This residue was distilled under reduced pressure to give 94.6 g. (30.9%) of acetopropyl alcohol and 12.2 g. (3.9%) of 1,4-pentanediol. The acetopropyl alcohol had the properties: b. p. 75° (3 mm.); d^{25}_4 0.993; n^{25}_D 1.4350.

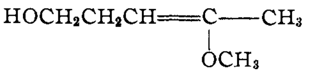
4,5-Dihydro-2-methylfuran.—This dihydromethylfuran was prepared from acetopropyl alcohol by the method of Kyrides and Zienty.[10] Acetopropyl alcohol (25 g.) was heated to boiling at atmospheric pressure in a flask equipped with a 14" × 3/4" helices-packed column. Distillate temperature did not exceed 72°. Near the end of the distillation heat was applied to the column to prevent excessive holdup.

The distillate consisting of water and dihydromethylfuran was transferred to a separatory funnel and the water layer removed. The dihydromethylfuran (19 g., 92.3%) contained a trace of water. After standing for twelve hours this water had reacted; redistillation gave pure dihydromethylfuran (b. p. 80°, n^{25}_D 1.4290, d^{25}_4 0.895) and a trace of acetopropyl alcohol.

This method was used by Kyrides and Zienty[10] to separate acetopropyl alcohol from 1,4-pentanediol. The dihydromethylfuran is readily converted back to acetopropyl alcohol by reaction with water catalyzed by a trace of acid.

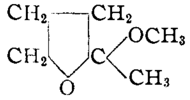
2-Methoxy-2-methyl-tetrahydrofuran.—4,5-Dihydro-2-methylfuran (10 g.) was dissolved in 10 cc. of methyl alcohol containing two drops of acetic acid. The temperature of the solution rose to 39° and remained there for fifteen minutes. The reaction mixture was then refluxed on a steam-bath for an additional fifteen minutes after which the acid was neutralized by addition of an excess of sodium methoxide. The undissolved solid was removed by filtration and the filtrate distilled. 2-Methoxy-2-methyltetrahydrofuran, having a menthol-like odor, was obtained in 88.6% yield: b. p. 114.5°; n^{25}_D 1.4110; d^{25}_4 0.932. *Anal.* Calcd. for $C_6H_{12}O_2$: C, 62.07; H, 10.34; OCH_3, 26.72. Found: C, 61.96; H, 10.36; OCH_3, 25.90.

Reasoning by analogy with the hydrolysis product from 4,5-dihydro-2-methylfuran the alcoholysis product may have either an open-chain or cyclic structure illustrated by formulas I and II



$$HOCH_2CH_2CH{=}\underset{OCH_3}{C}{-}CH_3$$

I



II

Molar refractivity of the compound obtained indicates the cyclic form (II). *Anal.* M_D found, 30.90. M_D calcd. for I, 32.61; for II, 30.99.

Treatment of 10 g. of 2-methoxy-2-methyl-tetrahydrofuran with 10 cc. of water effected a rapid hydrolysis to give methanol and acetopropyl alcohol (6.5 g.).

Summary

Methylfuran has been converted to 1,4-pentanediol in 50–60% yields by hydrogenation in the presence of water and a trace of acid.

Acetopropyl alcohol was prepared in 25–35% yield by interrupting the reaction after absorption of 1 mole of hydrogen/mole of methylfuran.

The reversible conversion of acetopropyl alcohol to 4,5-dihydro-2-methylfuran confirms a previously proposed mechanism by which 2-methylfuran is converted to acetopropyl alcohol.

2-Methoxy-2-methyl-tetrahydrofuran, a new compound having a menthol-like odor, has been prepared by methalcoholysis of 4,5-dihydro-2-methylfuran.

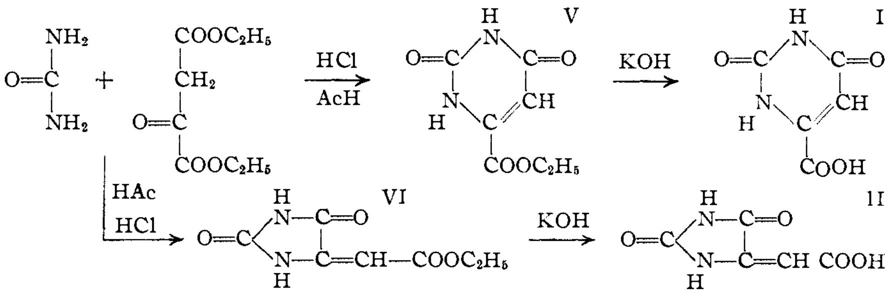
PEORIA 5, ILL. RECEIVED SEPTEMBER 30, 1946

[CONTRIBUTED FROM KERCKHOFF LABORATORIES OF BIOLOGY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Intermediates in the Synthesis of Orotic Acid from Oxalacetic Ester and Urea

BY HERSCHEL K. MITCHELL AND JOSEPH F. NYC

Müller in 1897[1] reported the synthesis of a compound, through condensation of oxalacetic ester and urea, to which he assigned a structure corresponding to an ester of 4-carboxy-uracil. This substance received little attention until after the isolation from milk, by Biscaro and Belloni,[2] of a nitrogenous heterocyclic acid (orotic acid). Although these investigators assigned a seven-membered ring structure to the acid, it was pointed out by Wheeler, Johnson and Johns[3] that the empirical formula was identical with that of a carboxyl derivative of uracil. The latter workers synthesized 5-carboxyuracil and found that this substance was not identical with orotic acid. The ester prepared by Müller[1] was then re-examined by Wheeler,[4] who considered that the synthesis might result in either a pyrimidinecarboxylic acid (I) or a substituted hydantoin (II) in accordance with the reactions



The acid obtained was identified as 4-carboxyuracil by conversion to 5,5'-dibromo-barbituric acid (III) with bromine water. On treatment with bromine water 5-(carboxy-methylidene)-

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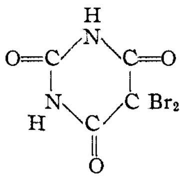
(1) R. Müller, *J. prakt. Chem.*, **56**, 480 (1897).

(2) G. Biscaro and E. Belloni, *Ann. Soc. Chim. Milano*, XI, fasc I and II (1905); *Chem. Zentr.*, [II] **63**, 64 (1905).

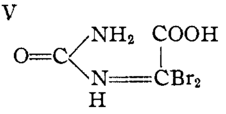
(3) R. L. Wheeler, T. B. Johnson and C. O. Johns, *Am. Chem. J.*, **37**, 392 (1907).

(4) H. L. Wheeler, *ibid.*, **38**, 358 (1907).

III

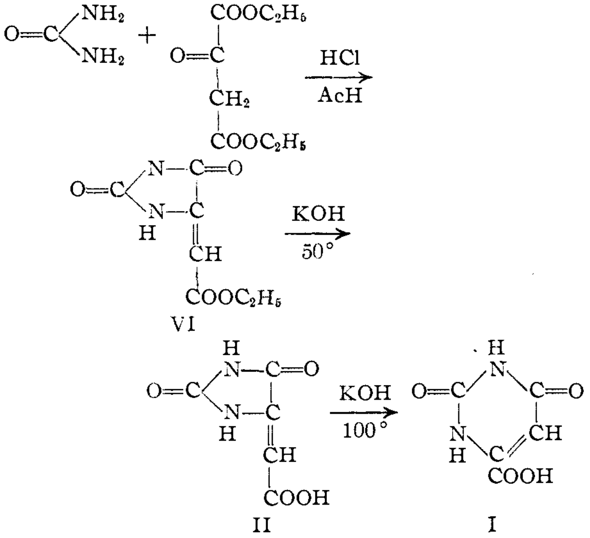


IV

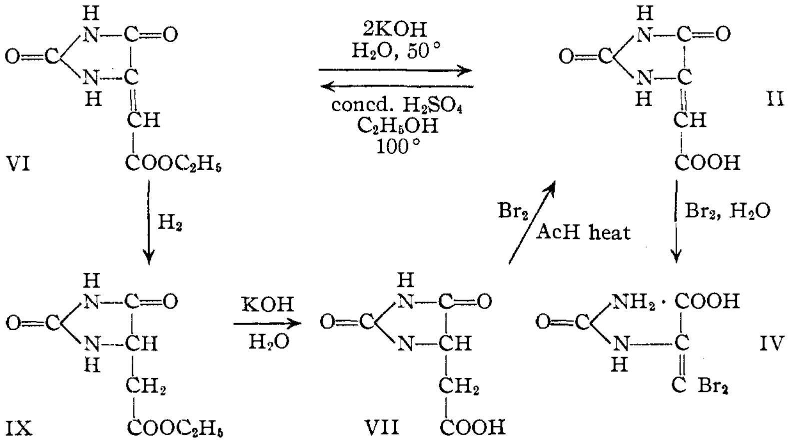


hydantoin (II) gives rise to the hydantoic acid (IV).[5] As a result of this work, that of Johnson and Caldwell[6] and of Bachstez[7] it was established that orotic acid is identical with 4-carboxyuracil (I).

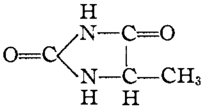
Conclusions from investigations carried out in this Laboratory are in accord with the accepted structure for orotic acid but they are *not* in agreement with the structure V accepted by Wheeler[4] and by Bachstez[7] for the ester prepared by Müller[1] from oxalacetic ester and urea. We have demonstrated that this ester has the structure VI and that the synthesis of orotic acid proceeds according to the following series of reactions



Proof by Wheeler of the structure of the ester (V) is dependent on hydrolysis of the compound to give the acid (I). His procedure calls for the evaporation to a small volume of a solution of the ester in aqueous alcoholic potassium hydroxide, and if this evaporation is carried out at 100°, orotic acid is indeed obtained. However, if the evaporation is carried out at 50° the hydantoin II is the major product. This hydantoin is in turn converted to orotic acid by heating with aqueous alkali at 100°. The two acids have the same empirical formula but differ markedly in acidic strength, decomposition temperature, reactivity toward bromine water, and absorption spectrum in ultraviolet light. The structures of the ester (VI) and the acid (II), both obtained from the reaction of oxalacetic acid and urea, have been established through the reactions shown.



The hydantoin (VII) was synthesized by Grimeau[8] and by Gabriel[5] from asparagin and aspartic acid, respectively. The latter investigator synthesized II from VII. In addition Gabriel prepared the hydantoic acid (IV) from the acid (II) and from 5-methyl-hydantoin (VIII)



VIII

thus establishing the hydantoin structure of II. Additional evidence for this structure comes from the work of Grimeau,[8] who synthesized a compound believed to be the amide of VII directly from asparagin and urea. Since asparagin is an amino acid the amide obtained is most probably a hydantoin derivative rather than a pyrimidine derivative. These compounds prepared by Grimeau[8] and by Gabriel[5] have been synthesized in this Laboratory according to their methods and compared with the products of the reaction of oxalacetic acid and urea.

Experimental

5-(Carbethoxymethylidene)-hydantoin (VI).—This compound was prepared from oxalacetic ethyl ester and urea according to the method of Müller[1]; yield 29%, m. p. 188–189° (cor.). Calculated for $C_7H_8O_4N_2$: C, 45.69; H, 4.38; N, 15.22. Found: C, 45.65; H, 4.56; N, 15.15. Absorption spectrum, Fig. 1, curve A.

5-(Carboxymethylidine)-hydantoin (II).—Three grams of 5-(carbethoxymethylidene)-hydantoin was dissolved in 36 ml. of boiling 95% ethyl alcohol followed by addition of 1.8 g. of potassium hydroxide dissolved in 6 ml. of water. The resulting pasty mass was dissolved by addition of 90 ml. of water and the solution was evaporated in vacuum at 50° to a volume of 20 ml. The solution was acidified with concentrated hydrochloric acid and filtered. The compound was recrystallized from a minimum volume

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(5) S. Gabriel, *Ann.*, **348**, 50 (1906).

(6) T. B. Johnson and W. T. Caldwell, THIS JOURNAL, **51**, 874 (1929).

(7) M. Bachstez, *Ber.*, **63**, 1000 (1930).

(8) E. Grimeau, *Ann. chim. phys.*, [5] **11**, 402 (1887).

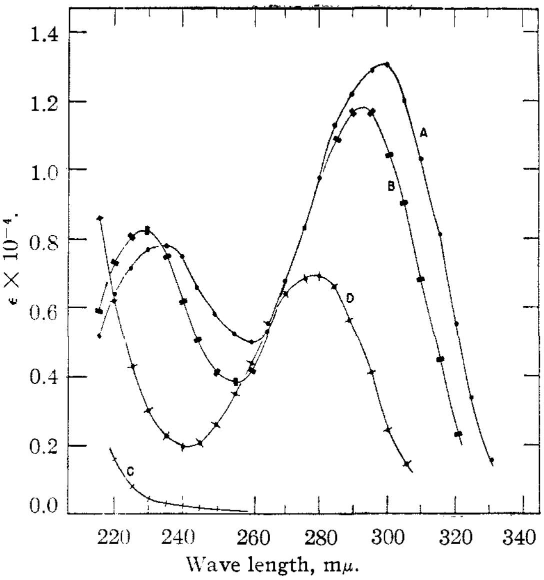

Fig. 1.—Absorption spectra: A, 5-(carbethoxymethylidene)-hydantoin; B, 5-(carboxymethylidene)-hydantoin; C, 5-(acetic acid)-hydantoin; D, orotic acid.

of boiling water; yield 1.45 g. (56%). The substance crystallizes without water of hydration and shows some decomposition above 300° but it does not melt or decompose completely below 400°. Calculated for $C_5H_4O_4N_2$: C, 38.48; H, 2.56; N, 17.94. Found: C, 38.51; H, 2.59; N, 18.20. Absorption spectrum, Fig. 1, curve B. Neutralization equivalent; 157. Potentiometric titration with a Beckman *p*H meter demonstrated the substance to be a dibasic acid.

5-(Carboxymethylidene)-hydantoin was also synthesized from aspartic acid by the method of Gabriel.[5] The compound so obtained was found to be identical in absorption spectrum and acidic properties with the product from the oxalacetic ester synthesis.

Esterification of 5-(Carboxymethylidene)-hydantoin.—A solution of 100 mg. of 5-(carboxymethylidene)-hydantoin in 5 ml. of 50% ethanol in concentrated sulfuric acid was heated to 100° for ten minutes. After cooling to room temperature the unreacted acid was removed by filtration. On dilution of the filtrate with water the ester crystallized. After recrystallization from water and drying at 100° the product melted at 188–189°. A mixed melting point with 5-(carbethoxymethylidene)-hydantoin prepared from oxalacetic ethyl ester and urea showed no depression. Ultraviolet absorption spectra of the two preparations were identical.

Attempts to carry out this esterification by means of ethanol saturated with hydrochloric acid were unsuccessful and the acid was recovered unchanged.

5-(Ethyl acetate)-hydantoin (IX).—A solution of 150 mg. of 5-(carbethoxymethylidene)-hydantoin in 25 ml. of absolute alcohol was placed in a low pressure hydrogenation apparatus with 10 mg. of Adams catalyst. After three hours at room temperature and at a pressure of 1.5 atmospheres one molecular equivalent of hydrogen had been absorbed and the reaction ceased. The solution was filtered, evaporated to dryness and the product crystallized from water. The crystalline product was subjected to sublimation at 150° and at 0.5 mm. pressure. This ester has not been previously described. It melts at 94–96°. Calculated for $C_7H_{10}O_4N_2$: C, 45.15; H, 5.42; N, 15.04. Found: C, 45.26; H, 5.67; N, 15.11.

5-(Acetic acid)-hydantoin (VII).—A solution of 77 mg. of 5-(ethyl acetate)-hydantoin in 1 ml. of 1 *N* potassium hydroxide was heated at 100° for ten minutes. The solution was then acidified with hydrochloric acid and evaporated to dryness. The resulting product was sublimed at 220° and 0.5 mm. of pressure. After one crystallization from water and drying at 100° the material melted between 215–217° (cor.).

The same compound was prepared from asparagin and urea according to the method of Grimeau.[8] This product melted between 216–217°. A mixed melting point of the above two preparations gave no depression. Absorption spectrum, Fig. 1, curve C.

α-Ureido-β,β'-dibromacrylic Acid (IV).—This compound was prepared from 5-(carboxy-methylidene)-hydantoin synthesized both from oxalacetic ester and urea and from asparagin and urea. The product from the first preparation melted over the range of 206–208° (cor.) and the latter over the range of 207–208° (cor.). No depression was observed in a mixed melting temperature determination. Gabriel reported a melting point of 208° for this compound. The hydantoic acid prepared from the hydantoin originating with asparagin gave the following analyses: Calculated for $C_4H_4O_3N_2Br_2$: N, 9.75; Br, 55.5. Found: N, 9.70; Br, 55.0.

Orotic Acid (I) from 5-(Carboxymethylidene)-hydantoin.—A solution of 310 mg. of 5-(carboxymethylidine)-hydantoin in 7.5 ml. of 1 *N* potassium hydroxide was heated at 100° for thirty minutes. Orotic acid crystallized on acidification with hydrochloric acid. The product was twice crystallized from water. This product melts sharply with vigorous decomposition at a temperature between 323 and 345° depending on the method of determination. The lower value was obtained by raising the temperature of the sample from 25 to 323° at a rate of 4° per minute. However, if the sample is placed in the bath at 330° the compound decomposes at 345° (cor.). Values of 345 and 347° were reported by Johnson and Schroeder[9] and Bachstez.[7] As previously reported orotic acid crystallized from water contains one molecule of tightly bound water of crystallization. Calculated for $C_5H_4O_4N_2$: C, 38.48; H, 2.56; N, 17.94. Found: C, 38.50; H, 2.81; N, 17.84. Ultraviolet absorption spectrum in water; Fig. 1, curve D. This spectrum was found to be identical with that of a sample of orotic acid generously supplied by Dr. T. B. Johnson of Yale University. This sample was synthesized by the method of Johnson and Schroeder.[9]

Discussion

As a result of these investigations several questions have arisen which as yet remain unanswered. Although the catalytic reduction of 5-(carbethoxymethylidene)-hydantoin proceeded according to expectations, the corresponding acid on like treatment consumed nearly two molecular equivalents of hydrogen yielding a very hygroscopic compound that has not been identified. However, the reduction of the acid 5-(carboxymethylidine)-hydantoin to 5-(acetic acid)-hydantoin has been carried out successfully by Gabriel.[5] Hydriodic acid was utilized as the reducing agent.

It is interesting to note that Bachstez[7] attempted to esterify orotic acid with hydrochloric acid in alcohol and obtained what he believed to be 6-ethoxyorotic acid. This conclusion, however was evidently based for the most part on the fact that the product was not identical with the beginning ester VI. This ester has now been identified as 5-(carbethoxymethylidene)-hydantoin rather than orotic acid ester. It appears quite possible that the compound obtained by Bachstez is actually the ethyl ester of orotic acid. In this connection it should be noted that the methyl derivatives of orotic acid reported by Wheeler[4] and Bachstez[7] probably should be considered in

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(9) T. B. Johnson and E. F. Schroeder, THIS JOURNAL, **54**, 2941 (1932).

the same way as the ethyl derivatives. In addition the "orotic acid methyl ester" synthesized by Bachstez[7] from oxalacetic acid methyl ester must be 5-(carbmethoxymethylidene)-hydantoin.

Acknowledgments.—These investigations were supported by the Rockefeller Foundation and the Williams–Waterman Fund of the Research Corporation of New York.

The authors are indebted for microanalyses to Dr. G. Oppenheimer and Mr. Glenn Sweinhart, of the Kerckhoff Laboratories of Biology, California Institute of Technology.

Summary

1. It has been demonstrated that the condensation of ethyloxalacetate with urea in acid solution yields the ester of a substituted hydantoin rather than the ester of orotic acid (4-carboxyuracil), as previously reported.
2. This ester or the corresponding acid 5-(carboxymethylidene)-hydantoin can be converted to orotic acid by treatment with aqueous alkali.
3. Ultraviolet absorption spectra in aqueous solutions are given for 5-(carbethoxymethylidene)-hydantoin, 5-(carboxymethylidine)-hydantoin, 5-(acetic acid)-hydantoin and orotic acid.
4. The ethyl ester of 5-(acetic acid)-hydantoin has been described.

PASADENA, CALIFORNIA RECEIVED NOVEMBER 13, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF WASHINGTON]

The Preparation of Fluorine Perchlorate from Fluorine and Perchloric Acid

BY GILSON H. ROHRBACK AND GEORGE H. CADY

It has been known since 1934 that fluorine reacts with nitric acid to form a gaseous compound whose formula is NO_3F.[1] This fact suggests the possibility that other acids may react in a similar manner, forming products in which the hydrogen of the acid has been replaced by fluorine. As a part of a study now under way to test the validity of this suggestion, the gaseous products of the direct fluorination of perchloric acid have been examined. One of the substances found was similar to fluorine nitrate, NO_3F, in many ways, including the tendency to explode easily and with violence.

Products formed in solution by the action of fluorine upon perchloric acid have been reported by Fichter and Brunner.[2]

Experimental

Preparation.—The reaction chamber used through most of this research is shown in Fig. 1. It consisted of a glass column packed with glass chips through which 60% perchloric acid flowed slowly. The acid supply was maintained by slow addition from the dropping funnel at a rate of about one drop per second. The fluorine supply tube entered near the top of the column and ran down through glass packing to a point just above the liquid seal. Undiluted fluorine gas then traveled upward against the counter flow of perchloric acid at an approximate flow rate of 2.5 liters per hour. The column was enclosed with a water jacket for temperature control. Any gaseous reaction product was carried out from the top of the chamber and collected in a trap cooled with liquid oxygen.

In addition to varying quantities of SiF_4, O_2 and OF_2, a white crystalline solid collected on the sides of the cold trap and on warming melted to a clear liquid. When appreciable quantities of this liquid were collected, a yellow substance, apparently chlorine, was also present. The liquid was purified by fractional distillation and the boiling point of the colorless liquid remaining after the removal of the yellow substances was $-15.9°$ at 755 mm. pressure. As a precautionary measure no sample of liquid larger than about 4 ml. was collected in any experiment.

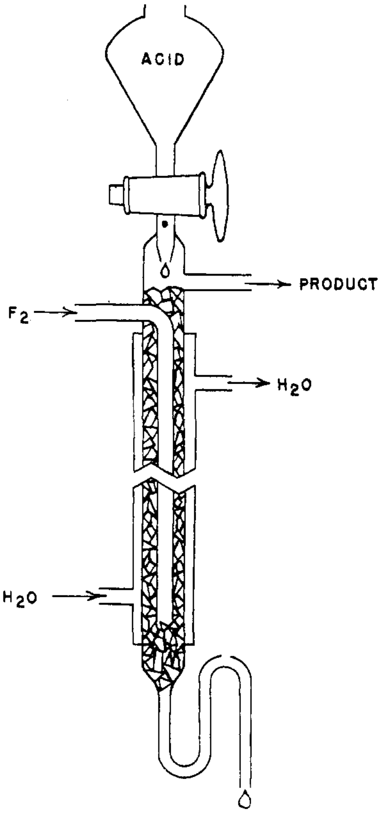

Fig. 1.

The described method for the preparation of this liquid was very inefficient. About one hundred cc. of 60% per-

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[1] G. H. Cady, THIS JOURNAL, **56**, 2635 (1934).

[2] Fr. Fichter and E. Brunner, *Helv. Chim. Acta*, **12**, 305–313 (1929).