[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

RESEARCHES ON HYDANTOINS. XLIV. PYVURIL AND DIPYRUVIC TRIUREIDE[1]

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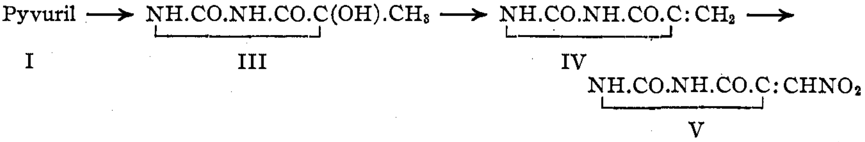
Pyvuril (homo-allantoin, 5-methyl allantoin) I results from the condensation of two mols. of urea with one of pyruvic acid.[2]

$$2\,NH_2.CO.NH_2 + CH_3CO.COOH = \underline{NH.CO.NH.CO.C}(CH_3).NH.CO.NH_2 \quad \text{I}$$

Dipyruvic triureide II is a more complex product arising from the union of three mols. of urea with two of pyruvic acid.[2,3]

$$3\,NH_2CO.NH_2 + 2\,CH_3CO.COOH = \underline{NH.CO.NH.CO.C}(CH_3).NH.CO.NH.\underline{C(CH_3).CO.NH.CO.NH} \quad \text{II}$$

These structures were assigned to these compounds by Grimaux on the basis of his synthesis and the action of mineral acids. He showed that both pyvuril and dipyruvic triureide are converted by reaction with concd. nitric acid into urea and nitropyruvic ureide V. The reaction in the case of pyvuril was assumed to take the course expressed by the formulas below;[4]



$$\text{Pyvuril (I)} \longrightarrow \underline{NH.CO.NH.CO.C}(OH).CH_3\ (\text{III}) \longrightarrow \underline{NH.CO.NH.CO.C}{:}CH_2\ (\text{IV}) \longrightarrow \underline{NH.CO.NH.CO.C}{:}CHNO_2\ (\text{V})$$

that is, preliminary hydrolysis to 5-oxy-5-methyl-hydantoin III, followed by dehydration to pyruvic mono-ureide or methylene-hydantoin IV, and subsequent nitration in the methylene group. A similar mechanism might also be written for the reaction in the case of dipyruvic triureide II. Grimaux attempted to isolate the intermediate 5-methylene-hydantoin IV by acting upon pyvuril I with concd. hydrochloric acid instead of with concd. nitric acid. By this procedure a product was obtained which had the expected composition and yielded nitropyruvic ureide V on treatment with nitric acid. Hence Grimaux considered it the desired intermediate product IV and thus substantiated the postulated mechanism of reaction. The constitution of nitropyruvic ureide V was not conclusively investigated. This subject will be dealt with in a later paper.

Andreasch,[5] while studying the action of bromine on 5-methyl-hydantoin

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[1] Constructed from part of a dissertation presented by David Davidson to the Faculty of the Graduate School of Yale University, June, 1924, in candidacy for the degree of Doctor of Philosophy. (Treat B. Johnson.)

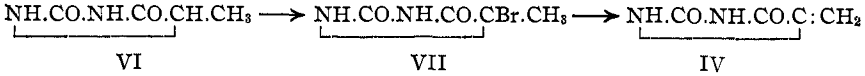
[2] Grimaux, *Ann. chim. phys.*, [5] **11**, 367 (1877).

[3] Simon, *Compt. rend.*, **136**, 506 (1903).

[4] *Bull. soc. chim.*, [II] **23**, 61 (1876).

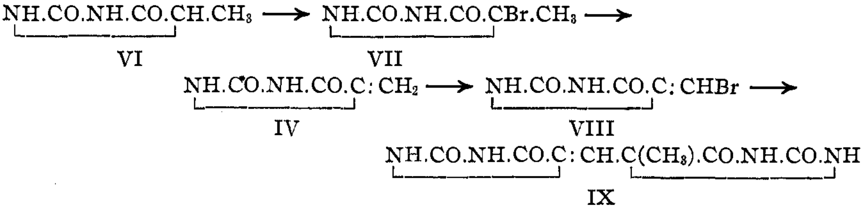
[5] Andreasch, *Monatsh.*, **23**, 813 (1902).

obtained a product which he found to be identical with Grimaux's pyruvic mono-ureide IV and whose formation he accounted for by the following reaction



$$\underset{\text{VI}}{\underline{\text{NH.CO.NH.CO.CH}}\text{.CH}_3} \longrightarrow \underset{\text{VII}}{\underline{\text{NH.CO.NH.CO.CBr}}\text{.CH}_3} \longrightarrow \underset{\text{IV}}{\underline{\text{NH.CO.NH.CO.C}}\text{:CH}_2}$$

Somewhat later Gabriel[6] investigated this product described by Andreasch as a mono-ureide IV, and concluded that it is actually a bimolecular compound IX which results from a secondary reaction of the primary product of bromination—bromopyruvic ureide VIII—with unchanged methyl-hydantoin VI. These various changes are expressed by the following formulas.



$$\underset{\text{VI}}{\underline{\text{NH.CO.NH.CO.CH}}\text{.CH}_3} \longrightarrow \underset{\text{VII}}{\underline{\text{NH.CO.NH.CO.CBr}}\text{.CH}_3} \longrightarrow$$

$$\underset{\text{IV}}{\underline{\text{NH.CO.NH.CO.C}}\text{:CH}_2} \longrightarrow \underset{\text{VIII}}{\underline{\text{NH.CO.NH.CO.C}}\text{:CHBr}} \longrightarrow$$

$$\underset{\text{IX}}{\underline{\text{NH.CO.NH.CO.C}}\text{:CH.}\underline{\text{C(CH}_3\text{).CO.NH.CO.NH}}}$$

Gabriel gave no consideration to a possible mechanism of reaction whereby a bicyclic molecule such as IX could result from Grimaux's pyvuril I. He also omitted to explain the production of nitropyruvic ureide V from a pyruvic ureide having the structure IX (Grimaux's reaction). In fact, the existence of nitropyruvic ureide was completely overlooked in his discussion. Probably as a result of this confusion, the new edition of Beilstein's Handbuch[7] lists pyvuril and dipyruvic triureide under "Umwandlungsprodukte der Brenztraubensäure von unbekannter Konstitution."

In this paper are now presented new data obtained by a further study of the chemical properties of pyvuril and dipyruvic triureide. Experimental results have been obtained whereby it is found possible to reconcile the work of Grimaux with that of Gabriel and to establish definitely the constitution of the substances involved.

Pyvuril reacts readily with bromine in glacial acetic acid solution. With one molecule of the halogen, the products formed are urea and bromopyruvic ureide VIII. With two molecules of bromine, urea and dibromopyruvic ureide X are produced. The mono- and dibromopyruvic ureides have previously been prepared by Gabriel[6] from 5-methylhydantoin VI and the dihalide derivative also by Fischer[8] from dibromopyruvic acid. The constitutions of both derivatives have been established by the work of these two investigators.

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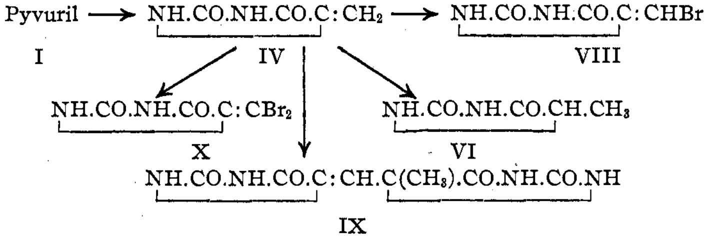
[6] Gabriel, *Ann.*, **348,** 50 (1906).

[7] Beilstein, 4th edition, vol. III, p. 613.

[8] Fischer, *Ann.*, **239,** 185 (1887).

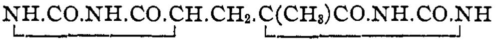
The action of bromine on pyvuril is seen, therefore, to be analogous to that of nitric acid, and it may be assumed in accordance with Grimaux's interpretation of the reaction mechanism, that urea and pyruvic mono-ureide IV are intermediate products of the reaction. The latter compound then interacts with bromine to form the corresponding mono- and di-halogen derivatives.



When an attempt is made to isolate the reactive intermediate IV by means of a strong but non-substituting acid, even under milder conditions than those employed by Grimaux, only the bicyclic product IX identical with that described by Gabriel is obtained.

In the light of these facts the question at once arises: does the bicyclic compound IX reflect the structure of pyvuril and are the substituted mono-ureides degradation products of this complex ureide; or, is the bicyclic ureide (dipyruvic ureide) IX formed by polymerization of the postulated intermediate pyruvic mono-ureide IV?

The behavior of pyvuril toward hydriodic acid affords a ready answer to this question. With this reagent 5-methylhydantoin VI is produced—a reaction which confirms the intermediate existence of pyruvic mono-ureide IV and indicates that dipyruvic ureide IX is a secondary product formed by its polymerization in the presence of acids when no substituting or reducing agent is present. Otherwise, the final product of the action of hydriodic acid on pyvuril I would be expected to be *hydrodipyruvic ureide* XI—which product has been obtained by Gabriel[6] by the action of hydriodic acid on dipyruvic ureide IX. Incidentally, this production of 5-methyl-hydantoin VI from pyvuril is analogous to the formation of hydantoin XIII from allantoin XII reported by Baeyer.[9]



$$\mathrm{NH.CO.NH.CO.CH.CH_2.C(CH_3)CO.NH.CO.NH}$$

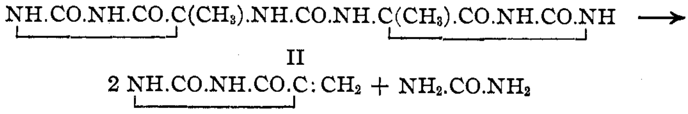
XI

$$\mathrm{NH.CO.NH.CO.CH.NH.CO.NH_2} \longrightarrow \mathrm{NH.CO.NH.CO.CH_2}$$

XII XIII

Dipyruvic triureide II exhibits exactly the same chemical properties as pyvuril. From this compound we may, therefore, represent the initial decomposition by the following equation,

[9] Baeyer, *Ann.*, **117,** 178 (1861).



$$\text{NH.CO.NH.CO.C(CH}_3\text{).NH.CO.NH.C(CH}_3\text{).CO.NH.CO.NH} \longrightarrow$$

II

$$2\ \text{NH.CO.NH.CO.C:CH}_2 + \text{NH}_2\text{.CO.NH}_2$$

IV

which indicates that like pyvuril, dipyruvic triureide suffers primary decomposition into urea and pyruvic mono-ureide IV, two mols. of the latter being formed instead of one. The reactive intermediate 5-methylenehydantoin IV behaves, of course, exactly the same, regardless of its source.

Experimental Part

Pyruvic Acid.—Commercial pyruvic acid was generously furnished us by the Calco Chemical Co., Bound Brook, New Jersey. It was purified by fractional distillation under diminished pressure and the fraction boiling at 70–73° (16 mm.) employed.

Pyvuril.—The method of Simon[10] was used for the preparation of this compound.

Dipyruvic Triureide.—A modification of the method described by Simon[9] was employed. To 75 g. of urea in 55 cc. of concd. hydrochloric acid in a 700cc. casserole was added 50 g. of pyruvic acid. The solution was allowed to stand for 45 hours, when it had completely solidified to a soft cake that was readily removed from the casserole; it was broken, spread upon filter paper and air-dried for six hours. The product was triturated with 400 cc. of cold water and the mixture filtered on a Büchner funnel. The solid was then removed from the filter, triturated with 400 cc. of hot water, the mixture filtered again and washed with 200 cc. of hot water. After being sucked dry, it was spread on a porous tile and dried on the hot plate; yield, 74 g.

For recrystallization, 6 g. of the pulverized ureide was made into a paste with a little water and dil. aqueous ammonia added while the mixture was stirred; about 34 cc. was required for solution. The solution was filtered and then poured into 700 cc. of hot water containing 30 cc. of glacial acetic acid. In this way a supersaturated solution of the ureide was obtained which, on cooling, deposited 5 g. of long, fibrous needles, resembling asbestos.

Action of Bromine on Pyvuril, I, (1) ONE MOLECULAR EQUIVALENT OF BROMINE.—To a suspension of 3.3 g. of pyvuril I in 20 cc. of glacial acetic acid was added 1 cc. of bromine and the mixture heated on the steam-bath under a reflux condenser. In about eight minutes decolorization took place. On cooling the solution, 1.7 g. of bromopyruvic ureide VIII separated; this was filtered off and washed with water. Evaporation of the mother liquor gave an additional 0.3 g. of the same product; yield, 2.0 g., or 60%. The compound was identified by its peculiar crystal form, separating in clusters of twinned rhombic plates resembling snow crystals and its melting point of 240° with decomposition.

Anal. Calcd. for $C_4H_3BrN_2O_2$: N, 14.7. Found (Kjeldahl): 14.6.

The presence of urea in the washings was demonstrated by the precipitation of characteristic hexagonal plates of urea nitrate upon the addition of nitric acid to the cold solution.

(2) TWO MOLECULAR EQUIVALENTS OF BROMINE.—A suspension of 3.3 g. of pyvuril was treated as in the experiment described above but with 2 cc. of bromine. On cooling the reaction mixture, 2 g. of dibromopyruvic ureide X separated; m. p., 305° (decomp.). Evaporation of the mother liquor gave 2.2 g. of material, which when washed with hot water yielded 1.7 g. of the same compound; yield, 3.7 g., or 71%. The hydantoin was identified by its melting point, solubility and analysis.

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[10] Simon, *Compt. rend.*, **133**, 587 (1901).

Anal. Calcd. for $C_4H_2Br_2N_2O_2$: N, 10.4. Found (Kjeldahl): 10.5.

When treated with an excess of bromine water it was converted into the soluble tribromopyruvic ureide[8] which crystallized in plates melting at 248°, and gave the odor of bromoform when it was boiled with water. Its identity was confirmed by analysis.

Anal. Calcd. for $C_4H_3Br_3N_2O_3$: N, 7.6. Found (Kjeldahl): N, 7.5.

The washings from the preparation of dibromopyruvic ureide yielded on evaporation a small quantity of plates melting at 200–205°, the properties of which agree with 5-dibromomethylene-hydantoic acid[6] obtained by Gabriel by the action of bromine water on bromopyruvic ureide.

Action of Sulfuric Acid on Pyvuril, I.—Three g. of finely pulverized pyvuril was treated with 3 cc. of concd. sulfuric acid. Heat was evolved and the solid dissolved. The reaction mixture was heated on the steam-bath for five minutes and then chilled. Ice was added to the viscous liquid whereupon 1.5 g. of dipyruvic ureide IX separated; this was filtered off, and washed with water. On recrystallization from 35 parts of boiling water it was obtained in colorless crystals decomposing at 290°.

Anal. Calcd. for $C_8H_8N_4O_4$: N, 25.0. Found (Kjeldahl): 25.0.

This product was shown not to be pyruvic mono-ureide IV by the fact that when treated with bromine in glacial acetic acid solution it yielded neither bromopyruvic ureide VIII nor dibromopyruvic ureide X but a new derivative, bromodipyruvic ureide which separated from hot water in sheaves of microscopic needles melting at about 265° with decomposition.

Anal. Calcd. for $C_8H_7BrN_4O_4$: N, 18.5. Found (Kjeldahl): 18.2.

Action of Hydriodic Acid on Pyvuril.—Three g. of finely pulverized pyvuril was suspended in about 25 cc. of glacial acetic acid. Five cc. of hydriodic acid (d., 1.7) was added to the mixture. The brown color of iodine appeared at once. After the mixture had been heated for 20 minutes on the steam-bath, the solvent was removed under diminished pressure, the iodine steam-distilled, and the residue allowed to evaporate spontaneously. After 24 hours some crystalline material had separated. This was filtered off, washed with an ether-alcohol mixture and dried on the hot-plate; m. p., 145°. It was identified as 5-methylhydantoin VI, since a mixture with an authentic sample melted at 145–146°.

Experiments with Dipyruvic Triureide, II.—Results identical with those described above were obtained when an equivalent amount of dipyruvic triureide was substituted for the pyvuril.

Summary

1. Grimaux's structures for pyvuril and dipyruvic triureide have been confirmed.

2. Pyruvic mono-ureide or methylenehydantoin is an intermediate product in the decomposition of pyvuril and dipyruvic triureide.

3. Free pyruvic mono-ureide has not been isolated on account of its reactivity. It undergoes polymerization giving dipyruvic ureide.

4. While pyruvic mono-ureide undergoes polymerization, its nitro, mono- and dibromo derivatives are stable compounds and can be isolated.

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