the brominated liquid acids. The physical characters, solubility and bromine content of this residue corresponded to those of dibromostearic acid.

Solid Acids

The separation of liquid and solid fatty acids by the lead salt-ether method gave 33.13% of solid acids, melting at 41.2° and having a mean molecular weight of 282.96, the latter being calculated from the neutralization value.

By fractional precipitation with magnesium acetate and crystallization from alcohol, two fractions melting at 64.0 and 58.0°, respectively, were obtained. Neutralization gave a calculated mean molecular weight of 281.7 for the fraction melting at 64.0° and of 264.6 for the portion melting at 58.0°. The quantity of material was not sufficient to permit the preparation of pure acids.

Summary

A specimen of boa-constrictor fat was prepared and examined. The unsaturated acids were found to consist of oleic acid, linolic acid and a highly unsaturated acid which formed an insoluble bromo addition product, tentatively identified as octobromostearic acid. The saturated acids evidently consisted of palmitic and stearic acids.

WASHINGTON, D. C.

[CONTRIBUTION FROM THE SECTION OF BIOCHEMISTRY OF THE MAYO FOUNDATION]

SOME HALOGEN AND HYDROXYL DERIVATIVES OF 2-OXO-DIHYDRO, 2-OXO-HEXAHYDRO-INDOLE-3-PROPIONIC ACID, AND OF 2-OXO-HEXAHYDROBENZOFURAN-3-PROPIONIC ACID

BY EDWARD C. KENDALL AND ARNOLD E. OSTERBERG

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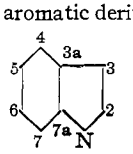
The preparation of 2-oxo-hexahydro-benzofuran-3-propionic acid has been described.[1] If this compound is treated in dilute aqueous hydrobromic acid with bromine, a monobromo derivative can be separated (I). If a solution of the sodium salts of the lactone is treated with bromine a monobromo derivative of the lactone crystallizes from solution (II). These two monobromo derivatives are not identical; the one prepared from the sodium salt has the percentage composition of a monobromo derivative of the lactone. However, it is a neutral compound possessing no acidic properties although the carboxyl group in the original lactone requires one equivalent of sodium hydroxide for its neutralization.

[1] Kendall, Osterberg and MacKenzie, THIS JOURNAL, **48**, 1384 (1926). The indole nucleus is referred to by the following numbers, and the open pyrrolidine ring compounds are numbered in the usual manner for aromatic derivatives.



The monobromo derivative prepared in dilute hydrobromic acid contains a carboxyl group, and it is much more soluble than the one which shows no acidic properties. It can be crystallized from xylene, but if the solution is refluxed for about an hour water is given off and, after cooling, crystals separate which are identical with the neutral monobromo derivative (II). The percentage composition of the monobromolactone with acidic properties (I) corresponds to that of a monobromo derivative of the original lactone with the addition of one molecule of water.

Both of these bromolactones give the same hydroxyl derivative when treated with sodium hydroxide. This hydroxyl derivative also exists in two forms, acidic and neutral, which corresponds to the bromolactone. If the hydroxyl derivative is heated with a slight excess of sodium hydroxide, two equivalents of alkali are required for the neutralization of the product. The terminal carboxyl and the carboxyl group of the lactone both exist in free form (VI). If the disodium salt is treated with an equivalent amount of mineral acid and the solution is allowed to stand at room temperature, one equivalent of carboxyl titration disappears and then only one equivalent of sodium hydroxide is required for its neutralization; this is evidence for the closure of the lactone ring in a slightly acid solution (IV). If this solution is now boiled, the remaining acid group reacts in such a manner that the resulting solution is neutral (V).

Identification of these compounds could not be carried out until the position occupied by the bromine was determined. Oxidation with permanganate or with ozone did not give products which were useful for the identification of the compound. Further bromination did not result in the breaking of the lactone and did not give any products which were of help. Fusion with sodium hydroxide caused a deep-seated reaction and the products of the alkaline fusion indicate the position of the bromine. When the disodium salt of the hydroxyl compound is heated with concd. sodium hydroxide in a distilling flask to 170°, a volatile oil is given off. This is soluble in water, but can be thrown out of solution with potassium carbonate. It is only slightly soluble in ether and when recrystallized from benzene it proved to be the *trans*-form of cyclohexane glycol.[2] In the sodium hydroxide fusion were found large amounts of succinic acid. Only traces of acetic acid resulted from the fusion. If the heating was carried on at a higher temperature valeric acid was found in the fusion melt; no acid-insoluble product resulted.

These reactions indicate that the bromine occupied Position 3 and that the ketocyclohexane-hydroxyl-glutaric acid had rearranged, giving cyclohexane glycol (VII). The resulting α-hydroxyl-glutaric acid was broken down into carbon dioxide and succinic acid. No butyrolactone was formed, but the succinic acid was a high percentage of the amount

[2] Bedos, *Compt. rend.*, **183**, 750 (1926).

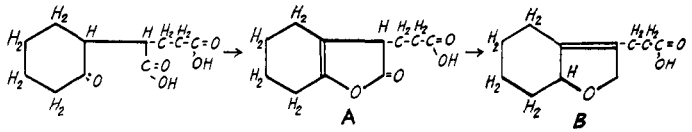
theoretically possible. Rupture of the cyclohexane ring probably explains the formation of the valeric acid at a high temperature.

After the identification of the position of the hydroxyl group in the lactone, it became necessary to explain the presence of the molecule of water in Form I and the loss of the carboxyl group in the neutral Form II. When two equivalents of bromine react with the sodium salt of the lactone one equivalent of bromine combines with the lactone, and the second equivalent is present in the solutions as sodium bromide. A yield of 90% of the monobromolactone was secured. This is conclusive evidence that the molecule of water is not present as an hydroxyl formed by oxidation of the lactone; still further evidence for this is the fact that the monobromolactone can easily be reduced to the original lactone, which separates without a molecule of water or an hydroxyl group.

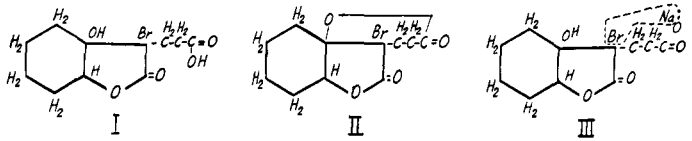
When the monobromolactone is heated in xylene the resulting compound, which is neutral (II), is not formed by the loss of hydrobromic acid, but is formed by the loss of water. In connection with the problem of explaining these reactions, we take pleasure in acknowledging a suggestion from E. P. Kohler, who says, "First there is a shift of the double linkage from Δ-7a, 3a to Δ-3, 3a, as shown by Formulas A and B. This is the usual change of an unconjugated to a conjugated system of double bonds—probably the most general property of β,γ-unsaturated acids." Next, when the lactone B is treated with bromine in the presence of water, bromine does not substitute but hypobromous acid is added. "This is what invariably happens when an α,β-unsaturated acid or any of its derivatives or α,β-unsaturated ketones are treated with bromine in the presence of water or bases. In such cases bromine goes into the alpha position and hydroxyl into the beta."

The double bond in 2-oxo-hexahydrobenzofuran-3-propionic acid is very resistant to reduction or to the addition of hydriodic or hydrobromic acids and bromine. It reacts slowly with potassium permanganate. However, it seems most probable that the course of the bromination as suggested by Kohler is through the addition of hypobromous acid to the double bond which occupies Position 3,3a in the lactone. Closure to the lactone between the terminal carboxyl and the hydroxyl group on Position 3a explains the loss of acidic properties in the neutral Form II.

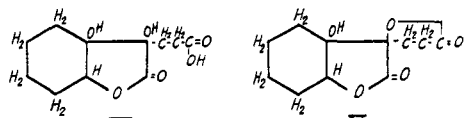
Another reaction which indicates that the disodium salt of the 3-hydroxyl derivative exists with hydroxyl groups on 3a and 7a, is the impossibility of forming the 3-hydroxyl-lactam from the 3-hydroxyl-lactone. Ketocyclohexane-glutaric acid will react with ammonia, giving a practically quantitative yield of the corresponding lactam, but when the 3-hydroxyl or the disodium salt of 3-hydroxyl-2-oxo-hexahydrobenzofuran-3-propionic acid is treated with ammonia no trace of lactam is produced. This is evidence that the ketone group is not present on Carbon 7a and that the structure probably is the 3,3a,7a-trihydroxyl derivative.



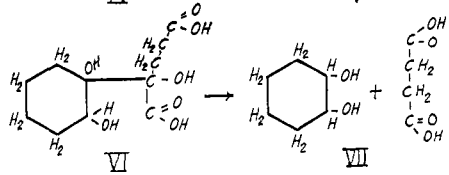
A B



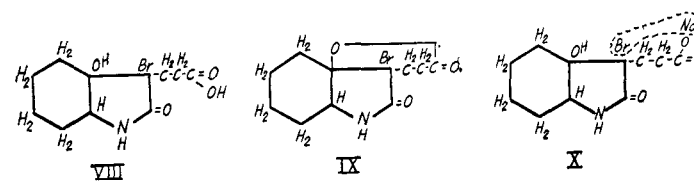
I II III



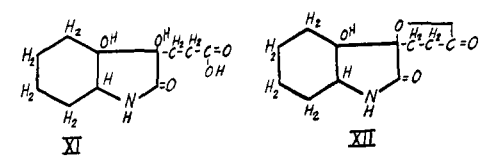
IV V



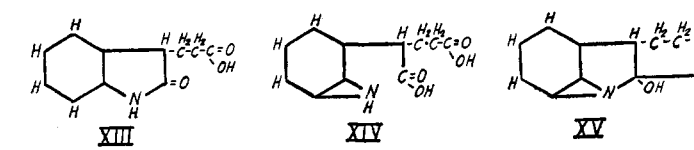
VI VII



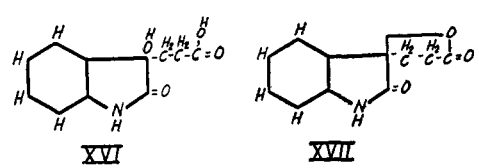
VIII IX X



XI XII



XIII XIV XV



XVI XVII

Conclusive proof of the structure of 2-oxo-hexahydrobenzofuran-propionic acid is furnished by the effect of ozone on this compound. Ozone reacts with this lactone in glacial acetic acid, with the formation of succinic acid. This decomposition could not occur unless the bond lay between Carbons 3 and 3a. Finally, if the 3-bromo-3a-hydroxyl derivative is treated with ozone no decomposition occurs. This is in agreement with the structure assigned, that is, a dihydroxyl derivative of octohydrobenzofuran.

The neutral form (II) of the monobromo derivative contains a δ-lactone, which is made by loss of water. If, however, the monobromolactone (I) is dissolved in a small amount of alcohol and water, and sodium hydroxide is added, it will remove most of the bromine attached to the lactone, and crystals separate from the solution (III). These crystals are neutral and are identical with the γ-lactone of the 3,3a-dihydroxyl derivative of the lactone (V). This is evidence that the second lactone grouping of this compound was made by loss of hydrobromic acid between the terminal carboxyl and the bromine attached to Carbon 3.

When the dihydroxyl derivative of the lactone (IV) is boiled in the presence of a small amount of mineral acid the γ-lactone derivative (V) separates from solution, and since this is identical with the compound made by loss of hydrobromic acid from the monobromolactone, the position of the second lactone ring in this compound probably is between the terminal carboxyl and the hydroxyl group attached to Carbon 3 (V). Still further evidence for this is the failure to substitute the hydroxyl group giving a lactone with halogen in Position 3 when the lactone derivative is treated with phosphorus oxychloride, phosphorus pentachloride and thionyl chloride.

These reactions indicate that the terminal carboxyl tends to form a lactone with the hydroxyl group in Position 3a if the hydrogen in Position 3 is substituted with bromine, but if an hydroxyl group is attached to Carbon 3 the terminal carboxyl forms a lactone with it.

The monobromolactone (I) reacts in a peculiar manner with sodium hydroxide. This is shown as follows. If to 100 mg. of the bromolactone 3.6 cc. of 0.1 *N* sodium hydroxide solution is added, the solution still reacts acid with phenolsulfonephthalein as indicator. If a total of 4 cc. is slowly added, all acidic properties are neutralized and the indicator becomes pink. At this hydroxyl-ion concentration, a second reaction is brought about and the alkalinity of the solution rapidly increases. Sulfuric acid, 0.1 *N*, can now be added until the solution reacts neutral, and this is soon followed by the liberation of more sodium hydroxide until a total of approximately 0.6 cc. of 0.1 *N* sulfuric acid has been added. Determination of the sodium bromide in the solution shows that only 1.9 cc. of 0.1 *N* sodium bromide is present; therefore, the increase in the alkalinity of the solution was due to closure of the lactone between the

terminal carboxyl and the hydroxyl group either on 3 or 3a. The total amount of alkali neutralized was 3.5 cc. of 0.1 *N*. The bromide removed was 1.9 cc., 0.1 *N*, which leaves 1.6 cc. of carboxyl neutralized with sodium hydroxide.

The relation between the sodium hydroxide required and the hydrobromic acid neutralized is evidence of lactone formation brought about by the sodium hydroxide. This was confirmed by separation of crystals of the γ-lactone of the 3,3a-dihydroxyl derivative (V). If, however, the sodium hydroxide first removes the bromine from Carbon 3, replacing it with hydroxyl, there is no evidence that the terminal carboxyl forms a lactone with an hydroxyl group on either Carbon 3 or 3a, at room temperature.

2-Oxo-hexahydro-indole-3-propionic acid[1] reacts with bromine in a manner entirely similar to the corresponding lactone. If the bromine is added to an aqueous solution of the lactam, the monobromolactam separates (VIII) and if the lactam is present as a monosodium salt in a solution containing sodium acetate the δ-lactone of the monobromo derivative separates (IX). It is, however, much easier to open the δ-lactone of the bromolactam than of the bromolactone. The last-mentioned compound can be heated in concd. hydrobromic acid without opening the second lactone ring. With the bromolactam the presence of even a small amount of mineral acid will bring about this reaction at room temperature. For each equivalent of bromine added to the lactam one equivalent of sodium bromide is formed. The bromine can be reduced from the monobromolactam with formation of the original material. Treatment with sodium hydroxide replaces the bromine forming the dihydroxyl derivative which exists in two forms (XI and XII) corresponding to the bromolactam.

Fusion of the 3,3a-dihydroxyl-lactam with sodium hydroxide decomposes this compound giving products similar to those obtained from the corresponding hydroxyl-lactone with sodium hydroxide. Succinic and acetic acids were identified, and an amine which precipitates from ether solution with carbon dioxide. Its chemical properties closely simulate those of *o*-aminocyclohexanol,[3] but insufficient material was obtained for its identification. The formation of this compound would correspond to the production of cyclohexane glycol from the hydroxyl-lactone. In addition to these compounds a volatile, crystalline substance was obtained which appeared to be a dimolecular derivative of the hydro-indole, $C_{11}H_8N$. No valeric or other acid-insoluble products were formed. These reactions are evidence that the hydroxyl groups are attached to Carbons 3 and 3a, and that the dihydroxyl-lactam decomposes in two ways, one giving succinic acid and a derivative of cyclohexane, the other giving a hydro-indole

[3] Osterberg and Kendall, THIS JOURNAL, **42**, 2616 (1920). Brunel, *Ann. chim. phys.*, **6**, 253 (1905).

derivative and malonic acid which decomposes into carbon dioxide and acetic acid.

In the lactone of the dihydroxyl derivative of the lactam (XII) the terminal carboxyl is probably combined with the hydroxyl group on Carbon 3. Evidence for this is the impossibility of forming the 3-halogen derivative of the lactam by treatment of the lactone of the dihydroxyl-lactam with phosphorus pentachloride, phosphorus oxychloride or thionyl chloride. Further evidence for this is the preparation of the γ-lactone by boiling the dihydroxyl-lactam (XI) in mineral acid. It is impossible to close the δ-lactone of the bromolactam by heating in acid. The γ-lactone of the 3,3a-dihydroxyl derivative is also made from the 3-bromo-3a-hydroxyl-lactam (VIII) with sodium hydroxide (X).

Reactions of 2-Oxo-dihydro-indole-3-propionic Acid with Halogen.—Mono-, di- and trihalogen derivatives of 2-oxo-dihydro-indole-3-propionic acid have been described.[1] At that time a tentative formula was given for these compounds.

Further work with this series of compounds has indicated the structures of the two forms of the halogen and hydroxyl derivatives of the hexahydrolactones and lactams, and investigation of the decomposition products of the derivatives of 2-oxo-dihydro-indole-3-propionic acid has resulted in identification of the positions held by the entering halogens and the chemical properties are satisfactorily explained by the following structures. The position first substituted in 2-oxo-dihydro-indole-3-propionic acid is the hydrogen attached to Carbon 3. If two equivalents of iodine are added to the sodium salt of the lactam, all the iodine is found in solution as sodium iodide and crystals may be separated which contain no iodine. This crystalline compound exists in two forms apparently similar to the lactones and lactams described. When treated with hydriodic acid it shows oxidizing power. Since the chemical properties and percentage composition of this substance correspond to the original lactam with the addition of a molecule of water and loss of two atoms of hydrogen, the original structure assigned was an open pyrrolidone ring with a bond between Carbon 7 and the nitrogen (XIV). The neutral form was assigned a lactone structure somewhat similar to the neutral forms of the lactams already described (XV).

Definite evidence for the structure of this compound is furnished by fusion with sodium hydroxide. The original lactam (XIII) heated in an atmosphere of hydrogen with sodium hydroxide to a temperature of 200° can be recovered unchanged. The product obtained after treating the lactam with two equivalents of iodine decomposes under similar conditions and aniline[4] is volatilized from the fusion flask. This is evidence that Carbon 3 is the point of attack, and the 3-hydroxyl derivative of the original

[4] Hofmann, *Ann.*, **53**, 11 (1845).

lactam is the probable structure of the product obtained after treatment with iodine (XVI). When this compound is heated it loses water and a γ-lactone is formed between the terminal carboxyl and the 3-hydroxyl group with loss of acidic properties (XVII). Such a compound would not add bromine or ozone to a double bond, but could react with hydrobromic acid and could be reduced with hydriodic acid or sodium amalgam.

When the 3-hydroxyl-lactam is treated with methyl sulfate a dimethyl derivative is obtained. One methyl group is attached to the hydroxyl and the second methyl group is presumably attached to the nitrogen, but only one methyl group can be determined with hydriodic acid, as the second methyl group apparently migrates from the nitrogen and is then stable to hydriodic acid.

If the dibromo or di-iodo derivative of this lactam is brominated,[1] the bromine enters a position in which it is exceedingly unstable. This trihalogen compound will lose hydrobromic acid in acetic acid with sodium acetate or in alcoholic solution with cold dil. sodium hydroxide. The resulting product is neutral, and has a percentage composition of a γ-lactone of a dihalogen derivative of the 3-hydroxyl-lactam. The bromine apparently substitutes the hydrogen in Position 3. This is confirmed by the result of alkaline fusion; a volatile oil was obtained which after purification proved to be 2,4-dibromo and 2,4-di-iodo-aniline.[5]

When 2-oxo-dihydro-indole-3-propionic acid is treated with bromine, Position 3 appears to be the primary point of attack; however, it is possible to prepare the 3-hydroxyl-lactam, and the γ-lactone of this compound will form a monobromo substitution product. The only point of interest of this compound is the position occupied by the bromine. Since the compound is easily decomposed with alkali it is difficult to separate sufficient of the monobromo-aniline for purposes of identification; this fact, however, suggests that the bromine occupies position 5 in the indole derivative, and is, therefore, *para* to the amine group. Bromine in the *para* position to the nitrogen is much less stable to alkaline fusion than it is in the *ortho* position. The traces which were separated melted too high for the *o*-bromo-aniline, although it was impossible to purify it sufficiently to obtain a sharp melting point which agreed with the *p*-monobromo-aniline.

The structures of the three halogenated compounds are, therefore, 5-monobromo-, 5,7-dibromo- and 3,5,7-tribromo-2-oxo-dihydro-indole-3-propionic acid.

A remarkable property of this series of compounds is the ease with which the hydrogen of Carbon 3 is oxidized to hydroxyl. In a slightly alkaline solution molecular oxygen will oxidize this lactam and at a P_H of 7.4, dibromo-indophenol will bring about this oxidation. The details of this

[5] Ref. 4, p. 47.

reaction have been described elsewhere,[6] and further investigations of this reaction will be reported in the near future.

Experimental Part

Five determinations have been applied to the compounds described in the Experimental Part. (1) The "direct titration" is the amount of 0.1 *N* sodium hydroxide solution required to neutralize carboxyl groups. This has been determined in alcohol with a 100mg. sample and with phenolsulfonephthalein as indicator. (2) The "total titration" is the amount of 0.1 *N* sodium hydroxide solution neutralized by 100 mg. of the material after it has been boiled for five minutes with 15 cc. of 0.1 *N* sodium hydroxide solution, and the solution has been back-titrated with 0.1 *N* sulfuric acid. Phenolsulfonephthalein has also been used as indicator in this titration. (3) The "halogen removed" is the halogen in the solution removed by alkali. It has been determined with 0.1 *N* silver nitrate by the method of Volhard. This titration has been made after the solution has been boiled with alkali and acidified with nitric acid. (4) The "cold oxidizing power" is the amount of 0.1 *N* iodine liberated by adding 100 mg. of the compound to a cold solution of 2 g. of potassium iodide and 2 cc. of 1:1 hydrochloric acid contained in 15 cc. of glacial acetic acid. The iodine set free was titrated with 0.1 *N* sodium thiosulfate solution. (5) The "total oxidizing power" is the total amount of iodine liberated by 100 mg. of material. It has been determined by adding the substance to the acetic acid solution of potassium iodide and hydrochloric acid, and then boiling the solution under an inside reflux condenser for five minutes. After the solution has been boiled, it is removed as rapidly as possible from under the reflux and immediately cooled. Water is added until the volume is approximately 100 cc. and the free iodine is determined by 0.1 *N* sodium thiosulfate, with starch as indicator. Unless the solution is cooled rapidly after the refluxing, atmospheric oxygen will liberate iodine. These five determinations will be described as "direct titration" for carboxyl; "total titration" for total acid groups; "halogen removed" for inorganic halogen after boiling with 15 cc. of 0.1 *N* sodium hydroxide; "cold oxidizing power," and "total oxidizing power" for the iodine liberated from hydriodic acid. All melting points are uncorrected.

2-Oxo-3-bromo-3a-hydroxyl-octohydrobenzofuran-3-propionic Acid (I).—One-twentieth mole (10.5 g.) of 2-oxo-2,3,4,5,6,7-hexahydrobenzofuran-3-propionic acid is dissolved in 200 cc. of hot water and poured into a 500cc. glass-stoppered bottle containing 6 cc. of 9 *N* hydrobromic acid; 2.5 cc. of bromine is added, the bottle tightly stoppered, shaken, placed in a beaker of water on a steam-bath, and heated until no free bromine is present. The solution is concentrated in a vacuum to about 30 cc. The crystals which separate are filtered, thoroughly washed, and dissolved in 50 cc. of alcohol to which 150 cc. of water is added. The solution is allowed to stand for about one hour,

[6] Kendall, and Ort, *J. Biol. Chem.*, **68**, 611 (1926).

A small amount of the δ-lactone form of the bromolactone may separate. This is filtered off and the solution concentrated in a vacuum. Crystals again separate from the solution, are filtered, washed and dried; yield, about 50%; m. p., 147°.

Anal. Calcd. for $C_{11}H_{15}O_5Br$: C, 42.99; H, 4.92; Br, 26.03. Found: C, 42.71; H, 4.85; Br, 26.00.

Direct titration, 4.8; total titration, 9.9; halogen removed, 3.3 cc.; oxidizing power, 6.4 cc.

To prepare the δ-lactone form, 2.9 g. of the monobromolactone is dissolved in 100 cc. of boiling xylene, which is refluxed for one hour; after standing for several hours crystals separate; yield, 1.9 g. These are treated with 5 cc. of alcohol to dissolve any unchanged material. Thirty cc. of water is then added and the solution filtered. The crystals recrystallized from xylene are identical with the δ-lactone form (II), m. p. 144°, and when mixed with the δ-lactone of the monobromolactone the melting point is unchanged.

δ-Lactone of 2-Oxo-3-bromo-3a-hydroxyl-octohydrobenzofuran-3-propionic Acid (II).—One-tenth mole (20.9 g.) of 2-oxo-2,3,4,5,6,7-hexahydrobenzofuran-3-propionic acid is dissolved in 300 cc. of water containing 20 cc. of 5 *N* sodium hydroxide and 5.3 g. of sodium carbonate. To this is slowly added 5.5 cc. of bromine. The solution is allowed to stand for 18 hours. The crystals which separate are filtered, washed and air dried; yield, 90%; m. p., 144°.

Anal. Calcd. for $C_{11}H_{13}O_4Br$: C, 45.67; H, 4.53; Br, 27.65. Found: C, 45.40; H, 4.46; Br, 27.25.

Direct titration, none; total titration, 10.6 cc.; halogen removed, 3.4 cc.; cold oxidizing power, none; total oxidizing power, 7.0.

2-Oxo-3,3a-dihydroxyl-octohydrobenzofuran-3-propionic Acid (IV).—The γ-lactone of the 3,3a-dihydroxyl-lactone (V) is dissolved in an excess of warm sodium hydroxide solution. The sodium hydroxide is then neutralized with just an equivalent amount of sulfuric acid and the solution is concentrated in a vacuum. After standing for a short time crystals separate; m. p., 164°; direct titration, 4.1 cc.; total titration, 8.6 cc.; oxidizing power, none. If this substance is boiled with 15 cc. of 0.1 *N* sulfuric acid, the solution will back-titrate 15 cc. of 0.1 *N* sodium hydroxide, and the γ-lactone of this derivative can be separated from solution.

γ Lactone of 2-Oxo-3,3a-dihydroxyl-octohydrobenzofuran-3-propionic Acid (V).—One-tenth mole (29 g.) of 3-bromo-3a-hydroxyl-octohydrobenzofuran-3-propionic acid is dissolved in 200 cc. of 1 *N* sodium hydroxide solution and heated to boiling. The solution is made slightly acid with 11 cc. of 10 *N* sulfuric acid and is boiled for 20 minutes. On cooling, crystals of the γ-lactone of the 3,3a-dihydroxyl derivative of the lactone separate. These may be recrystallized from aqueous alcohol; m. p., 146°.

Mol. wt. Subs., 0.2017; in C_6H_5OH, 15.07; Δt, 0.412°. Calcd. for $C_{11}H_{14}O_5$: mol. wt., 226. Found: 246.

Anal. Calcd. for $C_{11}H_{14}O_5$: C, 58.38; H, 6.24. Found: C, 58.34; H, 6.12.

Direct titration, none; total titration, 9.0 cc.; oxidizing power, none.

The γ-lactone of the 3,3a-dihydroxyl-lactone is prepared as follows.

One g. of the 3-bromo, 3a-hydroxyl-lactone is dissolved in a small amount of alcohol, to which 100 cc. of water is added. To this, 4 cc. of 1 *N* sodium hydroxide solution is added and the solution is concentrated in a vacuum. It is allowed to stand for several hours; crystals which separate are removed by filtration. After washing and drying, these crystals are identical with the γ-lactone of the 3,3a-dihydroxyl derivative of the lactone.

2-Oxo-3-bromo-3a-hydroxyl-octohydro-indole-3-propionic Acid (VIII).—One-

twentieth mole (10.5 g.) of the lactam is dissolved in 200 cc. of boiling water. The hot solution is poured into a pressure bottle containing 6 cc. of constant-boiling hydrobromic acid; 2.5 cc. of bromine is added by allowing the bromine to run down the side of the bottle. The stopper is quickly clamped and the contents are well shaken. Most of the bromine disappears in a few minutes and crystals separate as the solution cools. These are filtered, washed and dried; yield, 12 g.; m. p., 156°.

Anal. Calcd. for $C_{11}H_{16}O_4NBr$: C, 43.13; H, 5.27; Br, 26.11. Found: C, 43.12; H, 5.25; Br, 25.90.

Direct titration, 3.4 cc.; total titration, 6.8 cc.; halogen removed, 3.3 cc.; total oxidizing power, 6.5 cc.

It is impossible to make the δ-lactone of the 3-bromolactam by heating this substance in xylene. The solution becomes brown, and the bromolactam rapidly decomposes.

δ-Lactone of 2-Oxo-3-bromo-3a-hydroxyl-octohydro-indole-3-propionic Acid (IX).—One-tenth mole (21 g.) of 2-oxo-2,3,4,5,6,7-hexahydro-indole-3-propionic acid is dissolved in 100 cc. of water by the addition of 20 cc. of 5 *N* sodium hydroxide solution. To this is added 5 cc. of bromine in 100 cc. of 2 *N* sodium hydroxide solution. With agitation, 40 cc. of 5 *N* sulfuric acid is then added. The free bromine which has not reacted is removed in a vacuum and the crystals are filtered off; yield, 17 g.

An alternative method is to dissolve 0.1 mole of the lactam in water containing one equivalent of sodium hydroxide. The solution is made to contain 25% of acetic acid with a volume of about 300 cc. by the addition of acetic acid. By means of an air stream, 5 cc. of bromine is then aerated into the cold solution. Crystals separate in a few minutes; yield, 20 g. These crystals are the δ-lactone of the 3-bromo-3a-hydroxyl-lactam; m. p., 153°.

Anal. Calcd. for $C_{11}H_{14}O_3NBr$: C, 45.83; H, 4.90; Br, 27.76. Found: C, 45.77; H, 4.84; Br, 28.00.

Direct titration, none; total titration, 7.2 cc.; halogen removed, 3.5 cc.; cold oxidizing power, none; total oxidizing power, 7.0 cc.

2-Oxo-3,3a-dihydroxyl-octohydro-indole-3-propionic Acid (XI).—Fourteen g. (0.05 mole) of the 3-monobromo-3a-hydroxyl-lactam (VIII or IX) is dissolved in 40 cc. of 5 *N* sodium hydroxide solution, and the solution is warmed to 60°. After cooling, 42 cc. of 5 *N* sulfuric acid is added and the crystals which separate are filtered off; yield, 7.3 g.; m. p., 180°.

Anal. Calcd. for $C_{11}H_{17}O_5N$: C, 54.29; H, 7.04. Found: C, 54.37; H, 6.89.

Mol. wt. Subs., 0.1500; in C_6H_5OH, 12.66; Δt, 0.42°. Calcd. for $C_{11}H_{15}O_4N$: mol. wt., 225. Found: 213.

γ-Lactone of 2-Oxo-3,3a-dihydroxyl-octohydro-indole-3-propionic Acid (XII).—When the 3,3a-dihydroxyl-lactam is dissolved in boiling dilute mineral acid, the γ-lactone (XII) crystallizes from solution. The compound may be recrystallized from aqueous alcohol; m. p., 206°.

Anal. Calcd. for $C_{11}H_{15}O_4N$: C, 58.64; H, 6.66. Found: C, 57.96; H, 6.58.

Direct titration, none; total titration, 5.2 cc.; total oxidizing power, none.

This compound can be made from the 3-monobromo-3a-hydroxyl-lactam with dil. sodium hydroxide solution. One g. of the 3-monobromolactam is dissolved in a small amount of alcohol and water. To this, 4 cc. of 1 *N* sodium hydroxide is added. The solution is concentrated and allowed to stand. The crystals are filtered, washed and recrystallized from alcohol and water; m. p., 206°. When mixed with the γ-lactone of the 3,3a-dihydroxyl-lactam, the melting point is unchanged.

Formation of Cyclohexadiene Glutaric Acid from 2-Oxo-hexahydrobenzofuran-

3-propionic Acid with Sodium Hydroxide.—Ten g. of 2-oxo-hexahydrobenzofuran-3-propionic acid is heated with 50 cc. of saturated sodium hydroxide solution in a 300cc. Pyrex distilling flask, through which oxygen-free hydrogen is continually passed. The flask is immersed in a Woods' metal bath maintained at 180 to 200°. Water is driven out of the flask, and the contents crystallize to a solid, white mass. This is dissolved in water and when made acid with sulfuric acid crystals separate. These are purified from boiling water; yield, 75%; m. p., 219°; direct titration, 9.3 cc.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.82; H, 6.71. Found: C, 62.30; H, 6.44.

This compound slowly adds two atoms of bromine in acetic acid solution. The bromo addition product easily decomposes with loss of hydrobromic acid.

Formation of *trans*-Cyclohexane Glycol, Succinic Acid and Valeric Acid from 3,3a-Dihydroxyl-2-oxo-octohydrobenzofuran-3-propionic Acid.—Ten g. of the 3,3a-dihydroxyl derivative of the lactone is dissolved in 15 cc. of water containing a small amount of sodium hydroxide. To this is added 50 cc. of saturated sodium hydroxide solution. The flask is heated in a Woods' metal bath to 200° and oxygen-free hydrogen is passed through the flask. The water which volatilizes from the solution is saturated with potassium carbonate. A small amount of oil separates from the water which is removed and extracted with hot benzene. After evaporating the benzene to small volume, crystals separate; purified by recrystallization from benzene, m. p. 104°.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.01; H, 10.41. Found: C, 62.03; H, 9.82.

The melting point of the dibenzoyl derivative is 93°. The dibenzoyl derivative of *trans*-cyclohexane glycol prepared from cyclohexane oxide with water melted at 93°. When mixed with the dibenzoyl derivative of the gycol prepared from the alkaline fusion of the hydroxyl-lactone, the melting point was unchanged.

Separation of Succinic Acid.—The fusion melt in the flask, after the temperature reaches 200°, is dissolved in water and made acid with hydrochloric acid. The solution is evaporated to dryness and the sodium chloride residue and organic material are extracted with ether. The ether is evaporated to dryness and the residue purified by crystallization from water; m. p., 185°.

Neut. equiv. Subs., 0.1000: 16.90 cc. of 0.1 *N* alkali. Calcd. for $C_4H_6O_4$: 16.94 cc.

The *p*-toluide melts at 255°. The boiling point and saponification number of the diethyl ester of this acid agree with those of diethyl succinate.

Valeric Acid.—When the alkaline fusion of the 3-hydroxyl derivative of the lactone is heated to 300° in an atmosphere of hydrogen a volatile acid passes over with steam after the fusion melt has been acidified with hydrochloric acid. The acid is not easily soluble in water; it separates in oily drops. The aqueous distillate is extracted with ether and the ether is removed by distillation. The residue in the flask is distilled; 0.1100 g. required 10.2 cc. of 0.1 *N* sodium hydroxide, indicating a molecular weight of approximately 100. The acid chloride prepared by means of thionyl chloride may be converted to the acid amide with aqueous ammonia. The acid amide separates from the ammoniacal solution with potassium carbonate and on recrystallization from ether melts at 114°.

Anal. Calcd. for $C_5H_{11}ON$: N, 13.8. Found: 13.6.

Formation of an Indole Derivative, Succinic and Acetic Acids, from 2-Oxo-3,3a-dihydroxyl-octohydro-indole-3-propionic Acid with Sodium Hydroxide.—Sodium hydroxide converts 2-oxo-hexahydro-indole-3-propionic acid quantitatively into 2-keto-cyclohexane-1-α-glutaric acid, which is then changed into cyclohexadiene glutaric acid with alkaline fusion. The 3,3a-dihydroxyl derivative of 2-oxo-hexahydro-indole-3-propionic acid loses only a small amount of its nitrogen as ammonia when fused with sodium hydroxide. Ten g. of the 3,3a-dihydroxyl derivative is heated in the presence

of hydrogen in a 300cc. Pyrex flask, with 50 cc. of saturated sodium hydroxide, after the lactam has been dissolved in 15 cc. of water with a small amount of sodium hydroxide. When the temperature reaches about 170° a volatile oil, which crystallizes, distils with the water. The crystals are separated by extraction with ether and may be crystallized from a mixture of alcohol and water; m. p., 132°.

Anal. Calcd. for $C_8H_{11}N$: C, 79.28; H, 9.16; N, 11.57. Found: C, 79.39; H, 8.80; N, 10.64.

Mol. wt. Subs., 0.1392; in C_6H_5OH, 12.42: Δt, 0.468°. Calcd. for $C_{16}H_{22}N_2$: mol. wt., 242. Found: 182.

This compound in acid solution forms a bromine addition product which is decomposed in boiling water with the liberation of the original material, and bromine does not substitute hydrogen. The positions of the bonds in the molecule were not identified.

Sodium hydroxide separates an amine from the water which distils from the fusion flask. The oil is extracted with ether and if carbon dioxide is passed through the dried ether solution a precipitate is formed. This may be redissolved in water, precipitated with sodium hydroxide and re-extracted with ether. Its chemical properties suggest that it is *o*-aminocyclohexanole.

Succinic Acid.—Succinic acid was separated from the sodium hydroxide fusion in a manner entirely similar to the isolation of this material from the 3-hydroxyl-lactone. It was identified by melting point, carboxyl titration and the toluide.

Acetic Acid.—From the aqueous solution of the sodium hydroxide fusion a volatile acid is obtained after acidification with hydrochloric acid. Sodium hydroxide is added to the distillate and the solution evaporated to dryness. Sirupy phosphoric acid and ether are added to the beaker and the organic acid extracted with the ether. The ether is removed and the *p*-toluide prepared. Its melting point, 147°, is that of acetic acid toluide.

Fusion of 2-Oxo-dihydro-indole-3-propionic Acid with Sodium Hydroxide.—Ten g. of this lactam is heated in a 300cc. Pyrex distilling flask in an atmosphere of hydrogen with 50 cc. of saturated sodium hydroxide solution, after the material has been dissolved in a few cubic centimeters of water containing sodium carbonate. The atmosphere of hydrogen prevents oxidation of the lactam. The heating is carried out at 200° for one hour. The solution is cooled and water added in the presence of hydrogen. The solution of the fusion mass is made acid with hydrochloric acid. The original lactam precipitates unchanged.

Formation of Aniline from 3-Hydroxyl-2-oxo-dihydro-indole-3-propionic Acid.—When the 3-hydroxyl derivative is fused under similar conditions, a volatile oil is given off at about 210°. The oil is extracted with ether and treated with acetic anhydride. The acetyl derivative is purified by crystallization from hot water; m. p., 114°. The 5,7-dibromo derivative of the 3-hydroxyl-lactam decomposes with sodium hydroxide at 170–180°. The volatile oil is purified by steam distillation, and crystallized from alcohol and water; m. p., 79°; acetyl derivative, m. p. 146°. This agrees with the melting point of 2,4-dibromo-aniline and its acetyl derivative.

Anal. Calcd. for $C_6H_5NBr_2$: Br, 63.70. Found: 63.71.

The 5,7-di-iodo-3-hydroxyl derivative of this lactam, fused with sodium hydroxide, gives an oil which is crystallized from alcohol and water; m. p., 95°. When mixed with 2,4-di-iodo-aniline the melting point was unchanged.

Anal. Calcd. for $C_6H_5NI_2$: I, 73.59. Found: 73.15.

Methylation of 3-Hydroxyl-5,7-dibromo-2-oxo-dihydro-indole-3-propionic Acid.—Seven and two-tenths g. of the γ-lactone of 5,7-dibromo-3-hydroxyl-2-oxo-dihydro-

indole-3-propionic acid is dissolved in 40 cc. of 2 *N* potassium hydroxide solution, and treated with 24 cc. of dimethyl sulfate and 40 cc. of 6.5 *N* sodium hydroxide solution. The dimethyl sulfate and alkali are added alternately in 2cc. portions with vigorous shaking after each addition. Twenty cc. of 10 *N* sodium hydroxide is added and the products are saponified by boiling for 90 minutes. The solution is made acid and the semi-solid precipitate washed a few times in water. This is dissolved in 95% alcohol and diluted to approximately 50% with water. Crystals separate; yield, about 75%; m. p., 140°.

Anal. Calcd. for: $C_{13}H_{13}O_4NBr_2$: C, 38.32; H, 3.21; Br, 39.26. Found: C, 38.31; H, 3.21; Br, 39.00.

Direct titration, 2.5 cc.; total titration, 2.5 cc.; halogen removed, none; oxidizing power, none.

The methyl groups were determined according to the Zeisel micro method.

Anal. Calcd. for $2CH_3$, 7.37; $1CH_3$, 3.65. Found: CH_3, 3.65.

The ultimate analyses for carbon, hydrogen and bromine indicate the presence of two methyl groups, but as only one can be removed with hydriodic acid it seems probable that the hydroxyl group on Carbon 3 is reduced by the hydriodic acid, and that the methyl attached to the nitrogen then migrates probably to Position 3 and is stable to hydriodic acid under conditions which will remove a methyl group attached to nitrogen.

Summary

2-Oxo-hexahydro-indole-3-propionic acid and its corresponding lactone react with hypobromous acid forming monobromo, monohydroxyl derivatives in which the bromine substitutes the hydrogen in Position 3 and the hydroxyl group is attached to Position 3a. The terminal carboxyl will form a δ-lactone with the hydroxyl group on Carbon 3a.

The bromine in these halogen derivatives can be replaced with hydroxyl by treatment with sodium hydroxide. These dihydroxyl derivatives form γ-lactones between the terminal carboxyl and the hydroxyl group on Carbon 3. They do not form δ-lactones.

2-Oxo-dihydro-indole-3-propionic acid and its mono- and dihalogen derivatives are easily oxidized, resulting in the formation of an hydroxyl group on Carbon 3. The hydroxyl group of these compounds will form a γ-lactone with the terminal carboxyl group.

The positions occupied by the bromine in the mono-, di- and tribromo derivatives of 2-oxo-dihydro-indole-3-propionic acid which have been described in a previous publication[1] have been determined. These halogen derivatives are 5-mono-, 5,7,di- and 3,5,7,-tribromo-2-oxo-dihydro-indole-3-propionic acid, respectively.

ROCHESTER, MINNESOTA