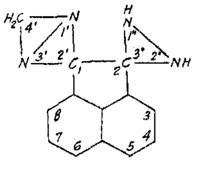

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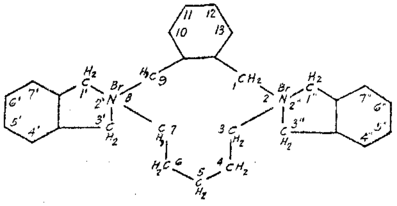

158 B3 IV (577)

XENIA, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

RESEARCHES ON HYDANTOINS. XLV. DIPYRUVIC UREIDE[1]

BY DAVID DAVIDSON AND TREAT B. JOHNSON

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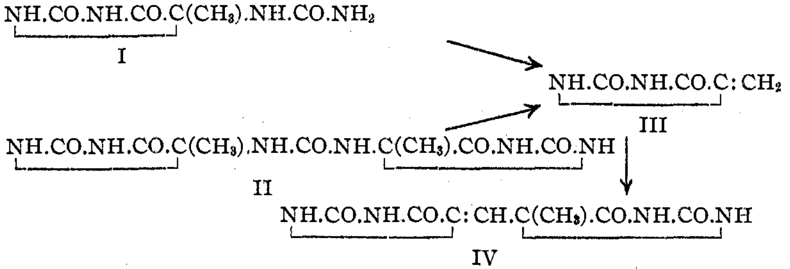
In a previous paper[2] from this Laboratory it has been shown that pyvuril (homo-allantoin) I and dipyruvic triureide II are transformed when heated with strong mineral acids to methylene-hydantoin III. In the absence of reagents which attack the methylene group, the latter undergoes polymerization giving dipyruvic ureide IV.



$\underbrace{NH.CO.NH.CO.C}(CH_3).NH.CO.NH_2$ I

$\underbrace{NH.CO.NH.CO.C}(CH_3).NH.CO.NH.\underbrace{C(CH_3).CO.NH.CO.NH}$ II

$\underbrace{NH.CO.NH.CO.C}{:}CH_2$ III

$\underbrace{NH.CO.NH.CO.C}{:}CH.\underbrace{C(CH_3).CO.NH.CO.NH}$ IV

The present paper deals with a study of some of the chemical properties of dipyruvic ureide IV and a consideration of the mechanism of its formation by polymerization of the hydantoin III.

Gabriel[3] who first recognized the true nature of dipyruvic ureide IV obtained it in the bromination of 5-methyl-hydantoin VI. According to his conception of the reaction this product results from a complex process, the final step of which is the direct condensation of bromopyruvic ureide V with 5-methyl-hydantoin VI as expressed below.

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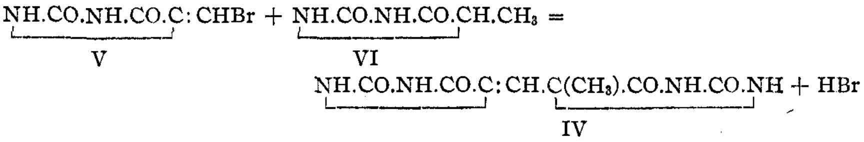
[1] Constructed from part of a dissertation presented by David Davidson to the Faculty of the Graduate School of Yale University in June, 1924, in candidacy for the degree of Doctor of Philosophy.

[2] Davidson, THIS JOURNAL, 47, 255 (1925).

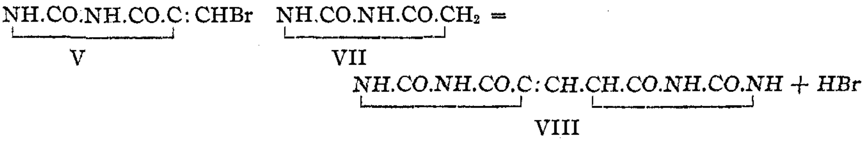
[3] Gabriel, *Ann.*, 348, 50 (1906).



$$\underset{\mathrm{V}}{\mathrm{NH.CO.NH.CO.C\!:\!CHBr}} + \underset{\mathrm{VI}}{\mathrm{NH.CO.NH.CO.CH.CH_3}} = \underset{\mathrm{IV}}{\mathrm{NH.CO.NH.CO.C\!:\!CH.C(CH_3).CO.NH.CO.NH}} + \mathrm{HBr}$$

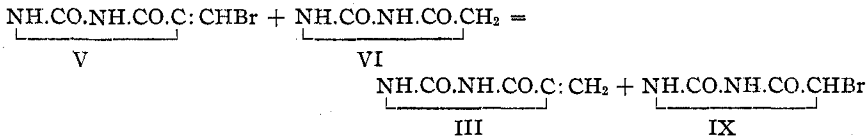
This view was sustained by the fact that dipyruvic ureide IV was actually formed when these two reagents were allowed to interact.

A weak point in this experimental evidence was revealed, however, when bromopyruvic ureide V was allowed to react with hydantoin VII itself. Here the product of reaction which was obtained was not the expected lower homolog of dipyruvic ureide VIII, but dipyruvic ureide IV itself, a most interesting result that Gabriel was unable to explain.



$$\underset{\mathrm{V}}{\mathrm{NH.CO.NH.CO.C\!:\!CHBr}} \quad \underset{\mathrm{VII}}{\mathrm{NH.CO.NH.CO.CH_2}} = \underset{\mathrm{VIII}}{NH.CO.NH.CO.C\!:\!CH.CH.CO.NH.CO.NH} + HBr$$

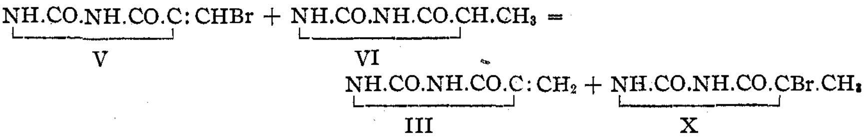
This unexpected result can be accounted for by assuming that the first stage of this transformation involves a normal double decomposition as expressed below.



$$\underset{\mathrm{V}}{\mathrm{NH.CO.NH.CO.C\!:\!CHBr}} + \underset{\mathrm{VI}}{\mathrm{NH.CO.NH.CO.CH_2}} = \underset{\mathrm{III}}{\mathrm{NH.CO.NH.CO.C\!:\!CH_2}} + \underset{\mathrm{IX}}{\mathrm{NH.CO.NH.CO.CHBr}}$$

Under the conditions that Gabriel employed, namely, glacial acetic acid containing hydrobromic acid as his reaction medium, the pyruvic monoureide or 5-methylene-hydantoin III would, of course, undergo rapid polymerization to the final product of this complex reaction—dipyruvic ureide IV.

A similar mechanism of reaction may be applied to explain the interaction of bromopyruvic ureide V with 5-methyl-hydantoin VI.



$$\underset{\mathrm{V}}{\mathrm{NH.CO.NH.CO.C\!:\!CHBr}} + \underset{\mathrm{VI}}{\mathrm{NH.CO.NH.CO.CH.CH_3}} = \underset{\mathrm{III}}{\mathrm{NH.CO.NH.CO.C\!:\!CH_2}} + \underset{\mathrm{X}}{\mathrm{NH.CO.NH.CO.CBr.CH_3}}$$

In this case the second product of metathesis is 5-bromo-5-methyl-hydantoin X, which is unstable and very readily loses hydrogen bromide giving a second molecule of 5-methylene-hydantoin III as a product of the reaction. The last stage of the transformation involves a polymerization of the 5-methylene-hydantoin III, in the presence of the strong acid employed, to dipyruvic ureide IV.

Since this hypothesis of preliminary double decomposition readily accounts for Gabriel's reactions and since it has previously been shown that pyruvic mono-ureide or 5-methylene-hydantoin III undergoes polymerization to dipyruvic ureide, one is led to accept the new mechanism just discussed as more tenable than the concept of direct condensation of bromopyruvic ureide and 5-methyl-hydantoin as proposed by Gabriel.

In the light of these facts it is now important to consider the nature of the polymerization of pyruvic mono-ureide III to dipyruvic ureide IV. Ingold[4] has adopted the hypothesis that double-bonded compounds generally tend, in the liquid state, to establish an equilibrium with the dimeric form, $2\mathrm{A:B} \rightleftharpoons \underbrace{\mathrm{A—B—A—B}}$. On the basis of this hypothesis, dipyruvic ureide is to be represented as a tricyclic compound XI and its formation would be expressed as follows.

$$2\,\underbrace{\mathrm{NH.CO.NH.CO.C}}\mathrm{:CH_2} \rightleftharpoons \underbrace{\mathrm{NH.CO.NH.CO.C}}{<}^{\mathrm{CH_2}}_{\mathrm{CH_2}}{>}\underbrace{\mathrm{C.CO.NH.CO.NH}}$$

III XI

This tricyclic structure XI is not in accordance with the behavior of dipyruvic ureide when subjected to the action of reducing agents. Gabriel[3] has shown that this compound contains a double bond that is readily saturated with hydrogen. This property has also been confirmed by catalytic reduction.

We are not confined to cyclical constructions in interpreting the course of reaction when 5-methylene-hydantoin undergoes polymerization. It can easily be shown that another type of reaction may be entered into here, which is characteristic of double-bonded compounds containing a methylene group adjacent to the double bond. This reaction depends on the saturation of the double bond of one molecule by the methylene group of another, $\mathrm{E:CH_2 + E:CH_2 = E:CH.E.CH_3}$. If, now, this concept is applied to pyruvic mono-ureide or 5-methylene-hydantoin III, two possible formulas for dipyruvic ureide may be presented.

$$\underbrace{\mathrm{NH.CO.NH.CO.C}}\mathrm{:CH.CH_2.}\underbrace{\mathrm{CH.CO.NH.CO.NH}}$$ and

XII

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

IV

It is possible to distinguish between these two structures XII and IV by the action of bromine. From the work of Gabriel[3] and of Wheeler, Johnson and Hoffman[5] it may be stated that *(1)* 5-alkyl derivatives of hydantoin of Type XIII react with one molecule of bromine to form 5-alkylene derivatives of Type XIV; *(2)* 5-alkylene derivatives of hydantoin of Type

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[4] Ingold, *J. Chem. Soc.*, **121**, 2795 (1922).

[5] Johnson and Hoffman, *Am. Chem. J.*, **47**, 26 (1912). Wheeler, Johnson and Hoffman, *J. Biol. Chem.*, **10**, 154 (1911). Wheeler and Hoffman, *Am. Chem. J.*, **45**, 376 (1911).

XIV react with one molecule of bromine to form 5-bromo-alkylene derivatives of Type XV.


$\mathrm{NH.CO.NH.CO.CH.CH_2.R}$

XIII

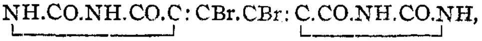

$\mathrm{NH.CO.NH.CO.C\!:\!CHR}$

XIV

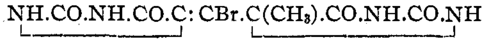

$\mathrm{NH.CO.NH.CO.C\!:\!CBrR}$

XV

These generalizations allow one to predict that a structure such as that expressed in Formula XII, which represents a double molecule containing a 5-alkylene and a 5-alkyl grouping, would react with three molecules of bromine to form the dibromo-dialkylene compound represented by Formula XVI. On the other hand, a structure such as is expressed in Formula IV contains a 5-alkylene grouping and also a 5-dialkyl configuration. Consequently, this would be expected to interact with only one molecular equivalent of bromine to give a monobromo compound corresponding to Formula XVII.


$\mathrm{NH.CO.NH.CO.C\!:\!CBr.CBr\!:\!C.CO.NH.CO.NH,}$

XVI


$\mathrm{NH.CO.NH.CO.C\!:\!CBr.C(CH_3).CO.NH.CO.NH}$

XVII

It has been found experimentally that dipyruvic ureide reacts with but one molecular equivalent of bromine to form a monobromo derivative. We conclude, therefore, that Formula IV represents the structure of dipyruvic ureide and Formula XVII that of its bromo derivative.

Since the 5 position in one hydantoin ring of IV is completely substituted and saturated, this part of the molecule is resistant to further attack and the whole construction may be viewed as a 5-alkylene-hydantoin of the type expressed by Formula XIV, in which R represents the complex but stable hydantoin radical, $\mathrm{NH.CO.NH.CO.C(CH_3)}$—.

Striking similarities may then be brought out by comparing dipyruvic ureide IV with bromopyruvic ureide V which is also a 5-alkylene-hydantoin of Type XIV. Both compounds react with one molecular equivalent of bromine in anhydrous medium giving bromodipyruvic ureide XVII and dibromopyruvic ureide XVIII, respectively. Both of these products are much less soluble in water than the mother substances. Gabriel[3] observed that bromopyruvic ureide V reacted with bromine water in quite a different manner than with bromine in glacial acetic acid, yielding instead of the insoluble dibromopyruvic ureide XVIII the very soluble 5-dibromo-methylene-hydantoic acid XIX. Similarly, dipyruvic ureide IV reacts with bromine water in a manner unlike that with bromine in glacial acetic acid to yield a very soluble product which by analogy is assigned the constitution represented by Formula XX. The two products just discussed, XIX and XX, are both much more soluble in water than the corresponding mother substances and differ structurally from the compounds XVIII and XVII by one molecule of water. The two hydantoic acids are converted into their respective hydantoins by the action of sulfuric acid.

Just as dibromopyruvic ureide, $\underline{\mathrm{NH.CO.NH.CO.C}}\mathrm{:CBr_2}$ (XVIII), fails to react further with bromine in glacial acetic acid, so bromodipyruvic ureide XVII is incapable of reacting further with this reagent, but does, like the former, interact with bromine in aqueous solution to give the open-chain, trisubstituted pyruvic ureide XXII analogous to tribromopyruvic ureide XXI. These two products XXI and XXII are intermediate in solubility in water between the mother substances V and IV and the other pair of open-chain derivatives XIX and XVII.

$\mathrm{NH_2.CO.NH.C(COOH):CBr_2}$ XIX

$\mathrm{NH_2.CO.NH.C(COOH):CBr.}\underline{\mathrm{C(CH_3).CO.NH.CO.NH}}$ XX

$\mathrm{NH_2.CO.NH.CO.CO.CBr_3}$ XXI

$\mathrm{NH_2.CO.NH.CO.CO.CBr_2}\underline{\mathrm{C(CH_3).CO.NH.CO.NH}}$ XXII

Action of Nitric Acid on Dipyruvic Ureide

As has been stated in a previous paper,[2] Grimaux,[6] who first obtained dipyruvic ureide IV, mistook it for pyruvic mono-ureide or 5-methylene-hydantoin III because of the fact that it yielded nitropyruvic ureide XXIII when treated with nitric acid. It was of interest, therefore, to verify this reaction. In a qualitative test it was found that the reaction is mainly one of oxidation, the principal products being parabanic acid XXIV and nitropyruvic ureide. While nitropyruvic ureide is obtained, the reaction is certainly much more complex than was intimated by Grimaux. Oxidation probably occurs at the double bond in IV, splitting the molecule into parabanic acid XXIV and 5-methyl-hydantoin-5-carboxylic acid XXV. Possibly the latter suffers simultaneous loss of carbon dioxide and oxidation to 5-hydroxy-5-methyl-hydantoin XXVI, which loses water and undergoes nitration to form nitropyruvic ureide XXIII.

$\underline{\mathrm{NH.CO.NH.CO.C}}\mathrm{O}$ XXIV

$\underline{\mathrm{NH.CO.NH.CO.C}}\mathrm{(CH_3).COOH}$ XXV

$\underline{\mathrm{NH.CO.NH.CO.C}}\mathrm{(OH).CH_3}$ XXVI

$\underline{\mathrm{NH.CO.NH.CO.C}}\mathrm{:CHNO_2}$ XXIII

Experimental Part

Dipyruvic Ureide.—Dipyruvic ureide IV may be obtained from pyvuril I or from dipyruvic triureide II by the action of sulfuric, hydrobromic or hydrochloric acids It is conveniently prepared directly from pyruvic acid as follows.

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

Ten g. of pyruvic acid is added to a solution of 15 g. of urea in 15 cc. of concd. hydrochloric acid in a beaker. After 36 hours, 17 cc. of concd. sulfuric acid is added to the paste of dipyruvic triureide, causing a vigorous evolution of hydrogen chloride. The beaker is placed on the steam-bath and heated until all is in solution, any lumps being broken up with a stirring rod. After cooling the mixture, 50 g. of ice and 150 cc. of water are added causing a precipitation of 8.1 g. of a slightly discolored, granular solid. After recrystallization from 250 cc. of boiling water and decolorizing with Norite, 6.4 g. of colorless, crystalline dipyruvic ureide is obtained; m. p., about 290°, with decomposition.

Anal.[7] Calcd. for $C_8H_8O_4N_4$: N, 25.0. Found: 25.0.

Contrary to the statement made by Gabriel,[3] dipyruvic ureide dissolves in alkali to give a colorless solution from which it is reprecipitated upon the addition of acid.

Catalytic Reduction of Dipyruvic Ureide.—Five and six-tenths g. of the pulverized ureide and 0.1 g. of platinum oxide[8] were suspended in 100 cc. of glacial acetic acid. The mixture was then shaken in an atmosphere of hydrogen. Approximately one molecular proportion of hydrogen was absorbed in eight hours. No further absorption occurred even after revivifying the catalyst. The mixture of hydrodipyruvic ureide[3] with catalyst was filtered off, and the product then extracted with boiling water from which it separated in rectangular plates. It melts with decomposition at about 300° and is less soluble in water than dipyruvic ureide.

Anal. Calcd. for $C_8H_{10}O_4N_4$: N, 24.8. Found: 24.9.

Action of Bromine on Dipyruvic Ureide.—To 4.5 g. of finely pulverized dipyruvic ureide IV suspended in 25 cc. of glacial acetic acid, during heating on the steam-bath under a reflux condenser, was added 2 cc. of bromine (2 molecular equivalents) in 10 cc. of glacial acetic acid. Complete solution was soon obtained. In about 10–15 minutes a solid began to separate and hydrogen bromide was evolved. Much bromine remained unconsumed even after the mixture had been heated for an hour. The solvent and an excess of bromine were distilled under diminished pressure and 5.3 g. of a pulverulent, yellow solid was obtained. This was purified by recrystallizing from about 75 parts of boiling water but more readily by dissolving in dil. ammonium hydroxide and adding the solution to 25 parts of boiling water containing an excess of acetic acid when, as the liquid cooled, the bromodipyruvic ureide XVII separated in clusters or sheaves of fine, white needles that decompose at about 265–270° after darkening.

Anal. Calcd. for $C_8H_7O_4N_4Br$: N, 18.5. Found: 18.4.

Action of Bromine Water on Dipyruvic Ureide.—To a suspension of 10.1 g. of pulverized dipyruvic ureide in 40 cc. of water was added 2.4 cc. of bromine. The mixture was gently warmed under a reflux condenser while being agitated. Complete decolorization took place in a few moments. Since a small amount of dipyruvic ureide remained undissolved, an additional 0.2 cc. of bromine was added and the heating continued. The ureide dissolved completely and the red bromine color persisted. The solution was then evaporated to crystallization and allowed to stand for 18 hours. The solid which separated was washed with cold water and collected; yield, 10 g. On recrystallization from a small amount of boiling water, bromomethenyl-5′-(5′-methyl)-hydantoin-5-hydantoic acid XX separated in large, transparent crystals containing three molecules of water. On being heated on the hot plate the crystals lost this water, became opaque and disintegrated into feathery needles of the anhydrous compound.

Anal. Calcd. for $C_8H_9O_5N_4Br.3H_2O$: N, 14.9. Found: 15.2.
Calcd. for $C_8H_9O_5N_4Br$: N, 17.5. Found: 17.5.

Conversion of Bromomethenyl-5′-(5′-methyl)-hydantoin-5-hydantoic Acid XX to the

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[7] The nitrogen analyses reported in this article were made by the Kjeldahl method.

[8] Adams and Shriner, This Journal, 45, 2171 (1923).

Corresponding Hydantoin, Bromodipyruvic Ureide XVII.—Six-tenths g. of Compound XX was treated with 1.5 cc. of concd. sulfuric acid and the mixture was heated on the steam-bath for 15 minutes when it dissolved completely. Addition of ice to the cooled liquid caused the precipitation of an insoluble solid which on recrystallization from hot water separated in sheaves of needles characteristic of bromodipyruvic ureide XVII; m. p., about 260–265° (decompn.).

Anal. Calcd. for $C_8H_7O_4N_4Br$: N, 18.5. Found: 18.4.

Action of Bromine Water on Bromodipyruvic Ureide XVII.—To a suspension of 6.7 g. of finely pulverized bromodipyruvic ureide XVII in 100 cc. of hot water in a flask attached to a reflux condenser was added 1.9 cc. of bromine in small portions through the condenser, the flask being heated on the steam-bath and well shaken between additions of bromine. The reaction took place readily, the bromodipyruvic ureide dissolving completely. The presence of an excess of bromine was indicated by the red color of the solution. The reaction mixture was transferred to a beaker and evaporated to a volume of about 20 cc.; 8 g. of dibromodipyruvic ureide XXII separated in brilliant, colorless, hexagonal plates. Evaporation of the mother liquor yielded 0.6 g. of the product; m. p., about 250° (decompn.). It is soluble in about 17 parts of boiling water.

Anal. Calcd. for $C_8H_8O_5N_4Br_2$: N, 14.0. Found: 14.1.

Action of Nitric Acid on Dipyruvic Ureide IV.—To 15 cc. of concd. nitric acid in a casserole on the steam-bath was gradually added 10 g. of pulverized dipyruvic ureide. A vigorous evolution of oxides of nitrogen occurred. The solution was allowed to evaporate to a paste, cooled, the residue treated with 10 cc. of cold water and the mixture filtered. The finely divided solid obtained was dried in the steam-oven; yield 3 g.; m. p., indefinite at 135–200°. When it was dissolved in 10 cc. of warm water and the solution allowed to cool, yellow, monoclinic prisms of nitropyruvic ureide XXIII were deposited; this substance decomposed at about 236°, gave a deep yellow solution in alkali and failed to give the nitrolic acid test for primary nitro compounds.

Anal. Calcd. for $C_4H_3O_4N_3$: N, 26.8. Found: 27.0.

The original filtrate yielded on spontaneous evaporation 2.2 g. of large, clear crystals that decrepitated violently at about 200° and melted at 240°; they gave the Andreasch[9] test for parabanic acid XXIV. When recrystallized from 5 cc. of boiling water, characteristic flat prisms of parabanic acid melting at about 240° were obtained.

Mol. wt. Calcd.: 114. Found (by titration): 113.
Anal. Calcd. for $C_3H_2O_3N_2$: N, 24.6. Found: 24.6.

Summary

1. Dipyruvic ureide is formed by the polymerization of pyruvic monoureide, $\underline{\mathrm{NH.CO.NH.CO.C}}\mathrm{:CH_2}$.

2. Its constitution is represented by the formula,

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

3. Dipyruvic ureide is reduced catalytically to the corresponding hydrodipyruvic ureide.

4. The actions of bromine and of nitric acid on dipyruvic ureide have been investigated.

New Haven, Connecticut

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[9] Andreasch, *Monatsh.*, 2, 285 (1881).