphthalene.

In order to prove the position on the naphthalene ring of the glyoxylic acid group in the lactone (XVIII), the lactone was methylated, using dimethyl sulfate to the dimethoxy acid and then oxidized, using potassium permanganate in 50% acetic acid to form 2,7-dimethoxynaphthoic acid (XX). A mixed melting point of this acid (XX) with a sample of the acid prepared by the method of Adams, Miller, McGrew and Anderson[15] gave no depression. The position of the carboxyl group in this acid (XX) had been proven by these investigators.[8]

On condensing ethyl cyanoformate with 7-methoxy-2-naphthol (XXII), 2-hydroxy-7-methoxynaphthylglyoxylic acid lactone (XXIII) was

(16) P. Hill, W. F. Short and H. Stromberg, *J. Chem. Soc.*, 940 (1937).



obtained. The position of the glyoxylic acid group was determined by methylation using dimethyl sulfate to form the same dimethoxy acid as that obtained by methylation of the 2,7-dihydroxynaphthylglyoxylic acid lactone (XVIII). A mixed melting point of these two acids showed no depression.

Staudinger, Schlenker and Goldstein[11] reported that they prepared the 2-hydroxy-7-methoxynaphthylglyoxylic acid lactone (XXIII) by condensing oxalyl chloride with 2,7-dimethoxynaphthalene (XXI) in the presence of aluminum chloride. The lactone that they made has a melting point of 184° (dec.) and its color was yellow-brown. These physical characteristics are different from those of the lactone obtained in this investigation. The melting point of the lactone which is now proven to be 2-hydroxy-7-methoxynaphthylglyoxylic acid lactone (XXIII) is 199.6–200.6° (dec.), and its color is a bright orange. It appears that Staudinger, Schlenker and Goldstein[11] did not have the lactone which they reported.

Neutral equivalents of the acids were obtained in the usual manner using a Beckman *p*H meter; however, the erratic and unpredictable deviations from the calculated values rendered them of little value. While some of the neutral equivalents were in agreement with the calculated results, others deviated quite appreciably. These results are in agreement with those found by Hunsberger and Amstutz[3] in the alkylphenylglyoxylic acid series.

Experimental[17]

4-Hydroxynaphthylglyoxylic Acid Monohydrate (I).—The preparation of this acid illustrates the general procedure used for all hydroxynaphthylglyoxylic acids prepared in this paper.

(17) All melting points are corrected.

To a 200-ml. three-necked flask fitted with a condenser, a large diameter gas inlet tube and a stirrer were added 14.4 g. (0.1 mole) of α-naphthol, 11.0 g. (0.11 mole) of ethyl cyanoformate,[18] 0.9 g. of freshly fused zinc chloride and 100 ml. of absolute ether. The solution was stirred until all the solids had dissolved and then it was cooled with an ice-bath. Dry hydrogen chloride gas was passed into the reaction mixture for two hours, with the excess going out the condenser and through a gas trap. The flask was then sealed from moisture and placed overnight in the refrigerator. The next day, dry hydrogen chloride was again passed into the cold solution for two hours. The flask was then placed in the refrigerator for three days. After three days a red, oily precipitate had separated out on the sides of the flask. This precipitate was filtered from the ether. More oily precipitate was obtained from the ether by addition of fresh absolute ether. These precipitates were combined and dissolved in a 2.5% sodium hydroxide solution, heated for 15 minutes and acidified with concentrated hydrochloric acid. A yellow-orange precipitate separated out along with some tarry material. After repeated treatments with Darco and several recrystallizations from boiling water, 8.8 g. (37.6%) of the fine, crystalline, yellow glyoxylic acid (I), m.p. 188.4–189.4° (dec.), settled out.

On analysis the acid (I) was found to contain one molecule of water.

Anal. Calcd. for $C_{12}H_8I_4 \cdot H_2O$: C, 61.54; H, 4.30; neut. equiv., 234.2. Found: C, 61.33; H, 4.19; neut. equiv., 290.3.

Drying the above glyoxylic acid over P_2O_5 at 80° for two days yielded the yellow anhydrous 4-hydroxynaphthylglyoxylic acid (II) which melted at 191.2–191.8° (dec.).

Anal. Calcd. for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.54; H, 3.98.

Repeated attempts to prepare the 2,4-dinitrophenylhydrazone of 4-hydroxynaphthylglyoxylic acid failed.

Methyl 4-Hydroxynaphthylglyoxylate Monohydrate (III).—For 30 minutes dry hydrogen chloride was passed into a cooled solution containing 0.5 g. (0.00213 mole) of 4-hydroxynaphthylglyoxylic acid monohydrate (I) in 20 ml. of absolute methanol. The solution was refluxed for 30 minutes, evaporated almost to dryness on the steam-bath and the yellow solid separated, treated with 10% sodium bicarbonate and filtered. The precipitate remaining was treated with Darco and recrystallized several times from boiling aqueous alcohol. The yellow crystalline ester (III), m.p. 142.8–143.5°, amounting to 0.44 g. (83.2%) was found to be a monohydrate.

Anal. Calcd. for $C_{13}H_{10}O_4 \cdot H_2O$: C, 62.90; H, 4.87. Found: C, 62.98; H, 5.08.

Methyl 4-Methoxynaphthylglyoxylate (IV). A. Methyl Iodide Method.—In a 25-ml. flask were placed 0.32 g. (0.00137 mole) of 4-hydroxynaphthylglyoxylic acid monohydrate (I), 10 ml. of acetone dried over anhydrous sodium sulfate, 1.95 g. (0.0137 mole) of methyl iodide and 0.9 g. of potassium carbonate. This mixture was refluxed for eight hours, the potassium carbonate filtered off, and the acetone evaporated. The mustard-colored oil obtained from the reaction was treated with Darco and recrystallized several times from aqueous methanol to yield 0.25 g. (74.9%) of a light yellow, crystalline ester, m.p. 84.8–85.6° (lit. m.p. 86–87°).[4]

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.69; H, 4.98.

B. **Diazomethane Method.**—To 1.08 g. (0.0046 mole) of 4-hydroxynaphthylglyoxylic acid monohydrate (I) in 20 ml. of ether was added slowly a solution containing 0.62 g. (0.015 mole) of diazomethane.[19] The ether solution stood for 24 hours and was then evaporated. The tan residue was then treated with Darco and recrystallized from methanol.

(18) W. Gluud, W. Nüssler and K. Keller, German Patent 592,539; *Chem. Zentr.*, **105**, II, 3437 (1934).

(19) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, Note 3, p. 166.

The light yellow crystalline ester which weighed 0.89 g. (79.5%) and melted at 84.8–85.8° was identical to that prepared by the methyl iodide method as shown by the method of mixed melting points.

4-Methoxynaphthylglyoxylic Acid (V).—A solution consisting of 0.39 g. (0.0016 mole) of methyl 4-methoxynaphthylglyoxylate (IV) was refluxed for ten minutes with 0.1 g. (0.0025 mole) of sodium hydroxide in 10 ml. of water. Acidification with dilute hydrochloric acid and subsequent and recrystallization from water yielded 0.33 g. (89.2%) of the yellow crystalline acid, m.p. 163.6–164.6° (dec.); lit. m.p. 164–165° (dec.).[4]

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38; neut. equiv., 230.2. Found: C, 67.92; H, 4.33; neut. equiv., 262.3.

4-Methoxynaphthoic Acid (VI).—In 15 ml. of 50% acetic acid was dissolved 0.1279 g. (0.000555 mole) of 4-methoxynaphthylglyoxylic acid (V). To this gently refluxing solution was slowly added a hot solution of 0.0374 g. (0.000236 mole) of potassium permanganate (5% more than needed for the oxidation) in 10 ml. of 50% acetic acid. Carbon dioxide was given off readily during the oxidation. The mixture was refluxed for 30 minutes, then poured into 25 ml. of water and the precipitate filtered, redissolved in 1% sodium hydroxide and filtered again to remove the manganese dioxide. This solution was acidified, the precipitate filtered and recrystallized from 95% alcohol. The acid, 0.0484 g. (43.1%), was obtained as fine white crystals, m.p. 241.8–242.8° (lit. m.p. 232°).[5]

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.40; H, 4.96.

A mixed melting point of 4-methoxynaphthoic acid (VI) as prepared above showed no depression with a sample prepared as follows:

A solution consisting of 11 ml. of water and 1.08 g. of sodium hydroxide in a three-necked flask fitted with a stirrer and thermometer was heated to 55° and then 1.0 g. (0.00537 mole) of 4-methoxynaphthaldehyde (VIII) and 1.24 g. (0.00537 mole) of silver oxide, prepared according to the directions of Pearl,[7] were added. The solution was heated for 45 minutes at 75°, cooled, extracted with ether to remove the unreacted aldehyde and acidified. The white precipitate was filtered off and after several recrystallizations from aqueous alcohol, a poor yield of the white acid (VI), m.p. 241.0–242.0°, was obtained.

4-Hydroxynaphthaldehyde (VII) and 4-Methoxynaphthaldehyde (VIII).—The former compound (VII) was prepared according to the method of Adams and Levine[6] and the latter compound (VIII), according to the method of Gattermann.[20]

2-Hydroxynaphthylglyoxylic Acid Lactone (IX).—This lactone prepared from β-naphthol in the same manner as that of 4-hydroxynaphthylglyoxylic acid monohydrate (I), m.p. 182–183° (dec.), lit. 182° (dec.),[9] 178° (dec.),[21] was obtained in a 50.0% yield as a bright orange crystalline compound from acetone.

Anal. Calcd. for $C_{12}H_6O_3$: C, 72.70; H, 3.05; neut. equiv., 198.2. Found: C, 72.59; H, 3.12; neut. equiv., 202.2.

2-Methoxynaphthylglyoxylic Acid (X).—2-Hydroxynaphthylglyoxylic acid (IX) was methylated with dimethyl sulfate in the usual manner[11] (62.8% yield). There was obtained, by recrystallization from water, a bright yellow crystalline compound, m.p. 153.8–154.6° (lit. m.p. 151°).[4]

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.82; H, 4.37; neut. equiv., 230.2. Found: C, 68.01; H, 4.60; neut. equiv., 217.2.

4,8-Dihydroxynaphthylglyoxylic Acid Lactone (XI).—This lactone was prepared from 1,5-dihydroxynaphthalene in the same manner as that of 4-hydroxynaphthylglyoxylic acid monohydrate (I). The red precipitate, which was obtained from the reaction, gave after repeated fractional crystallizations from aqueous alcohol a very small amount of a brick-red crystalline compound, m.p. 294.0–296.0° (dec.).[13]

Anal. Calcd. for $C_{12}H_6O_4$: C, 67.27; H, 2.82; neut. equiv., 214.2. Found: C, 67.11; H, 2.79; neut. equiv., 217.8.

From the filtrate of the above lactone (XI), a brick-red compound m.p. 284.0–295.0° (dec.) was obtained. Apparently, a small amount of the 1,5-dihydroxynaphthalene-2-glyoxylic acid lactone is present, which could not be separated in pure condition by fractional crystallization.

Anal. Calcd. for $C_{12}H_6O_4$: C, 67.27; H, 2.82. Found: C, 67.41; H, 2.99.

4,8-Dimethoxynaphthylglyoxylic Acid (XII).—The 4,8-dihydroxynaphthylglyoxylic acid lactone (XI) was methylated with dimethyl sulfate in the usual manner to give, on crystallization from benzene, a 60.0% yield of the yellow acid, m.p. 190.8–191.6° (dec.).

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65; neut. equiv., 260.2. Found: C, 64.63; H, 4.80; neut. equiv., 251.8.

4,8-Dimethoxynaphthoic Acid (XIII).—In 4 ml. of 50% acetic acid was dissolved 0.2 g. (0.000768 mole) of 4,8-dimethoxynaphthylglyoxylic acid (XII). To this solution was added slowly a hot solution consisting of 0.051 g. (0.000322 mole) of potassium permanganate dissolved in 5 ml. of 50% acetic acid. The solution was refluxed gently during the addition and CO_2 was evolved vigorously. After 30 minutes, the solution was poured into water. The tan precipitate obtained was dissolved in 2% sodium hydroxide, filtered to remove any manganese dioxide and acidified. The solution was filtered and the precipitate obtained recrystallized several times from aqueous alcohol. White crystals, m.p. 221.4–222.4° (lit. 222.5°),[15] were obtained.

A mixed melting point of 4,8-dimethoxynaphthoic acid (XIII) as prepared above showed no depression with an authentic sample prepared from 1,5-dimethoxynaphthalene (XIV) through 4,8-dimethoxybromonaphthalene (XVII).[16]

1,5-Dimethoxynaphthalene (XIV) and 5-Methoxy-1-naphthol (XV).—These compounds were prepared from 1,5-dihydroxynaphthalene according to the directions given by Bentley, Robinson and Weizmann[22] and also Fisher and Bauer.[23]

4-Hydroxy-8-methoxynaphthylglyoxylic Acid (XVI).—This acid was prepared from 5-methoxy-1-naphthol in the same manner as that of 4-hydroxynaphthylglyoxylic acid monohydrate (I). On recrystallization from aqueous alcohol, a 36.9% yield of the yellow 4-hydroxy-8-methoxynaphthylglyoxylic acid, m.p. 188.2–190.2° (dec.), was obtained.

Anal. Calcd. for $C_{13}H_{10}O_5$: C, 63.41; H, 4.10; neut. equiv., 246.2. Found: C, 63.57; H, 4.30; neut. equiv., 233.4.

4,8-Dimethoxynaphthylglyoxylic Acid (XII).—4-Hydroxy-8-methoxynaphthylglyoxylic acid (XVI) was methylated with dimethyl sulfate to give on crystallization from benzene a 66.9% yield of the yellow crystalline acid, m.p. 190.8–191.8° (dec.). A mixed melting point of this acid with the acid prepared from 4,8-dihydroxynaphthylglyoxylic acid lactone (XI) showed no depression.

2,7-Dihydroxynaphthylglyoxylic Acid Lactone (XVIII).—This lactone was prepared from 2,7-dihydroxynaphthalene in the same manner as that of 4-hydroxynaphthylglyoxylic acid monohydrate (I).

After several recrystallizations from aqueous alcohol, the red lactone, m.p. 280.0–282.0 (dec.) [lit. m.p. 280–282° (dec.)[10]], was obtained in a 80.5% yield.

Anal. Calcd. for $C_{12}H_6O_4$: C, 67.27; H, 2.82; neut. equiv., 214.2. Found: C, 67.32; H, 3.05; neut. equiv., 208.3.

2,7-Dimethoxynaphthylglyoxylic Acid (XIX).—2,7-Dihydroxynaphthylglyoxylic acid (XVIII) was methylated in the usual manner with dimethyl sulfate to give, on recrystallization from benzene, a 45.2% yield of the yellow crystalline acid (XIX), m.p. 150.6–151.4° (dec.).

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65; neut. equiv., 260.2. Found: C, 64.82; H, 4.81; neut. equiv., 254.3.

2,7-Dimethoxynaphthoic Acid (XX).—The oxidation of 2,7-dimethoxynaphthylglyoxylic acid (XIX) was carried out in the same manner as that of 4,8-dimethoxynaphthylglyoxylic acid (XII). From the reaction were obtained some white crystals which, after several recrystallizations from alcohol, melted at 112.2–113.2 (lit. m.p. 112–113°)[15] (poor yield).

(20) L. Gattermann, *Ber.*, **32**, 285 (1899).

(21) K. Fries and R. Frellstedt, *Ber.*, **41**, 4271 (1908).

(22) W. H. Bentley, R. Robinson and C. Weizmann, *J. Chem. Soc.*, **91**, 104 (1907).

(23) O. Fisher and C. Bauer, *J. prakt. Chem.*, [2] **94**, 16 (1916).

A mixed melting point of this acid (XX) with a sample of the acid prepared according to the directions of Adams, Miller, McGrew and Anderson[15] showed no depression.

2,7-Dimethoxynaphthalene (XXI) and 7-Methoxy-2-naphthol (XXII).—These compounds were prepared from 2,7-dihydroxynaphthalene according to the method of Fischer and Hammerschmidt.[24]

2-Hydroxy-7-methoxynaphthylglyoxylic Acid Lactone (XXIII).—This lactone was prepared from 7-methoxy-2-naphthol in the same manner as that 4-hydroxynaphthylglyoxylic acid monohydrate (I).

The orange precipitate which was obtained from the reaction was recrystallized from acetone and a 50.5% yield of the bright orange colored lactone, m.p. 199.6–200.6° (dec.) [lit. m.p. 184° (dec.) and color, brownish yellow[11]] was obtained.

Anal. Calcd. for $C_{13}H_8O_4$: C, 68.42; H, 3.53; neut. equiv., 228.2. Found: C, 68.23; H, 3.76; neut. equiv., 221.8.

2,7-Dimethoxynaphthylglyoxylic Acid (XIX).—2-Hydroxy-7-methoxynaphthylglyoxylic acid lactone (XXIII) was methylated in the usual manner with dimethyl sulfate.

A mixed melting point of this acid with the methylated acid prepared from 2,7-dihydroxynaphthylglyoxylic acid lactone (XVIII) showed no depression.

(24) O. Fischer and F. Hammerschmidt, *J. prakt. chem.*, [2] **94**, 24 (1916).

BETHLEHEM, PENNA. RECEIVED JANUARY 15, 1951

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF LAKESIDE LABORATORIES, INC.]

Mercurial Diuretics. IV. Methoxymercuration of Substituted Allylureas

BY R. L. ROWLAND, WENDELL L. PERRY AND SAMUEL GERSTEIN

A representative series of compounds of the general structure $R_1R_2NCONHCH_2CH(OCH_3)CH_2HgX$ has been prepared where R_1 and R_2 are alkyl, aryl, aralkyl or acyl and where X is chlorine, acetoxy or a carboxymethylmercapto group. Substitution in the propyl group has been studied by the preparation of $H_2NCONHCH_2C(CH_3)(OCH_3)CH_2HgCl$. The pharmacology of these compounds is discussed briefly.

The discovery that compounds of the structure $NH_2CONHCH_2CH(OR)CH_2HgX$ where R is an alkyl radical and X is halogen, succinimido, phthalimido, acetoxy, $-SCH_2COOH$, etc.,[1] are much more potent in the production of diuresis than the mercurial diuretics in current use has prompted investigation of compounds of related structure. Accordingly, a series of compounds of the structure $R_1R_2NCONHCH_2CH(OCH_3)CH_2HgX$ has been prepared by methoxymercuration of substituted allylureas. The acetoxymercurials formed by addition to the allyl group were converted to the chloromercurials by reaction with sodium chloride. The alkyl and aryl allylureas were synthesized by the reaction of an isocyanate with an amine. N-Allyl-N′-acetylurea and N-allyl-N′-benzoylurea were prepared both by the reaction of allylurea with acetic anhydride and with benzoyl chloride and by the reaction of allyl isocyanate with acetamide and with benzamide.

As an example of variation in the substituted propyl group of the mercurial, 3-chloromercuri-2-methoxy-2-methylpropylurea was prepared by the methoxymercuration of methallylurea.

Pharmacology.[2]—Solutions of the mercurials in dilute alkali were prepared for pharmacological evaluation. It was not possible to prepare solutions of compounds 10 and 14 of Table II.[3] N-3-Chloromercuri-2-methoxypropyl-N′-acetylurea was hydrolyzed in dilute alkaline solution to 3-chloromercuri-2-methoxypropylurea and the diuretic responses of this solution and of N-3-acetoxymercuri-2-methoxypropyl-N′-acetylurea were, accordingly, considered to be due to the hydrolysis products, 3-chloromercuri-2-methoxypropylurea and 3-acetoxymercuri- or 3-hydroxymercuri-2-methoxypropylurea, respectively. The constitution of the latter hydrolysis product was not determined but would depend upon the rate of hydrolysis of the 3-acetoxymercuri radical to the 3-hydroxymercuri radical.

Of the series, $R_1R_2NCONHCH_2CH(OCH_3)CH_2HgX$, only compounds 1 and 12 exhibited the same order of toxicity as those mercurials used clinically, *e.g.*, mercuhydrin, when the toxicity was determined as the LD_{50} at 14 days in rats; the remaining mercurials were 1.4 to 3.7 times as toxic. The degree of diuresis produced in dogs by a dosage of 0.006 millimole/kg. was, with only five exceptions, of the same order as or less than that produced by mercuhydrin. Each of the more potent diuretics, compounds 1, 2, 11, 12 and 18, effected diuresis which was three to five times that produced by the diuretics in current usage. As mentioned previously, the diuresis produced by 11 or 12 was considered to be that resulting from the hydrolysis products. Accordingly, only compounds 1 and 2, where substitution is the small methyl or ethyl radical, and compound 18 where the substituent contains another functional group, were more potent diuretics *per se*.

3-Chloromercuri-2-methoxy-2-methylpropylurea was found to be 8.5 times as toxic as mercuhydrin. Although this mercurial produced a pronounced diuresis at a dosage of 0.006 millimole/kg. in dogs, the diuretic response at 0.0015 millimole/kg. was negligible.

Experimental[4]

Substituted Allylureas.—N-Allyl-N′-phenylurea was prepared by the previously reported method from phenyl isocyanate and allylamine.[5] N-Allyl-N′-α-naphthylurea and N-allyl-N′-ethylurea were synthesized by the reaction of

(1) R. L. Rowland, W. L. Perry, E. L. Foreman and H. L. Friedman, THIS JOURNAL, **72**, 3595 (1950).

(2) We are indebted to Mr. P. A. Nuhfer of these laboratories for the pharmacological evaluation of these mercurials.

(3) The insoluble material which was collected after attempting to prepare a solution of compound 14 in dilute aqueous alkali differed from the N-(3-chloromercuri-2-methoxypropyl)-N′-benzoylurea. Analysis of the alkali-treated material indicated the removal of a molecule of hydrochloric acid, producing a polymer of the formula $H[N(COC_6H_5)CONHCH_2CH(OCH_3)CH_2Hg]_nCl$.

(4) All melting points over 70° are corrected.

(5) F. B. Dains, THIS JOURNAL, **21**, 136 (1899).