28 and 22%, respectively. Several other coupling syntheses of more complex biaryls are described in this paper.

3. The hitherto uncertain constitution of the bromo and the nitro derivatives of 4-methylbiphenyl has been definitely established.

4. Several new acids have been prepared by partial oxidation of our methylbiphenyl derivatives. From two of these, fluorenone derivatives were prepared in excellent yields. The coupling reaction seems to offer great promise for the preparation of such derivatives.

5. Two new triarylmethyls have been prepared, containing each 4-methylbiphenyl as one of the three aryl groups.

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE SECTION ON BIOCHEMISTRY, THE MAYO FOUNDATION]

THE PREPARATION OF 2-OXO-DIHYDRO- AND 2-OXO-HEXAHYDRO-INDOLE-3-PROPIONIC ACID AND SOME OF THEIR HALOGEN DERIVATIVES STUDIES ON THYROID ACTIVITY. V

BY EDWARD C. KENDALL, ARNOLD E. OSTERBERG AND BERNARD F. MACKENZIE

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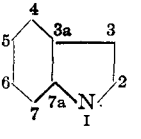
The isolation and identification of thyroxin was recorded in 1919.[1] At that time the ultimate analysis and chemical properties of the molecule indicated that the correct formula was 4,5,6-tri-iodo-2-oxo-2,4,5,6-tetrahydro-indole-3-propionic acid.[2] In order to prepare a series of compounds closely related to thyroxin and to prove the correctness of the structural formula assigned, an investigation was begun with the synthesis of thyroxin as its objective. Two possible methods of synthesis are (1) the preparation of 2-oxo-dihydro-indole-3-propionic acid with the subsequent hydrogenation of the benzene ring, and (2) the preparation of the hydro derivatives of 2-oxo-dihydro-indole-3-propionic acid and then, by appropriate oxidation, the formation of the nucleus which had been assigned to thyroxin. The latter course was adopted and all possible hydro derivatives have been made. In this paper, the synthesis of 2-oxo-dihydro- and 2-oxo-hexahydro-indole-3-propionic acid will be described.

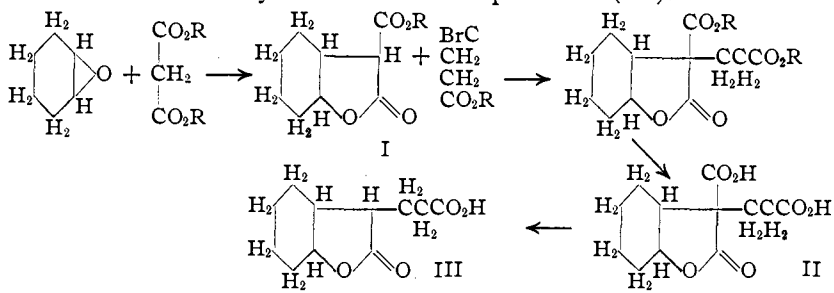
The general scheme of the synthesis involves the preparation of the corresponding lactones with the substitution of the oxygen of the lactone with

[1] Kendall and Osterberg, *J. Biol. Chem.*, **40**, 265 (1919).

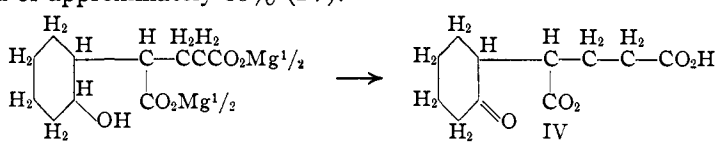
[2] The indole nucleus will be referred to by the following numbers, and the open pyrrolidone ring compounds will be numbered in the usual manner for aromatic derivatives.



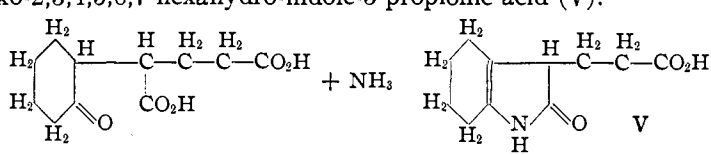
nitrogen to form the desired lactam. The synthesis of the lactones was accomplished through the condensation of cyclohexene oxide with malonic ester I and the subsequent addition of the propionic acid grouping. These reactions form a tricarboxylic compound which condenses into a dicarboxylic lactone when the sodium salt is acidified (II). When the dicarboxylic lactone is heated, carbon dioxide is given off and the propionic acid derivative of 2-oxo-octohydro-benzofuran is produced (III).



The oxygen in this lactone cannot be substituted with nitrogen, and great difficulty was encountered in producing any lactam from this substance. It was found, however, that oxidation of 2-oxo-octohydro-benzofuran-3-propionic acid could be brought about easily with bromine in an aqueous solution of its magnesium salt in the presence of magnesium hydroxide. The hydroxyl group which forms the lactone is oxidized to a ketone with a yield of approximately 85% (IV).

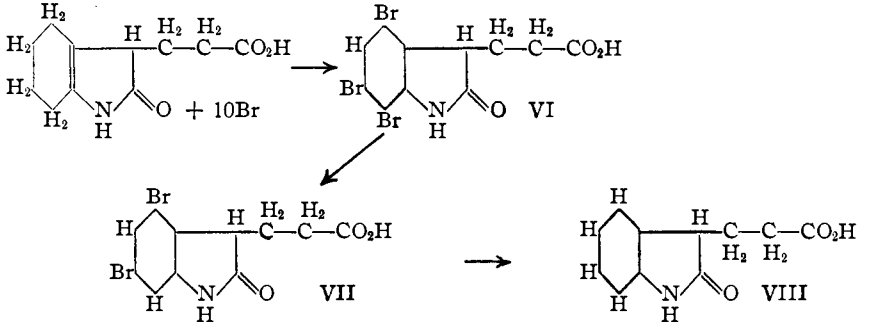


The resulting 2-keto-cyclohexane-α-glutaric acid is treated in alcohol saturated with ammonia gas. By this simple reaction an almost quantitative substitution of the ketone group occurs with the production of 2-oxo-2,3,4,5,6,7-hexahydro-indole-3-propionic acid (V).



The substitution of the ketone with the imino group NH and the formation of the lactam is a reversible reaction. When the lactam is boiled with sodium hydroxide, ammonia is expelled and the ketone acid is again formed. This lactam reacts with bromine in many different ways depending on the conditions present during the bromination. In glacial acetic acid bromine oxidizes the compound removing four atoms of hydrogen and substituting three others forming the 4,6,7-tribromo-2-oxo-dihydro-indole-3-propionic

acid (VI). This compound dissolved in glacial acetic acid is reduced with zinc dust to the 4,6-dibromo-2-oxo-dihydro-indole-3-propionic acid (VII). The sodium salt of this dibromo derivative in water can be reduced with sodium amalgam with the loss of the two atoms of bromine and the formation of 2-oxo-dihydro-indole-3-propionic acid (VIII).



This compound is readily soluble in boiling water and is quite insoluble in cold water so that its purification is easily accomplished. When dissolved in glacial acetic acid and treated with bromine, it again forms the 4,6,7-tribromo derivative. The reasons for placing two atoms of bromine in Positions 4 and 6 will be given in a later publication. The reasons for placing the third atom of bromine on Carbon 7 are as follows. Two of the bromine atoms are stable to alkali and to reduction with both zinc and hydriodic acid. The third bromine atom is removed with cold 0.1 *N* sodium hydroxide solution in alcohol, with zinc dust in cold acetic acid, and with warm hydriodic acid. It also breaks out of the molecule forming hydrogen bromide when the tribromo derivative is refluxed in glacial acetic acid.

The only positions which an atom of bromine could occupy and have these properties are on the nitrogen or carbon atoms 3 and 7. The bromine cannot be on the nitrogen as it is not reduced in cold hydriodic acid, and alkali does not remove it as sodium hypobromite. Furthermore, it is made in glacial acetic acid containing hydrobromic acid and any bromine attached to the imino group would tend to migrate from the nitrogen to carbon under these conditions. It cannot be on Carbon 3, as a derivative has been made with bromine in this position and its properties are markedly different. Carbon 7, therefore, is the only possible position which the third atom of bromine can occupy.

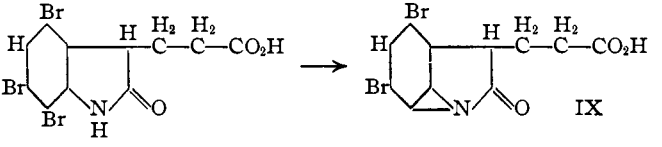
Formation of an Imine Group in 2-Oxo-dihydro-indole-3-propionic Acid[3]

This grouping is similar to that in ethylene-imine and its formation is quite similar. Ethylene-imine is produced by the removal of hydrogen bromide between a primary amine group and an adjacent carbon atom,

[3] Kendall, *Ind. Eng. Chem.*, **17**, 525 (1925).

to which bromine is attached. The formation of a similar bond between Carbon 7 and the nitrogen follows the same course.

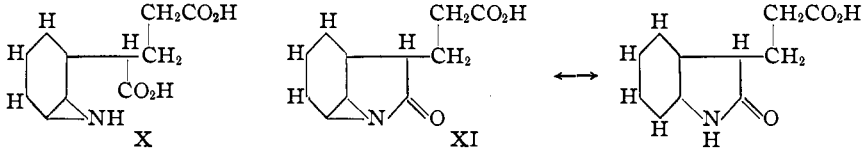
When 4,6,7-tribromo-2-oxo-dihydro-indole-3-propionic acid is dissolved in glacial acetic acid and sodium acetate is added, hydrobromic acid splits out of the molecule between Carbon 7 and the nitrogen forming an imine grouping. This compound IX exists with the pyrrolidone ring open or closed. In this paper this bond will be referred to as the nitrogen bond.



IX

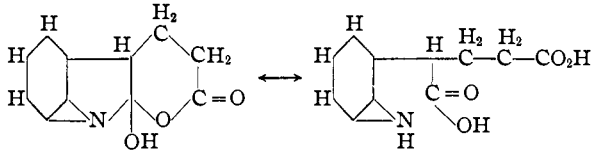
When 2-oxo-dihydro-indole-3-propionic acid is treated in acetic acid with iodine and iodic acid, the bond from Carbon 7 to the nitrogen is first formed (XI). Iodine then substitutes on Carbon 6 and finally on Carbon 4. Bromine does not add to the nitrogen bond in this molecule but hydriodic acid reduces the bond and forms 4,6-diiodo-2-oxo-dihydro-indole-3-propionic acid.

When 2-oxo-dihydro-indole-3-propionic acid is dissolved in a solution of four molecular equivalents of sodium hydroxide, and two equivalents of iodine are added to this solution, it is found that almost no free iodine is present when the solution is made acid. However, no iodine is organically combined. The solution may be made acid, the hydriodic acid removed, the water solution evaporated to a small volume and a crystalline material separates which is not the original lactam. Analysis of these crystals shows that they agree with a formula which contains two hydrogen atoms less than 2-oxo-dihydro-indole-3-propionic acid and in which the pyrrolidone ring is open. This compound is α(2,3-iminophenyl)glutaric acid (X). The carboxyl group is found to be present as one equivalent, by titration, using phenolsulfonephthalein as indicator. When these crystals are heated to 175° they melt, water is given off and the material that now can be crystallized from water is much less soluble. Its analysis agrees with that of a compound containing two hydrogen atoms less than 2-oxo-dihydro-indole-3-propionic acid but with the pyrrolidone ring closed. This compound is 2,3-dihydro-2-oxo-tricyclo-indole-3-propionic acid. The carboxyl in this compound does not affect phenolsulfonephthalein in aqueous or alcoholic solution. Its melting point is 116°. When it is boiled with alkali the open-ring form of 2-oxo-dihydro-indole-3-propionic acid with the bond from Carbon 7 to the nitrogen is again recovered. Furthermore, the nitrogen bond reduces easily with hydriodic acid, with the quantitative liberation of two equivalents of iodine, and 2-oxo-dihydro-indole-3-propionic acid is recovered after the reduction. The oxidation and reduction are reversible.



X XI

A full discussion of the structural formulas for this series of compounds will be reserved until a later publication. At this time data will be given concerning the properties of the terminal carboxyl group. All derivatives of 2-oxo-dihydro- and hexahydro-indole, which have a halogen on Carbon 7 or which contain the nitrogen bond, may be shown by titration to contain one acid equivalent when the pyrrolidone ring is open. None of these compounds, however, possesses acid properties in alcoholic or water solution when the pyrrolidone ring is closed. The explanation for this behavior is the fact that the side chain makes an addition product with the carbonyl group on Carbon 2 (XII). This 6-membered ring is stable in boiling water and acid, but is readily opened with dilute alkali. After the 6-membered ring and the pyrrolidone ring are open the terminal carboxyl has one acid equivalent indicated by titration.



It was furthermore found that the addition of bromine and iodine on Positions 4 and 6 alters the acidic properties of the molecule. When the unhalogenated lactam containing the nitrogen bond is boiled with three molecular equivalents of sodium hydroxide the terminal carboxyl may be shown by titration to contain one full acid equivalent. With the dibromo and diiodo derivatives, however, the titration value obtained after boiling with alkali indicates the presence of somewhat more than one carboxyl equivalent. The only explanation for this is the fact that the carboxyl group which forms the pyrrolidone ring does not react in titration to more than a small percentage of its total actual acid equivalent.

Another property which is affected by the addition of the halogen is the ease of reduction of the nitrogen bond. Hydriodic acid in boiling acetic acid reduces the bond of the unhalogenated molecule easily. The addition of one bromine in Position 6 renders the reduction more difficult, and the addition of two bromine atoms in Positions 4 and 6 necessitates prolonged refluxing before the bond is reduced.

Experimental Part

o-Chloro-cyclohexanol.[4,5]—Ten liters of water containing 900 g. of sodium hydroxide

[4] Fortney, *J. Chem. Soc.*, **73**, 932 (1898).

[5] Kendall and Osterberg, THIS JOURNAL, **42**, 2616 (1920).

and 250 g. of sodium carbonate is placed in an 18-liter carboy immersed in a jar of water and ice.

Chlorine is passed into this solution, the temperature being kept below 20° until the concentration of hypochlorite is such that 1 cc. of the solution will liberate iodine equivalent to about 17 cc. of 0.1 *N* sodium thiosulfate solution. (This is determined by periodically withdrawing 1cc. samples, adding water and potassium iodide, making acid with phosphoric acid, and titrating the iodine with 0.1 *N* thiosulfate solution.) When between 15 and 20 cc. is required for titration, cyclohexene is added. For every cubic centimeter required in titration, 50 cc. of cyclohexene is used.

From 500 to 800 cc. of carbon tetrachloride is added for the purpose of dilution and to raise the specific gravity so that the final water solution can be decanted. A rapid current of carbon dioxide is now passed into the solution, which is mechanically stirred for about ten minutes. The carbon dioxide is then stopped for about two minutes, but the stirring is continued. The gas is again passed in for about ten minutes. Treatment with carbon dioxide is continued in this manner until no iodine is liberated from potassium iodide by the withdrawn samples.

The intermittent addition of carbon dioxide is to prevent the separation of sodium bicarbonate. If this does occur, it is filtered with suction and washed with carbon tetrachloride.

The top layer is decanted and the lower layer distilled.

The carbon tetrachloride solution is placed in a 2-liter flask and distilled until the temperature is 120° with the thermometer immersed in the solution, and then cooled. The distillation is then carried on with water suction. A low-boiling fraction containing some carbon tetrachloride is separated up to 90° with the thermometer in the neck of the flask.

The fraction boiling from 90° to 130° in a vacuum is collected and may be purified by redistillation; b. p., 92° (10 mm.); yield, 70%.

Cyclohexene Oxide.[6]—Nine moles (360 g.) of sodium hydroxide is dissolved in 2000 cc. of water in a 5-liter flask and the solution is cooled to room temperature. To this solution 1000 cc. of *o*-chlorocyclohexanol is added and the mixture is stirred vigorously with a mechanical stirrer for one hour. The top layer is separated and fractionated through an efficient fractionating column. Three fractions are taken; (1) 100° to 129°, (2) 129° to 134°, and (3) 134° to 145°, the apparatus being dried between the distillation of the first and second fractions to insure an anhydrous material. This is essential for success in the subsequent steps.

The first and third fractions are fractionated and the material boiling between 129° and 134° is used as sufficiently pure cyclohexene oxide for the reactions described subsequently; yield, 70–75%; b. p., 133°.

2-Oxo-octohydro-benzofuran-3-propionic Acid. III.—Sixty-nine g. of sodium is entirely dissolved in a liter of absolute alcohol in a 5-liter flask, and 480 g. of malonic ester is added. This mixture is allowed to stand for ten minutes and then 300 cc. of cyclohexene oxide is added.[7] The solution is allowed to stand in a water-bath at 50° overnight. The alcohol is removed in a vacuum.

Three liters of benzene is added and the solid cake cut up into blocks small enough for a mechanical stirrer to reduce it to a thick, creamy consistency. To the suspension of this sodium addition product in benzene, 543 g. of β-bromopropionic acid ester is added and the suspension allowed to react at room temperature for three days.[8,9,10] Two

[6] Brunel, *Compt. rend.*, **136**, 384; **137**, 62 (1903). *Bull. soc. chim.*, **39**, 883 (1903).

[7] Traube and Lehmann, *Ber.*, **32**, 720 (1899); **34**, 1971 (1901).

[8] Conrad, *Ann.*, **204**, 127 (1880).

[9] Conrad and Brückner, *Z. physik. Chem.*, **7**, 283 (1891).

[10] Schey, *Rec. trav. chim.*, **16**, 356 (1897).

liters of benzene is removed on the steam-bath, the residue cooled and water added. Then the sodium bromide is washed from the benzene solution of the ester with two additions of water and the esters are fractionated as follows.

The benzene and water are removed at atmospheric pressure and a temperature of 100°. Then the residue is put under suction and raised to 170° in order to remove any unused propionic ester and malonic ester. The residue is cooled and washed with 300 cc. of 5 *N* sodium hydroxide solution. This removes the 2-oxo-octohydro-benzofuran that has not reacted with the bromopropionic ester. The residue is now weighed and 600 cc. of 5 *N* sodium hydroxide solution added for every 312 g. of substance. In order to saponify the esters rapidly, enough alcohol is used to effect a clear solution (about 500 cc.). When saponification is complete, the alcohol is removed by distillation until the temperature is 100° and then the sodium hydroxide is neutralized with an equivalent amount of sulfuric acid. The solution is boiled to close the lactone and then cooled to about 40° when the dicarboxylic lactone separates and is filtered off (II). The lactone recrystallized from toluene melts at 199° with evolution of carbon dioxide.

Anal. Calcd. for $C_{12}H_{16}O_6$: C, 56.22; H, 6.29. Found: C, 56.28; H, 6.30.

The mother liquor is extracted with ether to remove any further amount. The combined extracts are now heated to 200° for one hour in order to decarboxylate the substance by splitting off carbon dioxide from Carbon 3. The residue is then poured into a mortar and on cooling becomes a solid mass III. It may be purified by recrystallization from hot water; yield, 70–80%; m. p., 81°. Only one carboxyl group reacts upon titration; 100 mg. requires 4.71 cc. of *N*/10 sodium hydroxide.

2-Oxo-octohydro-benzofuran-3-carboxylic Acid Ester. I.—By treatment of the sodium addition product with acidulated water before the addition of bromopropionic acid ester, the 2-oxo-octohydro-benzofuran-3-carboxylic acid ester may be isolated by ether extraction and distillation; b. p., 199° (30 mm.).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.22; H, 7.59. Found: C, 62.05; H, 7.67.

By saponification and crystallization from water, the free acid is obtained; m. p., 120°, with loss of carbon dioxide.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.66; H, 6.56. Found: C, 58.47; H, 6.31.

***o*-Keto-cyclohexane-α-glutaric Acid and Its Lactone. IV.**—Two moles (424 g.) of 2-oxo-octohydro-benzofuran-3-propionic acid is dissolved in 1700 cc. of 5 *N* sodium hydroxide solution in a 5-liter flask by heating the mixture to boiling. The flask is placed under a stirrer and a hot solution of 1000 g. of magnesium sulfate heptahydrate in 700 cc. of water is slowly run in. The liquid is placed in an ice-bath and cooled below 10°. During stirring, 28 + 28 + 28 + 25 cc. of bromine are added in four portions at such a rate that the temperature does not rise above 10°. About three hours are required. It is allowed to stand overnight in the ice-bath. After the bromine is all added, no more ice is required, the bath being allowed to resume room temperature.[11,12]

The next morning 450 cc. of 10 *N* sulfuric acid is added and the solution is concentrated by boiling until the salts cause bumping. It is then cooled and the sirupy keto-cyclohexane-α-glutaric acid extracted with 1000 + 400 cc. of ether.

The ether is distilled and the last trace of ether and water removed by holding the flask under suction in a boiling water-bath for one hour. About 400 g. of crude acid remains in the flask.

Pure *o*-Keto-cyclohexane-α-glutaric Acid.—One mole (210 g.) of the lactone, described in the next paragraph, purified by recrystallization from benzene, is refluxed

[11] Houben-Weyl, "Die Methoden der organischen Chemie," Georg Thieme, Leipzig, 2nd. ed. **1922,** vol. ii, part 2, p. 49.

[12] Examples of similar oxidations are given by Houben-Weyl.

with 600 cc. of 5 *N* sodium hydroxide solution for two hours. After it has cooled, 200 cc. of 10 *N* sulfuric acid is added and the whole treated with Norite to decolorize it. The mixture is filtered and 100 cc. of 10 *N* sulfuric acid added. It is boiled down until the separation of sodium sulfate makes further boiling impossible. After being cooled, it is extracted with ether. The ether is removed and the residue dried in a vacuum at not above 100°. It is then poured into a mortar and crystallized. This acid, recrystallized from water, melts at 131°.

2-Oxo-hexahydro-benzofuran-3-propionic Acid.—The crude keto-cyclohexane-α-glutaric acid as already obtained is heated at 200° in a vacuum for two hours. The lactone closes with loss of one molecule of water. It is cooled to about 100° and poured into a 1-liter beaker containing about 600 cc. of benzene. On further cooling the lactone crystallizes in small white crystals. One more crystallization from boiling benzene usually suffices to give a pure product; yield, about 80%; m. p., 100°.

The carboxyl titrations and the properties of the lactone serve to identify these two substances. Titration of *o*-keto-cyclohexane-α-glutaric acid indicates the presence of two carboxyl groups; 100 mg. requires 8.76 cc. of 0.1 *N* sodium hydroxide solution, phenolsulfonephthalein being used as indicator. Titration of the lactone made by heating the keto acid to 200° indicates the presence of one carboxyl group; 100 mg. requires 4.70 cc. of 0.1 *N* sodium hydroxide solution. When the lactone is boiled with twice the calculated amount of 0.1 *N* sodium hydroxide solution the lactone opens slowly. This is shown in Table I. The lactone, 0.01 mole (2.09 g.), was dissolved in 400 cc. of 0.1 *N* sodium hydroxide. The solution was refluxed for four and one-fourth hours; 50 cc. portions were removed at the times indicated and titrated.

TABLE I

RATE OF OPENING LACTONE WITH SODIUM HYDROXIDE

Time, min.	0	15	45	75	105	135	195	255
0.1 *N* H_2SO_4 req. cc.	37.5	33.4	30.5	28.6	27.2	26.4	25.6	25.4
Lactone opened, %	0	32	55	70	82	88	94	96

Although many lactones are opened by boiling in alcohol in the presence of a mineral acid, this lactone cannot be opened in that manner. The terminal carboxyl group alone is esterified. To make the ester, 0.1 mole of the lactone is refluxed in 150 cc. of absolute alcohol and 3 cc. of concd. sulfuric acid overnight. The alcohol is removed in a vacuum. After the addition of water the mixture is extracted with ether. The neutral ester is obtained; b. p., 195–200° (8 mm.); yield, 84%.

When the keto-cyclohexane-α-glutaric acid is refluxed in absolute alcohol with sulfuric acid, the lactone ring is not closed but the di-ester is formed. The conditions for making the di-ester of the keto acid are the same as those for making the monoester of the lactone. Evidence for the ketone group in both the acid and the diester is given by the formation of the two hydrazones. To make the hydrazone of the keto-cyclohexane-α-glutaric acid, 1 mole (228 g.) of the keto acid is dissolved in 500 cc. of absolute alcohol in a 2-liter distilling flask. To this is added 100 cc. of phenylhydrazine. The alcohol is removed in a vacuum, care being taken that the temperature does not rise above 35° at any time. When a thick mass of crystals has formed, the distillation is stopped and the contents of the flask are filtered. The crystals are washed with benzene until pure white. The hydrazone recrystallized from benzene melts at 146°.

A second crop may be obtained by removing the alcohol and benzene from the filtrate in a vacuum. This usually has a reddish color that cannot be removed by washing with benzene.

About four crops may be obtained altogether. The last three are suspended in chloroform and pulverized. This treatment removes most but not all of the color.

Titration of the hydrazone indicates the presence of two carboxyl groups; 100 mg. requires 6.28 cc. of 0.1 *N* sodium hydroxide solution. The hydrazone boiled in xylene loses water, forming the pyridazinone melting at 126°. The pyridazinone can also be made by dissolving the hydrazone in concd. sulfuric acid, warming to 45°, allowing to stand for ten minutes and then pouring into cold water. The precipitate is recrystallized from xylene. Titration of this compound indicates the presence of one carboxyl group; 100 mg. requires 3.33 cc. of 0.1 *N* sodium hydroxide solution.

The ester hydrazone is made in the same manner as the hydrazone of the acid. However, it is much more soluble and the yield is poor. After the crystals are filtered and washed with benzene, they turn dark quite rapidly and decompose; m. p., 110°.

2-Oxo-2,3,4,5,6,7-hexahydro-indole-3-propionic Acid. V.—The hydro derivatives of 2-oxo-benzofuran-3-propionic acid show great differences in their ability to substitute nitrogen for oxygen. The lactone produced by heating keto-cyclohexane-α-glutaric acid does not substitute the imino group for oxygen. It has been found, however, that the keto acid itself when treated with alcoholic ammonia gives a practically quantitative yield of the corresponding lactam.[13,14]

Four hundred g. of crude keto-cyclohexane-α-glutaric acid is dissolved in 650 cc. of 95% alcohol and the solution divided equally among four pressure bottles, saturated with ammonia at a temperature of about 40°, stoppered and heated at 100° for four hours.

After cooling the alcohol solution it is poured into a 2-liter distilling flask, 500 cc. of water is added and about 400 cc. of water and alcohol is distilled; 500 cc. more of water is added and distilled. Finally, 500 cc. more of water is added and the distillation continued until the temperature reaches 100°. The solution is poured into a beaker and 200 cc. of 10 *N* sulfuric acid added. The lactam immediately crystallizes. It is cooled and filtered off. To recrystallize and purify, it is heated to 80° in 600 cc. of water containing 100 cc. of 10 *N* sodium hydroxide solution, Norite is added and the mixture filtered. A pale yellow solution is obtained. To it 100 cc. of 10 *N* sulfuric acid is added. After cooling, the crystals of the lactam are filtered off; m. p., 173°.

Anal. Calcd. for $C_{11}H_{15}O_3N$: C, 63.11; H, 7.23; N, 6.69. Found: C, 63.00; H, 7.18; N, 6.76.

Titration of this lactam in 25 cc. of 95% alcohol indicates the presence of one carboxyl group; 100 mg. requires 4.78 cc. of 0.1 *N* sodium hydroxide solution, phenolsulfonephthalein being used as indicator; yield, about 330 g. When pure keto acid is used the yield is almost quantitative.

When 2-oxo-2,3,4,5,6,7-hexahydro-indole-3-propionic acid is boiled in concd. sodium hydroxide solution, the ammonia is slowly but quantitatively expelled and the keto acid is regenerated. One-tenth mole (20.9 g.) of the lactam was slowly boiled with 80 cc. of 5 *N* sodium hydroxide solution in 400 cc. of water contained in an 800cc. Kjeldahl flask, until the volume was 100 cc.; 80 cc. of 5 *N* sulfuric acid was added. The solution was again concentrated and extracted with ether, and the keto-cyclohexane-α-glutaric acid separated in pure form. It was identified by carboxyl titration and by the formation of its hydrazone which gave the correct melting point for this substance.

4,6,7-Tribromo-2-oxo-dihydro-indole-3-propionic Acid. VI.—Eighty-four g. of 2-oxo-hexahydro-indole-3-propionic acid in 425 cc. of glacial acetic acid is heated, in a 1-liter distilling flask fitted with an inside reflux condenser, at 100° with 50 cc. of bromine until the drop of acetic acid on the end of the reflux condenser is colorless. This requires from 20 to 30 minutes. The hydrogen bromide is conducted from the flask

[13] Borsche and Fels, *Ber.*, **39**, 3877 (1906).

[14] Conversion of the ketone acid to the lactam closely resembles the conversion of certain diketones to the corresponding lactams.

through the side neck. The contents of the flask are now heated to 111°. After cooling, 50 cc. of bromine is added and the temperature kept at 100° for 15 minutes. The flask is attached to a condenser set for downward distillation and heated to 107°. After cooling, 20 cc. of bromine is added and the temperature is kept at 100° for 40 minutes. The mixture is now concentrated in a vacuum to a volume of approximately 150 cc. After the addition of 150 cc. of acetic acid it is again concentrated to the same volume. It is then allowed to crystallize for four hours. The crystals formed are filtered off, suspended in acetic acid and again filtered off; yield of 4,6,7-tribromo-2-oxo-dihydro-indole-3-propionic acid, 90 g.; m. p., 189°.

Anal. Calcd. for $C_{11}H_8O_3NBr$: Br, 54.26. Found: 53.46.

When the 4,6,7-tribromo derivative of the lactam is boiled in glacial acetic acid or is treated in cold alcohol with 0.1 *N* sodium hydroxide solution, one molecule of hydrobromic acid is quantitatively removed. One hundred mg. of the 4,6,7-tribromo derivative was dissolved in 50 cc. of cold alcohol and titrated with 0.1 *N* sodium hydroxide solution; 2.5 cc. was neutralized. The sodium hydroxide was not neutralized by a carboxyl group, however, but by hydrogen bromide which broke out of the molecule between carbon 7 and the nitrogen. The sodium bromide in the solution equaled 2.25 cc. of 0.1 *N* silver nitrate solution (calcd., 2.26 cc.).

The oxidizing power of this series of compounds was determined as follows. Two g. of potassium iodide, 2 cc. of 1:1 hydrochloric acid, and 20 cc. of glacial acetic acid were placed in a 125cc. Erlenmeyer flask; 100 mg. of the sample was added and the solution was refluxed for five minutes. The flask was then cooled as rapidly as possible to room temperature and the liberated iodine titrated with 0.1 *N* sodium thiosulfate solution. A blank similarly made titrated from 0.3 to 0.4 cc., and this amount is subtracted from the total volume of thiosulfate required. This determination will be referred to as the "oxidizing power." The "oxidizing power" of 4,6,7-tribromo-2-oxo-dihydro-indole-3-propionic acid is 4.9 cc. of 0.1 *N* sodium thiosulfate solution.

To prepare this tribromo derivative in pure form the purified 4,6-dibromo lactam described in the next paragraph is rebrominated; 18 g. of 4,6-dibromo-2-oxo-dihydro-indole-3-propionic acid is added to 100 cc. of glacial acetic acid containing 2.7 cc. of bromine. The solution is warmed to 60° when the bromine substitutes rapidly on Carbon 7 and after a few minutes crystals of the tribromo derivative separate. The hydrobromic and acetic acids and the slight excess of bromine are removed by evaporation in a vacuum to a volume of 50 cc. After two hours the crystals are filtered off, washed and dried; yield, 95%.

4,6-Dibromo-2-oxo-dihydro-indole-3-propionic Acid. VII.—Ninety g. of the 4,6,7-tribromo derivative made from 2-oxo-hexahydro-indole-3-propionic acid is suspended in 200 cc. of acetic acid in an 800cc. beaker. Small amounts of zinc dust are added during stirring until a total of about 30 g. has been added; then the mixture is heated over a free flame during constant stirring until the acetic acid is at its boiling point. As complete solution is never effected, caution must be observed to prevent charring. At the boiling point of acetic acid, the reduction takes place rapidly with the simultaneous crystallization of the dibromo compound. The mixture is allowed to cool, is filtered and the solid washed well with water. In order to remove the last of the acetic acid, it is necessary to suspend the substance in water, and again filter and wash.

The crystals are suspended in 400 cc. of 95% alcohol and dissolved with 50 cc. of 10 *N* sodium hydroxide solution forming a pale straw-colored liquid which is filtered to remove the undissolved zinc. One hundred cc. of 1:1 hydrochloric acid is added rapidly and the solution allowed to stand for ten minutes for complete crystallization. The substance is then filtered off and washed well with water.

Four hundred cc. of 10% sodium carbonate solution is heated to boiling in a 1-

liter beaker. The dibromo derivative is added to this and heating is continued until the crystals are all dissolved. On cooling, the monosodium salt of the open pyrrolidone ring form crystallizes. This is filtered on a Büchner funnel, washed with a small amount of water and pressed as dry as possible. After being removed from the funnel it is placed in a beaker, covered with 200 cc. of 95% alcohol, dissolved with 50 cc. of 5 *N* sodium hydroxide solution, and precipitated by the rapid addition of 100 cc. of 1:1 hydrochloric acid. After ten minutes, it is filtered off and well washed with water; yield, 55 g.

An additional 4 g. may be obtained in an impure condition by acidifying the sodium carbonate filtrate. This may be purified by another treatment in a smaller volume; m. p., 245°.

Anal. Calcd. for $C_{11}H_9O_3NBr_2$: C, 36.51; H, 2.50; Br, 44.07. Found: C, 36.23; H, 2.58; Br, 44.00.

Titration of 100 mg. of substance in 25 cc. of 95% alcohol requires 2.75 cc. of 0.1 *N* sodium hydroxide solution, indicating the presence of one carboxyl group.

4,6-Dibromo-2,3-dihydro-2-oxo-tricyclo-indole-3-propionic Acid. IX.—Twenty-two g. of pure tribromo derivative made by rebrominating the dibromo-lactam is placed in a beaker with 50 cc. of glacial acetic acid and 5 g. of sodium acetate.[15,16,17] The solution is heated to boiling for 20 minutes. On cooling, crystals separate to such an extent that the entire mass becomes solid. After filtration, the crystals are placed in a mortar, washed well with water and filtered again; yield, 18 g.; m. p., 219°.

Anal. Calcd. for $C_{11}H_7O_3NBr_2$: C, 36.56; H, 1.95; Br, 44.29. Found: C, 36.59; H, 1.88; Br, 44.10.

Titration of 100 mg. of substance dissolved in 25 cc. of 95% alcohol requires 0.15 cc. of 0.1 *N* sodium hydroxide solution; after boiling with 15 cc. of 0.1 *N* sodium hydroxide solution and back titrating with 0.1 *N* sulfuric acid, 3.1 cc. of 0.1 *N* sodium hydroxide solution is neutralized. The full "oxidizing power" of this derivative is determined only after it has been refluxed for from 30 to 40 minutes.

α-(4,6-Dibromo-2,3-iminophenyl)glutaric Acid.—Eighteen g. of 4,6-dibromo-2,3-dihydro-2-oxo-tricyclo-indole-3-propionic acid IX is boiled for three minutes with 25 cc. of 5 *N* sodium hydroxide solution in 100 cc. of water. After this mixture is cool, 100 cc. of 95% alcohol and 25 cc. of 1:1 hydrochloric acid are added. The solid formed is filtered off and well washed; yield, 18 g.; m. p., 199°, followed by recrystallization and second melting, 219°.

Anal. Calcd. for $C_{11}H_9O_4NBr_2$: C, 34.82; H, 2.31; Br, 42.11. Found: C, 34.81; H, 2.41; Br, 42.00.

Titration of 100 mg. of this substance dissolved in 25 cc. of 95% alcohol requires 2.6 cc. of 0.1 *N* sodium hydroxide solution; after the solution has been boiled with 15 cc. of 0.1 *N* sodium hydroxide solution and back titrated with 0.1 *N* sulfuric acid, 3.0 cc. of 0.1 *N* sodium hydroxide solution is neutralized. The full "oxidizing power" of this derivative is determined only after the solution has been refluxed for from 30 to 40 minutes.

2-Oxo-dihydro-indole-3-propionic acid. VIII.—One thousand g. of mercury is placed in a 1-liter suction flask and covered with 500 cc. of xylene; 30 g. of sodium in small pieces weighing about 5 g. each is introduced into the mercury by means of a glass rod. The addition of the sodium requires about two minutes. The xylene is decanted, and a stream of air is applied to the surface of the amalgam to evaporate as much of the

[15] Gabriel and Stelzner, *Ber.*, **21**, 1049 (1888); **28**, 2929 (1895).

[16] Howard and Marckwald, *Ber.*, **32**, 2036 (1899).

[17] Marckwald and Frobenius, *Ber.*, **34**, 3544 (1901).

adhering xylene as possible. Four hundred cc. of water and 36 g. of the dry crystals of 4,6-dibromo-2-oxo-dihydro-indole-3-propionic acid are now added. The flask is stoppered and placed on a boiling water-bath. A tube dipping below the surface of water in a beaker is connected to the side neck of the flask in order to exclude the oxygen of the air from the flask. Atmospheric oxygen will oxidize this lactam in an alkaline solution. At the end of two hours at 100° the reduction is complete. The solution is decanted from the mercury into a 1-liter beaker containing 120 cc. of 10 *N* sulfuric acid. After the liquid has been cooled the crystals formed are filtered off and washed with about 200 cc. of water.

The crystals thus obtained are contaminated with finely divided mercury. They are dissolved in 600 cc. of boiling water and the solution is filtered through a hot-water funnel. With slow cooling, long, thick, needle crystals are formed; yield, 95%.

2-Oxo-dihydro-indole-3-propionic acid is soluble in water to the extent of about 67 g. per liter at 100° and 1.2 g. per liter at 25°; m. p., 174°.

Anal. Calcd. for $C_{11}H_{11}O_3N$: C, 64.36; H, 5.46. Found: C, 64.32; H, 5.37.

Titration of 100 mg. of this substance in 25 cc. of 95% alcohol requires 4.85 cc. of 0.1 *N* sodium hydroxide solution.

α-(2,3-Iminophenyl)glutaric Acid. X.—A solution of 0.1 mole (20.5 g.) of 2-oxo-dihydro-indole-3-propionic acid in 100 cc. of *N* sodium hydroxide solution prepared by gently warming, is cooled to about 10° and two equivalents (25.4 g.) of finely divided iodine is added; 60 cc. of 5 *N* sodium hydroxide solution is added slowly during stirring. The action of the sodium hydroxide on the iodine and the lactam forms a blue compound which is probably an addition product of iodine and the 7-mono-iodo derivative of the lactam. The blue color is all discharged when the 60 cc. of alkali is added and the iodine has been dissolved. The solution is allowed to come to room temperature. In order to remove the sodium iodide, 80 cc. of 5 *N* sulfuric acid is added and then 7.1 g. of iodic acid dissolved in 100 cc. of water. The liberated iodine is flocculated by warming the solution which is then filtered by suction through a pad of Norite previously boiled with 5% sulfuric acid and washed until neutral.

The filtrate is concentrated in a vacuum. Crystals soon separate, which are filtered off and washed with a little water. The crystals, which weigh about 20 g., are redissolved in about 500 cc. of water, boiled with Norite, filtered off, and the solution is concentrated in a vacuum. The crystals are purified by repeated solution in water and treatment with Norite. Titration of the mother liquors shows that less and less of the material remains in solution as the purification proceeds. When pure the substance crystallizes directly from solution without first separating as an oil and the mother liquor when titrated does not require more than 20 cc. of 0.1 *N* acid for each 100 cc.

The nitrogen bond, open-ring form of this lactam, prepared by this method, is obtained in a yield of 80–90%. The losses are due to its solubility and not to side reactions during its formation. Titration of the solution after the oxidation with iodine showed that only 16 cc. of 0.1 *N* iodine, and 1984 cc. of 0.1 *N* sodium iodide were present out of the total of 2000 cc. of 0.1 *N* iodine added.

The crystals are dried at 100°; m. p., 199°. When this compound is titrated one carboxyl group is indicated; 100 mg. requires 4.45 cc. of 0.1 *N* sodium hydroxide solution, phenolsulfonephthalein being used as indicator (calcd., 4.48 cc.). The "oxidizing power" is 9.0 cc. The hydriodic acid, oxidized by 100 mg. of the material, shows that two equivalents of iodine are liberated.

Anal. Calcd. for $C_{11}H_{11}O_4N$: C, 59.70; H, 5.01. Found: C, 59.48; H, 4.98.

2,3-Dihydro-2-oxo-tricyclo-indole-3-propionic Acid. XI.—The open-ring form of this compound when heated to 175° melts, loses water, and closes the pyrrolidone ring. This treatment, however, produces some oily impurity which is removed with

difficulty. A better method to close the ring is to suspend the open-ring crystals in acetic anhydride, in which they are insoluble, and heat at 100° until solution is complete. This requires from 30 to 60 minutes. The acetic anhydride is removed in a vacuum and the residue is dissolved in boiling water. It is impossible to close the pyrrolidone ring by boiling in water or dilute acid and it is also impossible to open the closed-ring form by this means.

Whether the ring is open or closed is easily determined by titration: when 100 mg. of the open pyrrolidone ring is titrated, the presence of one carboxyl group is indicated, 4.45 cc. of 0.1 *N* sodium hydroxide solution being required before, and 5.0 cc. after boiling with 15 cc. of 0.1 *N* sodium hydroxide solution; 100 mg. of the closed ring is found to be neutral in hot water or alcohol and upon titration, shows the presence of a little more than one carboxyl group, 5.1 cc. of 0.1 *N* sodium hydroxide solution being required, after the solution has been boiled with 15 cc. of 0.1 *N* sodium hydroxide solution. The "oxidizing power" is 9.7 cc. (calcd., 9.86 cc.).

When the nitrogen bond, closed-ring lactam is crystallized from water it separates, combined with one-half molecule of water; m. p., 90°.

Anal. Calcd. for $C_{11}H_{10}O_{32}N$: C, 62.24; H, 4.75. Found: C, 62.24; H, 4.72.

When the compound containing one-half molecule of water of crystallization is heated in an oven at 100°, it melts and then crystallizes again after the water has been driven off. The crystals then melt at 116° and do not contain water of crystallization.

Anal. Calcd. for $C_{11}H_9O_3N$: C, 64.99; H, 4.46. Found: C, 64.79; H, 4.49.

α-(4-Mono-iodo-2,3-iminophenyl)glutaric Acid.—One-twentieth mole (10.25 g.) of 2-oxo-dihydro-indole-3-propionic acid is added to a mixture of 100 cc. of glacial acetic acid and 50 cc. of 1:1 sulfuric acid; 6.5 g. of iodine and 5.3 g. of iodic acid crystals are added and the flask is warmed to 30°. After one to two hours crystals separate. The heating is continued until all of the iodic acid has dissolved and the solution is thick with crystals. The crystals are filtered off, washed with water and suspended in a 1-liter beaker. The water is boiled and a current of air passed through the solution to volatilize the iodine. When the suspension is colorless, it is filtered. The crystals are then dissolved in 500 cc. of 0.2 *N* sodium hydroxide solution; 100 cc. of *N* sulfuric acid is added and the solution filtered. Any di-iodo compound which has formed precipitates and is easily removed. After a few hours crystals separate; m. p., 162°, followed by recrystallization and decomposition at 250°. Titration of 100 mg. in 25 cc. of 95% alcohol requires 2.8 cc. of 0.1 *N* sodium hydroxide solution. The "oxidizing power" is a little above that calculated, 5.6 cc. when the refluxing is prolonged.

Anal. Calcd. for $C_{11}H_{10}O_4NI$: C, 38.04; H, 2.90; I, 36.57. Found: C, 37.81; H, 2.89; I, 37.60.

6-Mono-iodo-2,3-dihydro-2-oxo-tricyclo-indole-3-propionic Acid.—The closed-ring form of the nitrogen bond mono-iodo derivative is made by boiling the aqueous solution of the open pyrrolidone ring form. Although the open pyrrolidone ring form crystallizes slowly, crystals of the closed-ring compound quickly separate in hair-like needles when the solution is boiled; m. p., 251°. The "oxidizing power" is a little above that calculated, or 6.0 cc. when the refluxing is prolonged.

Anal. Calcd. for $C_{11}H_8O_3NI$: C, 40.12; H, 2.45; I, 38.57. Found: C, 40.05; H, 2.59; I, 38.58.

Titration of 100 mg. in 25 cc. of 95% alcohol requires 0.10 cc. of 0.1 *N* sodium hydroxide solution directly and 3.4 cc. after the liquid has been boiled with 15 cc. of 0.1 *N* sodium hydroxide solution.

6-Mono-iodo-2-oxo-dihydro-indole-3-propionic Acid.—Ten g. of the nitrogen bond form of the mono-iodo derivative in open- or closed-ring form is added to 30 cc. of glacial

acetic acid containing 4 g. of potassium iodide and 4 cc. of 1:1 hydrochloric acid. The solution is refluxed with an inside condenser for about 30 minutes, during which time small pieces of yellow phosphorus are added. When the solution is no longer colored with iodine, water is added and the mono-iodo derivative in the reduced form separates. The crystals are filtered off and washed with water. They are then dissolved in a small volume of sodium carbonate solution by warming and an equal volume of 95% alcohol is added. The solution is filtered and then made acid with hydrochloric acid. The crystals separate slowly either as plates or needles. Although this compound has no oxidizing bond, 20 minutes' refluxing of 100 mg. liberated iodine equivalent to 2.1 cc. of 0.1 *N* thiosulfate solution. The liberation of iodine, therefore, must be brought about by the reduction of the iodine on the benzene ring. When this compound is titrated, the presence of exactly one carboxyl group is indicated: 100 mg. neutralizes 3.0 cc. of 0.1 *N* sodium hydroxide solution; m. p., 172°.

Anal. Calcd. for $C_{11}H_{10}O_3NI$: C, 39.87; H, 3.04; I, 38.34. Found: C, 39.64; H, 3.05; I, 38.43.

α-(4,6-Di-iodo-2,3-iminophenyl)glutaric Acid.—When 2-oxo-dihydro-indole-3-propionic acid is treated with iodine and iodic acid, it adds iodine according to the medium in which the reaction is carried out. In the presence of 50% acetic acid, iodine, iodic acid and dil. sulfuric acid no di-iodo derivative is formed. Some crystals separate which are insoluble in alcohol and water or in aqueous or alcoholic sodium hydroxide. They can be recrystallized from boiling acetic acid. Titration of 100 mg. requires 2.3 cc. of 0.1 *N* sodium hydroxide solution; it reduces hydriodic acid, this amount liberating 9 cc. of 0.1 *N* iodine solution. These crystals contain 36.8% of iodine. Their exact composition has not been established. They are produced only when water, sulfuric acid, iodic acid and only a small amount of acetic acid are present. They are not formed in acetic acid alone or when 1:1 sulfuric acid is used in place of dil. sulfuric acid. The high "oxidizing power" suggests an iodoso derivative.

The 4,6-di-iodo derivative of 2-oxo-dihydro-indole-3-propionic acid, in its nitrogen bond form, is prepared in good yield by using 0.05 mole (10.25 g.) of the lactam, 100 cc. of glacial acetic acid, 0.1 mole (12.7 g.) of iodine, and 4 g. equivalents (7.1 g.) of iodic acid with from 10 to 50 cc. of 1:1 sulfuric acid. Although there is not much difference between the yields obtained by using from 10 to 50 cc. of 1:1 sulfuric acid, some sulfuric acid is necessary. Two experiments were made, each with 10.3 g. of the lactam, 12 g. of iodine, 7.1 g. of iodic acid and 100 cc. of glacial acetic acid. To one of these 5 cc. of 1:1 sulfuric acid was added; the other contained no sulfuric acid. The two flasks (500 cc. Erlenmeyer flasks with inside condensers) were heated at 60° for six hours. The first contained mono-iodo crystals which changed to the di-iodo derivative 90 minutes after the heating was begun. The second flask, with acetic acid alone, showed no separation of either mono- or di-iodo crystals during six hours. Fifty cc. of 1:1 sulfuric acid was then added, and crystals of the mono- and di-iodo derivatives separated within 20 minutes.

The lactam, acetic acid, iodine, sulfuric acid and crystals of iodic acid are placed in a round-bottomed, short-necked 1-liter flask and the solution is vigorously stirred with a glass mechanical stirrer. The flask is heated to 60° and the stirring is continued for four hours. The mono-iodo derivative first separates, in curved needles, and is then dissolved, forming the diiodo compound which separates in flat blades. It has been found necessary to use coarse crystals of iodic acid and they should not be dissolved in any medium but added directly to the acetic and sulfuric acids. If the iodic acid is finely divided or is dissolved in water, the yield is materially reduced, and dark-colored decomposition products are present in the solution. When the reaction is carried out as described above, the yield is approximately 21 g. The first crude product is suspended in about a liter of water in a 3-liter, round-bottomed flask, and is then boiled. A rapid

current of air is passed through the suspension to volatilize any iodine. The almost white crystals are then dissolved in sodium hydroxide and the solution made acid. The di-iodo derivative separates in the open pyrrolidone ring form and can be filtered off immediately. It is purified by crystallization of its monosodium salt. For this purification 40 g. of the di-iodo open-ring derivative is dissolved in 400 cc. of water containing 15 g. of sodium carbonate. The solution is heated to boiling until the crystals have dissolved, and it is then allowed to cool. The monosodium salt separates and is recrystallized from water. The crystals are dissolved in 75% alcohol with 20 cc. of 5 *N* sodium hydroxide solution and the liquid acidified with 1:1 alcoholic hydrochloric acid. The free carboxyl, open pyrrolidone ring form of the di-iodo derivative, separates; m. p., 252°. Titration of this compound indicates the presence of one carboxyl group; 100 mg. requires 2.10 cc. of 0.1 *N* sodium hydroxide solution. It liberates slightly more than the calculated amount of iodine from hydriodic acid when the "oxidizing power" is determined as described above under 4,6,7-tribromo-2-oxo-dihydro-indole-3-propionic acid. This increased liberation of iodine is caused by the reduction of the iodine on Carbon 6.

Anal. Calcd. for $C_{11}H_9O_4NI_2$: C, 27.91; H, 1.91; I, 53.67. Found: C, 28.01; H, 1.99; I, 53.45.

4,6-Di-iodo-2,3-dihydro-2-oxo-tricyclo-indole-3-propionic Acid.—The pyrrolidone ring is easily closed by boiling 20 g. of the open-ring form in 300 cc. of glacial acetic acid containing 5 cc. of concd. sulfuric acid. The solution should be complete and the boiling is continued for ten minutes. The closed-ring form separates in long crystals and can be washed by suspending in alcohol and extracting two or three times with hot alcohol. The criterion for the closed ring is the titration value of the terminal carboxyl: upon titration of 100 mg. of the closed-ring form 0.15 cc. of 0.1 *N* sodium hydroxide solution is required. After the substance has been boiled with 15 cc. of 0.1 *N* sodium hydroxide solution and the liquid back titrated with sulfuric acid, it is shown that 2.4 cc. of sodium hydroxide solution has been neutralized. The "oxidizing power" of 100 mg. is 4.9 cc.; m. p., 242°.

Anal. Calcd. for $C_{11}H_7O_3NI_2$: C, 29.01; H, 1.55; I, 55.80. Found: C, 28.98; H, 1.57; I, 55.73.

4,6-Di-iodo-2-oxo-2,3-dihydro-indole-3-propionic Acid.—Twenty g. of the crude di-iodo derivative in its nitrogen bond, closed-ring form is placed in a 250cc. Erlenmeyer flask with 50 cc. of glacial acetic acid, 4 g. of potassium iodide and 4 cc. of 1:1 hydrochloric acid and is refluxed with an inside condenser. As iodine appears, small pieces of yellow phosphorus are added to the boiling solution, an excess of phosphorus being avoided. Boiling is continued for about 30 minutes by which time there should be no iodine color in the solution. The suspension of crystals at first dissolves and the reduced di-iodo compound then crystallizes. It is filtered off with the small amount of phosphorus not oxidized and is then dissolved with the aid of heat in 150 cc. of water containing sodium carbonate in slight excess to form the monosodium salt. The phosphorus is removed by filtering through a pad of Norite on a suction funnel. The Norite is washed and 250 cc. of 95% alcohol followed by sufficient hydrochloric acid in 95% alcohol to acidify the sodium salt is added. A better crystallization is obtained when the hydrochloric acid added is mixed with alcohol before the solution is acidified. Crystals immediately separate. After the solution is cold, it is filtered; yield, 18 g. This yield includes the loss occurring in purification of the crude diiodo nitrogen-bond form. The crystals are oval-shaped plates; m. p., 244°.

Titration of 100 mg. of this compound indicates accurately the presence of one carboxyl group, 2.2 cc. of 0.1 *N* sodium hydroxide solution being required. Although the nitrogen-bond form of the 4,6-di-iodo derivative can exist with the pyrrolidone ring open,

the 4,6-di-iodo derivative without the nitrogen bond precipitates with the pyrrolidone ring closed as soon as its sodium salt in water is made acid.

Anal. Calcd. for $C_{11}H_9O_3NI_2$: C, 28.89; H, 1.98; I, 55.55. Found: C, 28.62; H, 1.95; I, 55.46.

The 4,6-di-iodo-2-oxo-dihydro-indole-3-propionic acid forms a slightly soluble monosodium salt when it is added to water containing sodium carbonate and the solution heated until the crystals are dissolved. After the solution is cold, the monosodium salt of the open pyrrolidone ring form separates. It can be recrystallized from distilled water, washed with water and dried. A solution of this salt is neutral to phenolsulfonephthalein.

Carboxyl Titration of 2-Oxo-dihydro-indole-3-propionic Acid and its Derivatives.— The results given in Table II were obtained by dissolving 100 mg. of the various compounds in 25 cc. of 95% alcohol. Two or three drops of a 0.1% solution of phenolsulfonephthalein were added and the solutions titrated with 0.1 *N* sodium hydroxide solution. The end-point found was noted and then a total of 15 cc. of 0.1 *N* sodium hydroxide solution was added in each case and the solution boiled for five minutes, cooled to room temperature, and back titrated with 0.1 *N* sulfuric acid. The back titration subtracted from 15 cc. gave the amount of sodium hydroxide neutralized.

TABLE II

CARBOXYL TITRATION

Substance	Direct titration	Titration after boiling with 15 cc. of 0.1 *N* NaOH soln.
2-Oxo-dihydro-indole-3-propionic acid	4.80	5.0
α-(2,3-Iminophenyl)glutaric acid	4.45	5.0
2,3-Dihydro-2-oxo-tricyclo-indole-3-propionic acid	0.00	5.1
6-Mono-iodo-2-oxo-dihydro-indole-3-propionic acid	3.00	3.4
α-(4-Mono-iodo-2,3-iminophenyl)glutaric acid	2.80	3.1
6-Mono-iodo-2,3-dihydro-2-oxo-tricyclo-indole-3-propionic acid	0.10	3.4
4,6-Di-iodo-2-oxo-dihydro-indole-3-propionic acid	2.20	3.1
α-(4,6-Di-iodo-2,3-iminophenyl)glutaric acid	2.08	2.5
4,6-Di-iodo-2,3-dihydro-2-oxo-tricyclo-indole-3-propionic acid	0.15	2.4
4,6-Dibromo-2-oxo-dihydro-indole-3-propionic acid	2.75	4.2
α-(4,6-Dibromo-2,3-iminophenyl)glutaric acid	2.60	3.0
4,6-Dibromo-2,3-dihydro-2-oxo-tricyclo-indole-3-propionic acid	0.15	3.1
4,6,7-Tribromo-2-oxo-dihydro-indole-3-propionic acid	0.25	3.15

This compound loses 1 HBr quantitatively in alcohol with cold 0.1 *N* sodium hydroxide solution, giving an acid titration of 2.26 cc. The values in Table II for the tribromo derivative were obtained by subtracting the number of cubic centimeters of 0.1 *N* sodium bromide from the total number of cubic centimeters of sodium hydroxide neutralized.

Summary[18]

1. 2-Oxo-octohydro-benzofuran-3-carboxylic acid has been prepared by condensing cyclohexene oxide and malonic ester. β-Bromopropionic

[18] The authors wish to express their thanks to Marschelle Power for material assistance given during the preparation of some of the tricyclo-indole derivatives.

ester reacts with the sodium addition of the benzofuran derivative forming a tricarboxylic compound which condenses into a dicarboxylic lactone when the sodium salt is acidified. This dicarboxylic lactone when heated gives off carbon dioxide and is converted into 2-oxo-octohydro-benzofuran-3-propionic acid.

2. 2-Oxo-octohydro-benzofuran-3-propionic acid in the form of its magnesium salt can be oxidized to 2-keto-cyclohexane-α-glutaric acid. This compound, when treated with "ammonia" in alcohol, is converted almost quantitatively into the corresponding lactam, 2-oxo-hexahydro-indole-propionic acid.

3. 2-Oxo-hexahydro-indole-3-propionic acid reacts with ten atoms of bromine giving 4,6,7-tribromo-2-oxo-2,3-dihydro-indole-3-propionic acid.

4. The bromine substituting on Carbon 7 is easily reduced with zinc in cold acetic acid or with hydriodic acid dissolved in warm acetic acid and is easily removed with cold 0.1 *N* sodium hydroxide solution in 95% alcohol. When the bromine is removed by reduction, 4,6-dibromo-2-oxo-2,3-dihydro-indole-3-propionic acid is produced. When the 4,6,7-tribromo derivative is treated with a dilute solution of sodium hydroxide or sodium acetate in glacial acetic acid, 4,6-dibromo-2-oxo-2,3-dihydro-tricyclo-indole-3-propionic acid is produced, one molecule of hydrogen bromide being removed between Carbon 7 and the nitrogen. This bond does not take up bromine but adds hydriodic acid and can be reduced, taking up two atoms of hydrogen.

5. Sodium amalgam reduces 4,6-dibromo-2-oxo-2,3-dihydro-indole-3-propionic acid by removing the two atoms of bromine and gives the unhalogenated lactam. This lactam in acetic acid again adds bromine, giving the 4,6,7-tribromo derivative. When it is treated with iodine and iodic acid in acetic acid, it first forms the tricyclo derivative with the bond from Carbon 7 to the nitrogen. Iodine then substitutes on Carbon 6 and finally on Carbon 4, resulting in the 4,6-di-iodo derivative.

6. When 2-oxo-2,3-dihydro-indole-3-propionic acid is dissolved in water containing four equivalents of sodium hydroxide, and two equivalents of iodine are added to the solution, there is no substitution of iodine on the molecule but the bond from Carbon 7 to the nitrogen is formed. This substance exists with the pyrrolidone ring open or closed. The bond will not react with bromine but can be reduced with hydriodic acid.

7. Substitution of Carbon 7 with halogen or formation of a bond from Carbon 7 to the nitrogen does not affect the carboxyl titration if the pyrrolidone ring is open. The terminal carboxyl in this compound titrates one full equivalent with 0.1 *N* sodium hydroxide solution, phenolsulfonephthalein being used as indicator. None of these compounds, however, show acidic properties when dissolved in alcohol or water if the pyrrolidone ring is closed. After boiling with dil. sodium hydroxide solution with the

resultant opening of the pyrrolidone ring, the carboxyl group is again active. The reason for the loss of acidic properties with the closed pyrrolidone ring is the formation of a six-membered ring between the terminal carboxyl and the carbonyl group on Carbon 2.

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THE ELECTROLYTIC REDUCTION OF ACROLEIN[1,2]

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The reduction, by electrochemical means of α,β-unsaturated aliphatic aldehydes has been investigated to only a slight extent. According to Law[3] the electro-reduction of crotonaldehyde yields only butyl alcohol. On the other hand, Hibbert and Read,[4] using very similar conditions, showed that the same aldehyde yielded not only butyl alcohol and butyraldehyde but also a new product, dimethyl-cyclopentene aldehyde.

The appearance of dimethyl-cyclopentene aldehyde during the reduction of crotonaldehyde was quite unexpected, and the structure ascribed to it was later confirmed[5] by its direct synthesis from β-bromobutyraldehyde diethyl acetal.

It seemed advisable, in view of the desirability of settling definitely the course of the reaction leading to the formation of the dimethyl-cyclopentene aldehyde, to study the reduction of another member of the same series. Acrolein was, therefore, chosen, inasmuch as all of the possible reduction products, that is, propionaldehyde, propyl alcohol, allyl alcohol, dipropenyl glycol and cyclopentene aldehyde,[6] have been identified.[7]

A discussion of the nature of the chemical reduction of crotonaldehyde has been given in a previous paper,[4] the amounts of the various products formed, that is, butyraldehyde, crotyl alcohol, butyl alcohol and dipropenyl glycol, varying with the conditions and reagent employed. On the other hand, the electrochemical reduction of this aldehyde did not yield

[1] Communicated to the Organic Division, American Chemical Society, Baltimore, Maryland, April, 1924.

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[3] Law, *J. Chem. Soc.*, **101**, 1016 (1912).

[4] Hibbert and Read, THIS JOURNAL, **46**, 983 (1924).

[5] Read and Hibbert, *ibid.*, **46**, 1281 (1924).

[6] As the semicarbazone, Baeyer and von Liebig, *Ber.*, **31**, 2106 (1898). The aldehyde has not been isolated heretofore.

[7] Linnemann, *Ann.* (Supp.), III, 257 (1864–65). Griner, *Ann. chim. phys.*, [6] **26**, 368 (1892). Sabatier, *ibid.*, [8] **4**, 398 (1905). Harries, *Ann.*, **330**, 226 (1903). Skita, *Ber.*, **45**, 3312 (1912).