by the evolution of hydrogen chloride. Leaving the ammonium chloride out of consideration, we may assume the reactions to be

$$C_7H_{16} + NOCl \longrightarrow C_7H_{15}NO + HCl$$

$$\underset{\text{(blue).}}{C_7H_{15}NO} \longrightarrow \underset{\text{(oil).}}{C_7H_{14}NOH}$$

$$C_7H_{14}NOH + H_2O \longrightarrow C_7H_{14}O + NH_2OH.$$

A satisfactory explanation of the reduction of the hydroxylamine to ammonia has not yet presented itself.

It has been found that petroleum ether, b. p. 45–70°, gives apparently the same reaction as does heptane. We may assume, therefore, that any of the liquid paraffin hydrocarbons will react in the same way. The reaction of nitrosyl chloride on these hydrocarbons opens up a field in the chemistry of the paraffins which should be found exceedingly fruitful. The absence of ready reaction with most reagents has hitherto proved an obstruction in the study of the saturated chain compounds, and it is hoped that nitrosyl chloride will be of material aid. Furthermore, there is also the probability of using nitrosyl chloride as a reagent for other classes of compounds, such as benzene and its derivations, the cycloparaffins, heterocyclic compounds, etc. Indeed, there is hardly a limit to the speculative possibilities.

Finally, a further study of this interesting reaction of nitrosyl chloride on heptane and other paraffin hydrocarbons will, doubtless, enlighten us considerably regarding its reaction on pinene and on the other terpenes and related substances.

MADISON, WISCONSIN.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN.]

# FOUR-MEMBERED CYCLIC-UREAS. I. HISTORY AND NOMENCLATURE.

BY WILLIAM J. HALE.

Received August 26, 1918.

The four-membered cyclic-urea structure was first proposed by H. Schiff in 1869.[1] Through a comprehensive study of a large number of condensations between urea and various aldehydes it was observed that the product (I) resulting from the action of acetaldehyde upon urea possessed properties slightly different from those products obtained when urea was brought into action with various aromatic aldehydes. When, for example, this ethylidene-urea of Schiff was boiled with aniline alone there followed a decomposition of the molecule into urea and acetaldehyde (the latter through further condensation with excess of aniline separated finally as a form of ethylidene diphenylamine). On the other hand,

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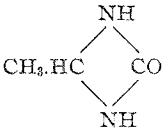
[1] *Ann.*, 151, 206 (1869).

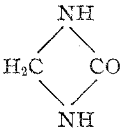
the second type of Schiff's condensation products, known as ureides, decomposed under this same action of aniline in a similar manner but with much greater difficulty. The ethylidene-urea possessed no basic properties whatsoever. It did not form salts with platinum or gold chlorides. Cold conc. mineral acids or warm water sufficed for its hydrolysis into the original constituents. The compound melted with decomposition at about 160° and dissolved but slightly in the ordinary solvents. These observations of Schiff were mainly corroborated by J. E. Reynolds,[1] who obtained ethylidene-urea by heating a saturated solution of urea in acetaldehyde in an autoclave at 100°. Reynolds, however, looked upon the compound as a derivative of pseudo-urea,

$$CH_3.CH : N.C(OH) : NH.$$

The action of formaldehyde upon urea was reported by Tollens and Hölzer[2] as yielding a white insoluble substance identical with that compound prepared later by Lüdy[3] in the condensation of urea with methylene chloroacetin ($ClCH_2.C_2H_3O_2$) and regarded by him as methylene-urea (II). Hemmelmayr[4] next employed chloromethyl alcohol in condensation with urea and obtained good yields of a white substance extremely insoluble in all of the ordinary solvents. By analysis this product accorded with the formula $C_2H_4ON_2$ and was considered as methylene-urea. The action of mineral acids sufficed for its hydrolysis into the original constituents; organic acids failed in this direction. The compound melted with decomposition at 240°. Its marked insolubility recalls this same property in the ethylidene-urea of Schiff.



(I).



(II).

$H_2N.CO.N:CH_2$

(III).

The condensation of formaldehyde with urea was reported by Carl Goldschmidt[5] as leading to several products—a compound, $C_5H_{10}O_3N_4$, insoluble in water if the condensation took place in acid medium; a dimethylol-urea, $CO(NHCH_2OH)_2$, soluble in water, if in alkaline medium; and a variable mixture of these two if in neutral medium. Tollens[6] and his coworkers obtained only an insoluble product which accorded by analysis with the formula as proposed by Lüdy (II) or with that of (III).

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[1] *Chem. News*, **24**, 87 (1871).

[2] *Ber.*, **17**, 659 (1884).

[3] *Monatsh.*, **10**, 297 (1889).

[4] *Ibid.*, **12**, 94 (1891).

[5] *Ber.*, **29**, 2438 (1896); *Chemiker-Zeitung*, **21**, 460 (1897); *Centralbl.*, **1897**, [II] 736.

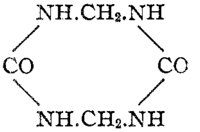
[6] *Ber.*, **29**, 2751 (1896).

The inadequate description in Goldschmidt's reports led Einhorn and Hamburger[1] to repeat these experiments. They ascertained the exact conditions necessary for the isolation of dimethylol-urea as well as monomethylol-urea (the alkaline solution of barium hydroxide required neutralization with carbon dioxide within a very few minutes). The production of N-methylol compounds under such conditions is in exact agreement with results obtained by Einhorn[2] on acid amides and formaldehyde.

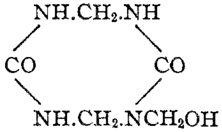
In a recent article A. E. Dixon[3] presents a concise résumé of the complexities of the formaldehyde-urea condensation and explains admirably the production of the comparatively stable methylol-urea,

$$NH_2.CO.NH.CH_2OH,$$

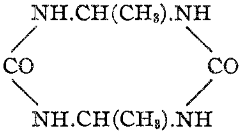
as the first product of the reaction. This compound may be expected to change into a chloro derivative, $NH_2.CO.NH.CH_2Cl$, under the influence of hydrochloric acid and finally yield a residue—$NH.CO.NH.CH_2$—which through simple polymerization could give the ring structure IV. This is indeed a polymer of the so-called "methylene-urea" (II) and from all of the characteristics of the compound accords best with its true structure. The work of Chattaway[4] on dichloro-urea and its condensation to *p*-urazine is analogous. The presence of excess of formaldehyde in the acid medium of the urea condensation would naturally be expected to produce a methylol derivative (V) of "methylene-urea" and this portrays the probable constitution of Goldschmidt's compound $C_5H_{10}O_3N_4$. Dimethylol-urea was best prepared by evaporation of a neutral solution of urea in sufficient formaldehyde and crystallization of residue from alcohol. Upon acidification of its aqueous solution this compound as anticipated passed over into the Goldschmidt compound $C_5H_{10}O_3N_4$ with loss of water and formaldehyde. It would appear, therefore, that the amorphous insoluble products heretofore described as "methylene-urea" and also "ethylidene-urea" cannot longer be explained upon the simple structure II and I, but more favorably upon the structures IV and VI, respectively.



(IV).



(V).



(VI).

Several isolated cases may be cited in which reference is made to four-membered cyclic-ureas. Biginelli[5] assumed this structure for one of the products obtained in the condensation of *m*-nitrobenzaldehyde and

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[1] Ber., **41**, 24 (1908).

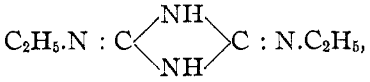
[2] *Ann.*, **343**, 207 (1905).

[3] *J. Chem. Soc.*, **113**, 238 (1918).

[4] *Ibid.*, **95**, 236 (1909).

[5] *Gazz. chim. ital.*, [1] **23**, 369 (1893).

urea; Schiff (*loc. cit.*) reported the same product as a triureide. H. Guillemard[1] explained the condensation of ethyl carbylamine dibromide (ethyliminocarbonyl bromide) with ammonia as proceeding to a compound of structure



melting at 90°. The action of aniline and other amines upon this dibromide yielded, however, simple substituted guanidines as

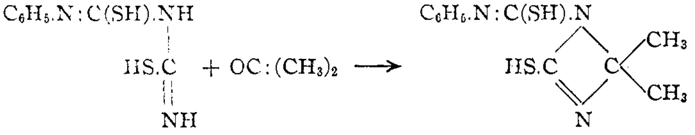
$$C_2H_5N : C : (NHR)_2.$$

Until further evidence is forthcoming there is no special reason to consider this action of ammonia as other than a substitution of the two bromine atoms by an imino group. The compound formed,

$$C_2H_5N : C : NH,$$

or a polymer of this, would correspond in analysis to the values reported by Guillemard and would possess the marked basic properties which the compound displays.

An unsaturated form of a four-membered heterocyclic ring containing two nitrogen atoms was first announced by Fromm.[2] Through an exhaustive study of the condensations of various dithiobiurets with aldehydes and ketones, under the influence of dry hydrogen chloride, Fromm was able to establish the structure of the condensation products as derivatives of four-membered heterocyclic rings. Thus from phenyl dithiobiuret and acetone was obtained $\alpha$-phenyl-dithio-di-C-methyl keturet (VII).



(VII).

The product was called an "alduret" if from an aldehyde and a "keturet" if from a ketone (as in illustration).

In general, these aldurets and keturets are high-melting crystalline substances insoluble in water, but more or less soluble in alcohol. They are decomposed by conc. acids which, through hydrolytic action eliminate first the aldehyde or ketone concerned; they are comparatively stable in presence of alkalies. There can be little or no doubt concerning the structure of this class of compounds, as so well demonstrated by Fromm. The names attached to the two types are in no way accurately descriptive. They were employed simply to denote the origin—one of

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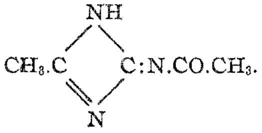
[1] *Bull. soc. chim.*, [3] 31, 605 (1904); *Ibid.*, [3] **33**, 652 (1905).

[2] *Ann.*, **275**, 20 (1893); *Ber.*, **28**, 1102 (1895); **348**, 166 (1906); *Ibid.*, **394**, 282 (1912).

an aldehyde and biuret (alduret); and the other of a ketone and biuret (keturet). A formula of similar structure (VIII) was proposed by Korndörfer[1] for the anhydride of diacetylguanidine. Further investigation is here required to establish the claims set forth.



(VIII).

The most striking synthesis of an unsaturated four-membered cyclic-urea was announced by Frerichs and Hartwig.[2] These investigators heated urea with cyanoacetic ester and interpreted the reaction as proceeding between this latter and cyanic acid (here of course isocyanic acid is to be considered the active component) liberated in the decomposition of urea.

(IX).

The final product was considered as a derivative of a cyclomethine-urea in analogy to the Schiff formula for "methylene-urea." It is soluble in alcohol or ether but insoluble in water. It is acid in character and gives a red coloration with ferric chloride. Complete decomposition by strongly heating with aniline yielded ammonia and sym. diphenyl-urea. This fact led to the assumption that isocyanic acid as such was still present in the molecule, producing with the aniline first a monophenyl-urea and then, with a second molecule of aniline, a diphenyl-urea and ammonia. The high temperature of the reaction is indeed sufficient to break the ring structure as here indicated.

From such decomposition in the presence of aniline we should naturally expect the results obtained by these investigators. Their attempts, however, to prepare similar compounds by the action of various nitriles upon urea met with no success.

Of considerable interest in the cyclic urea syntheses is the recent work of Senier and Shepheard.[3] The interaction of aryl thiocarbimides and aryl methylenediamines at 150–200° was found to produce quinazolines and also cyclic-ureas. When the para position in some one of the aryl

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[1] *Arch. der Pharmacie*, **241**, 449 (1903).

[2] *J. prakt. Chem.*, [3] **72**, 489 (1905); *Ibid.*, [3] **73**, 44 (1906).

[3] *J. Chem. Soc.*, **95**, 504 (1909).

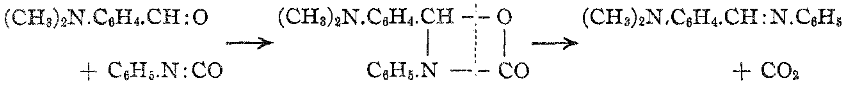
groups is occupied by a substituent, quinazolines are formed, but when the para position is open or when isocyanates replace the thiocyanates, cyclic methylene-ureas resulted. As the latter break up with ease their presence could be recognized only at such temperatures through a study of the decomposition products, namely—formaldehyde and the diaryl ureas. In the case of methyleneaniline and phenyl isocyanate they found that the reaction proceeded at room temperature in a dry benzene solution, as indicated below:

$$\begin{matrix} H_2C:N.C_6H_5 \\ + \\ C_6H_5.N:CO \end{matrix} \longrightarrow \begin{matrix} H_2C - N.C_6H_5 \\ | \quad\quad | \\ C_6H_5.N - CO \end{matrix}$$

(X).

After a week or more a colorless product (X) separated out in crystalline form, melting at 198°. It was called methylene diphenylcarbamide. Though only sparingly soluble in the ordinary solvents, warming with acids or water effected hydrolysis into formaldehyde and sym. diphenylurea.

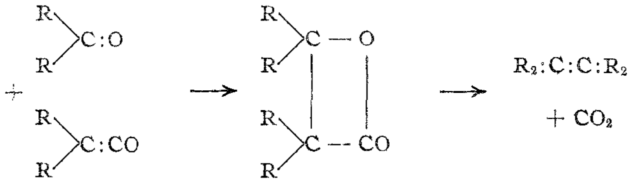
The action of phenyl isocyanate, as just discussed, at once recalls the property of ketenes to add to unsaturated compounds. This analogy has been brought out quite recently by Staudinger and Endle[1] and several examples were studied by way of illustration. With phenylisocyanate and *p*-dimethylaminobenzaldehyde the reaction is shown below:



$$\begin{matrix} (CH_3)_2N.C_6H_4.CH:O \\ + C_6H_5.N:CO \end{matrix} \longrightarrow \begin{matrix} (CH_3)_2N.C_6H_4.CH - O \\ | \quad\quad\quad | \\ C_6H_5.N - CO \end{matrix} \longrightarrow \begin{matrix} (CH_3)_2N.C_6H_4.CH:N.C_6H_5 \\ + CO_2 \end{matrix}$$

(XI).

The condensation could not be accomplished at ordinary temperatures, but at 190° was easily effected. The condensation product, however, was at once subject to decomposition (as indicated by the dotted line) and the final result showed the presence only of *p*-dimethylaminobenzylideaniline and carbon dioxide. These investigators consequently assumed that the four-membered heterocyclic ring (XI) must have been produced as the intermediate step. This is evidenced by the close comparison between the reaction above and several of the regular ketene additions, as shown below:



$$\begin{matrix} R_2C:O \\ + \\ R_2C:CO \end{matrix} \longrightarrow \begin{matrix} R_2C - O \\ | \quad\quad | \\ R_2C - CO \end{matrix} \longrightarrow \begin{matrix} R_2:C:C:R_2 \\ + CO_2 \end{matrix}$$

[β-Lactone.]

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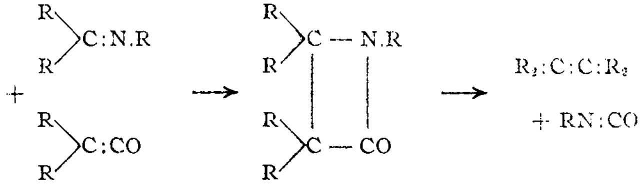
[1] *Ber.*, 50, 1042 (1917).

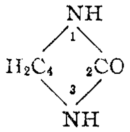


[β-Lactam.]

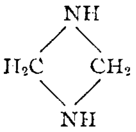
The decomposition of the phenylisocyanate addition product (XI) is seen, therefore, to be strictly in conformity with the decomposition reactions as illustrated in each of the ketene addition products above cited. When these facts are considered, together with the results obtained by Frerichs and Hartwig (*loc. cit.*) there can no longer be any doubt concerning the product (IX) which these investigators obtained in the action of urea upon cyanoacetic ester.

The actual production of four-membered heterocyclic compounds containing two nitrogen and two carbon atoms alternately placed is no longer to be questioned. The doubt which therefore has prevailed in the minds of chemists concerning the structure of the four-membered cyclic-ureas, as advanced by Schiff, has received its confirmation. There remains therefore the question, which must be solved for each compound under discussion, whether or not the characteristics of certain condensation products of the ureas with aldehydes do or do not entitle these compounds to a position in the four-membered heterocyclic series. Numerous examples, where certain condensation products received their provisional constitutional formula as derivatives of "methylene-urea," will gradually be found in which no real proof of structure is apparent save in analogy. In the succeeding articles, which will present a study of various derivatives of the four-membered cyclic-ureas, stress will be laid chiefly upon the methods of formation and the simple hydrolytic decomposition products.

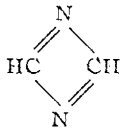
Heretofore the few instances of four-membered cyclic-urea structure have found more or less simple terms of nomenclature As we progress in the number of derivatives from the stem substance we shall find it utterly impossible to adhere to the names now in use. In order to simplify the matter of nomenclature it will be necessary to base our reasoning upon the following structural representations:



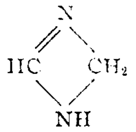
1. Uretidone.



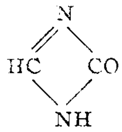
2. Uretidine.



3. Urete.



4. Uretine.



5. Uretone.

In (1) we have the supposed "methylene-urea" structure as proposed by Schiff (II). The name is misleading since the chain Formula III is also a methylene-urea. More correctly the ring form should have been called cyclomethylene-urea. According to Maquenne[1] this ring may be looked upon as uriminomethane. The suggestion of Frerichs and Hartwig (*loc. cit.*) of the name cyclomethine-urea for the stem substance of their compound (IX) as of type (5) is certainly in keeping with the previous suggestion. The completely reduced form of the ring (2) is already mentioned in the literature[2] as dimethylene-1,3-diimine. The name, however, takes on a far too complex character so soon as we try to indicate the presence of keto structure. Thus (1) must be considered as 2-keto-dimethylene-1, 3-diimine or 2-carbonyl-4-methylene-1, 3-diimine. In one of the earlier suggestions by Richter[3] we find the name proposed for Formula 1 to be butenediazenedihydrene-(1,3,2,4)-one-2. For these ketone structures it would appear that cyclomethylene-urea (1) and cyclomethine-urea (5) might become the more acceptable terms for general use were it not for the fact that the reduced forms of these rings may often come into consideration; possibly tautomeric forms (as discussed indeed by Frerichs and Hartwig) may also require study but possibly the term pseudocyclomethine-urea might find application in this instance.

It has seemed best at the outset of this work that a simple system of nomenclature should be devised. In the suggestion of entirely new names one is ever pressed by hesitancy. Happily, however, the work of Fromm (*loc. cit.*) has actually demonstrated that a four-membered heterocyclic compound of the desired arrangement was at hand. The names applied to these compounds by this investigator were looked upon only as descriptive of their constituent parts—"alduret" for a combination of an aldehyde and a certain biuret and "keturet" for a combination of a ketone and a certain biuret. The presence of a four-membered heterocyclic ring of two nitrogen and two carbon atoms in alternate position actually accounts for the distinctive properties of these compounds, and so distinctive in this respect that a position in the literature[2] has now been accorded them. The actual detailed names which Fromm further employed to distinguish the various compounds of this type, which he prepared, carry no significance whatsoever. They are in fact poorly descriptive. In the same manner we may attach no weight to the meanings of the prefixes "ald" and "ket" as attached to the form "uret"—the terms monomethyl and dimethyl would have been far more explanatory. The substance under consideration in all of these cases is a four-membered heterocyclic ring originating from urea as a base, consequently as descriptive of this structure we may accept the term "uret." In order to simplify the term for further derivation the form "urete" should be used to denote the com-

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[1] *Bull. soc. chim.*, [3] **9**, 911 (1893).

[2] Meyer and Jacobson, *Lehrbuch d. organischen Chemie,* [2] **3**, 44 (1915).

[3] *Ber.*, **29**, 595 (1896).

pletely unsaturated type as shown in (3). The first step in the hydrogenation (4) may then be called "uretine" and the final step (2) "uretidine." Keto derivatives may accordingly be named by number or given the suffix "-one." Thus (5) would become 2-ketouretine or simply "uretone," whereas (1) the old familiar "cyclomethylene-urea" would then become "2-ketouretidine" or simply "uretidone." So soon as we adopt some simple term for the stem ring the entire system of nomenclature, upon the Geneva system, is readily applicable.

We suggest therefore that this stem of Fromm's name for his compounds be applied now to all four-membered heterocyclic rings containing two nitrogen and two carbon atoms in alternate position. The slight change in the word ending, as shown for the completely unsaturated form "urete," is highly desirable in order that no confusion may arise between this and the well-established name "biuret." From a study of a biuret we have seen that the first authentic proof of structure for these heterocyclic compounds was reported.

It should be emphasized that the ending *ete* is the only portion of the names used by Fromm for his compounds that is now proposed for the first time for possible adoption to denote four-membered heterocyclic rings. The stem *ur*, occurring in biuret and numerous urea derivatives, may be looked upon as demanding the grouping $=\mathrm{N.CO.N}=$ but it was actually employed by Fromm for this same grouping in its reduced form, $=\mathrm{N.}\underset{/\ \backslash}{\mathrm{C}}\mathrm{.N}=$. If we grant this usage, then the coupling of the ending *ete* to this stem *ur* brings us to an interpretation of the term *urete* in accord with the data already found in the literature. It may be urged, and rightly so, that a stem *1,3-diaz* would be more accurate. When this is coupled with the *ete* ending, denoting four members to the ring, we derive the following names for the Formulas 1, 2, 3, 4, and 5, respectively: 1,3-diazetidone, 1,3-diazetidine, 1,3-diazete, 1,3-diazetine, and 1,3-diazetone. It is only by way of recognition of the work of Fromm and our inclination to employ a term already in use that we select preferably that system based upon the stem *ur*. The name dimethylene-1,3-diimine has been used (*loc. cit.*) for the systematic name for the completely reduced form of this class of compounds. It would appear more rational if the name 1,3-cyclodicarbodiazane were here adopted, a suggestion for which the author is indebted to Dr. W. A. Noyes, of the University of Illinois.

In the succeeding articles this proposed system of nomenclature will be employed. As the subject under consideration is that of four-membered cyclic-ureas we at once enter into a study of uretidones of which the first important representative will be 1,4-diphenyluretidone.

ANN ARBOR, MICH.