chaulmoogric acid by saponification with alcoholic potassium hydroxide and treatment with mineral acids).

Anal. Subs., 0.5095, 0.5119: HgS, 0.1936, 0.1945. Calcd. for $C_{24}H_{44}O_6Hg$: Hg, 32.72. Found: 32.76, 32.76.

Subs., 0.4810, 0.3747: AgI, 0.3548, 0.2907. Calcd. for $C_{24}H_{44}O_5Hg$ (two ethoxy groups): C_2H_5O, 14.67. Found: 14.15, 14.88.

Subs., 0.4947, 0.4670: KOH to neutralize CH_3COOH evolved, 0.04664, 0.04265. Calcd. for $C_{24}H_{44}O_5Hg$ (one acetoxy group): CH_3COO, 9.63. Found: 9.91, 9.60.

Summary

From mercuric acetate and chaulmoogric acid a crystalline compound can be prepared which is shown to be the anhydride or inner salt of hydroxymercuri-ethoxy-chaulmoogric acid.

Under similar conditions, mercuric acetate and ethyl chaulmoograte give a crystalline ethyl acetoxymercuri-ethoxy-chaulmoograte.

These compounds are being used experimentally in the treatment of leprosy.

HONOLULU, HAWAII

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

CERTAIN SUBSTITUTED BIURETS

BY ELIZABETH STUART GATEWOOD[1]

RECEIVED JUNE 16, 1924 PUBLISHED FEBRUARY 5, 1925

Because biurets have recently been obtained as oxidation and decomposition products of certain purines, it becomes increasingly necessary to know more about the chemistry of these substances. The preparation and the exact determination of the structures of the phenyl- and methyl-phenyl-biurets are of immediate interest in connection with the mechanism of the oxidation of certain phenyl-substituted uric acids by hydrogen peroxide.[2]

The phenyl-biuret melting at 165° has now been synthesized in a way that shows definitely its unsymmetrical structure. It is formed when ethyl N^{ω}-phenyl-allophanate, prepared by the action of chloro-formanilide on urethan, is heated with a concentrated aqueous ammonia solution for an hour at 100°: $C_6H_5NHCOCl + NH_2COOC_2H_5 = C_6H_5NHCONHCOOC_2H_5 + HCl$; $C_6H_5NHCONHCOOC_2H_5 + NH_3 = C_6H_5NHCONHCONH_2 + C_2H_5OH$.

ω-Phenyl-biuret can be directly methylated with dimethyl sulfate. A monomethyl-phenyl-biuret, m. p. 183°, is obtained. The method of formation gives no indication as to the position of the methyl group.

When ethyl N^{ω}-phenyl-allophanate is heated with an aqueous 33% methylamine solution at 100°, a beautifully crystalline substance is formed

---

[1] National Research Fellow in Chemistry.

[2] Moore and Gatewood, THIS JOURNAL, **45**, 135 (1923).

which also has the composition of a monomethyl-phenyl-biuret. It is evident that the methyl group can only be at the end of the chain, and the biuret must be, therefore, ω′-methyl-ω-phenyl-biuret: $C_6H_5NHCONHCOOC_2H_5 + CH_3NH_2 = C_6H_5NHCONHCONHCH_3 + C_2H_5OH$.

It melts at 133°. The differences in melting points and in optical properties show that this methyl-phenyl-biuret is not the same as the one obtained by methylating phenyl-biuret. The latter, therefore, may be *ms*-methyl-ω-phenyl-biuret, $C_6H_5NHCONCH_3CONH_2$.

The interaction of these two substances with aniline is significant. When the methyl-phenyl-biuret melting at 133° is warmed with aniline just below its boiling point, ω,ω′-diphenyl-biuret is formed. The phenyl group has replaced the methyl group, which shows, again, that the methyl is at the end of the chain.

The action of aniline on the methyl-phenyl-biuret melting at 183° is apparently more complicated. It requires a higher temperature and longer heating and yields diphenyl-urea. The course of the reaction may be similar to that assumed by Schiff[3] to explain the formation of diphenyl-urea from *ms*-phenyl-biuret. In this case, a methyl-diphenyl-biuret would be first formed, which would be decomposed by the ammonia to methyl-phenyl-urea and phenyl-urea. Both ureas, then, with aniline would give diphenyl-urea. It has been found that methyl-phenyl-urea and, of course, phenyl-urea do yield diphenyl-urea when treated with aniline under the same conditions. This explanation supports the proposed structure for the methyl-phenyl-biuret.

Since ω′-methyl-ω-phenyl-biuret has been synthesized, Biltz[4] has reported a methyl-phenyl-biuret, prepared by heating methyl-urea, dried above its melting point for four hours, with phenyl isocyanate at 120–130° for one hour. He gives this substance the same structure—$C_6H_5NHCONHCONHCH_3$—but it is not the same biuret as that formed from ethyl N^{ω}-phenyl-allophanate and methylamine, for it melts 40° higher, at 173°. He determines its constitution, however, only by analogy, which is certainly not a dependable method. It is known that methyl isocyanate and methyl-urea react at 100° to give ω,ω′-dimethyl-biuret,[5] and phenyl isocyanate and phenyl-urea at 125° yield ω,ω′-diphenyl-biuret.[6] But both these reactions were carried out at temperatures below the melting points of the ureas used, whereas the reaction of methyl-urea with phenyl-isocyanate takes place 18–28° above the melting point of methyl-urea (m. p., 102°).

Now, Davis and Underwood[7] have recently shown that the "urea de-

---

[3] Schiff, *Ann.*, **352**, 73 (1907).

[4] Biltz, *Ber.*, **56**, 1925 (1923).

[5] Ref. 4, p. 1921.

[6] Kühn and Henschel, *Ber.*, **21**, 504 (1888).

[7] Davis and Underwood, THIS JOURNAL, **44**, 2595 (1922).

arrangement" takes place when urea and substituted ureas are heated above their melting points. A mono-substituted urea, such as methyl-urea, may dearrange in two ways: $CH_3NH_2 + HNCO \rightleftharpoons CH_3NHCONH_2 \rightleftharpoons CH_3NCO + NH_3$. It is really possible, therefore, for phenyl isocyanate to react with methyl-urea at 120–130° in the five ways indicated below.

$$C_6H_5NCO + CH_3NH_2 \rightarrow C_6H_5NHCONHCH_3 \xrightarrow{HNCO} \begin{array}{ll} \nearrow C_6H_5NHCONCH_3CONH_2 & (1) \\ \searrow NH_2CONC_6H_5CONHCH_3 & (2) \end{array}$$

$$C_6H_5NCO + NH_3 \rightarrow C_6H_5NHCONH_2 \xrightarrow{CH_3NCO} C_6H_5NHCONHCONHCH_3 \quad (3)$$

$$HNCO + NH_3 \rightarrow NH_2CONH_2 \xrightarrow{C_6H_5NCO} NH_2CONHCONHC_6H_5 \quad (4)$$

$$CH_3NCO + CH_3NH_2 \rightleftharpoons CH_3NHCONHCH_3 \xrightarrow{C_6H_5NCO} CH_3NHCONCH_3CONHC_6H_5 \quad (5)$$

Of these, the last reaction can be discarded, for dimethyl-urea at the temperature of the reaction would be dearranged, too. Of the other four, the first or second, and not the third (Biltz' reaction), is the most probable, for methyl-phenyl-urea is the most stable toward heat since it has the highest melting point (150°). Consequently, the final product would be either *ms*-methyl-ω-phenyl-biuret or ω-methyl-*ms*-phenyl-biuret rather than ω′-methyl-ω-phenyl-biuret, and of these two the first was probably the substance obtained, as isocyanic acid usually adds to the more positive nitrogen when both are substituted.

Phenyl isocyanate and methyl-urea if heated together *below* the melting point of the latter should give ω-methyl-ω′-phenyl-biuret. This proved to be the case. When the reaction was carried out at 80–90°, the product obtained melted at 133° and was identical with the methyl-phenyl-biuret from ammonia and ethyl N^{ω}-phenyl-allophanate.

Biltz' methyl-phenyl-biuret may be the same as the one obtained by methylating ω-phenyl-biuret, even though its melting point is 10° lower. The lower melting point might easily be accounted for by the presence of traces of the other methyl-phenyl-biurets which could have been formed during the reaction. If they are the same, the phenyl group must obviously be on an end nitrogen. Furthermore, the melting point indicates that the central nitrogen is probably substituted by methyl, for of the mono- and di-substituted biurets known, those with alkyl substituents on the central nitrogen melt near the melting point of biuret itself (m. p., 190°), while those with either one or both of the end nitrogens substituted with alkyl melt considerably lower. Unfortunately, it has not as yet been possible to repeat Biltz' preparation, so that the two cannot be directly compared.

It was hoped that a synthesis of *ms*-methyl-ω-phenyl-biuret could be effected that would leave no doubt as to its structure and as to the probable identity of these two substances with it. Such a synthesis was to be attempted by heating ethyl N^{ms}-methyl-N$^{\omega}$-phenyl-allophanate with ammonia at an appropriate temperature.

$$C_6H_5NHCOCl + CH_3NHCOOC_2H_5 = C_6H_5NHCONCH_3COOC_2H_5 + HCl$$
$$C_6H_5NHCONCH_3COOC_2H_5 + NH_3 = C_6H_5NHCONCH_3CONH_2 + C_2H_5OH$$

The allophanic acid ester, however, could not be prepared.

Biltz has prepared *ms*-phenyl-biuret, $NH_2CONC_6H_5CONH_2$, from ethyl N^{ms}-phenyl-allophanate and ammonia. An effort was made to repeat this preparation in order to compare this phenyl-biuret thoroughly with the third phenyl-biuret[8] obtained as an oxidation product of 9-phenyl-uric acid. It was also hoped that ω-methyl-*ms*-phenyl-biuret, $CH_3NHCONC_6H_5CONH_2$, might be synthesized in a similar manner from the allophanic acid ester and methylamine. The preparation of this substance was particularly to be desired, because it may probably be an intermediate in the oxidation of both 7-methyl-9-phenyl-uric acid and 1,3-dimethyl-9-phenyl-uric acid with hydrogen peroxide.[9] Neither synthesis was accomplished, however, because the preparation of ethyl N^{ms}-phenyl-allophanate from phenyl-urethane and urea chloride could not be repeated, although many attempts were made.

Experimental Part

ω-Phenyl-Biuret.—Attempts to prepare chloro-formanilide, the starting point in the synthesis, from phenyl-urethane and phosphorus pentachloride, as suggested by Folin,[10] failed. The older method of Hentschel,[11] however, in which dry hydrogen chloride is passed into pure phenyl isocyanate, gave good results. From 50 g. of phenyl isocyanate, between 60 and 70 g. of chloro-formanilide, m. p. 56–58°, was easily obtained.

Ethyl N$^{\omega}$-phenyl-allophanate was prepared by the method of Folin;[12] 14 g. of chloro-formanilide and 8 g. of urethan yielded 10 g. of the allophanic acid ester; m. p., 106–107°.

OPTICAL PROPERTIES.—Habit, thin plates; extinction, symmetrical, γ parallel to elongation; interference figure, biaxial; indices,[13] $\alpha = 1.445^+$, $\gamma = 1.610^-$.

A solution of ethyl N$^{\omega}$-phenyl-allophanate (8 g.) in concd. aqueous ammonia (120 cc.) was heated in a pressure flask at 100° by partially immersing the flask in boiling water. It was shaken frequently. The heating was continued for an hour and the solution was then allowed to cool. Soon it became thick with glistening scales. The solid (5.2 g.) was filtered off and recrystallized from hot water. It melted at 165–166°, either alone or mixed with pure phenyl-biuret from the oxidation of 9-phenyl-uric acid. The optical properties were the same.

---

[8] Gatewood, THIS JOURNAL, **45**, 146 (1923).

[9] Ref. 2, p. 138.

[10] Folin, *Am. Chem. J.*, **19**, 337 (1897).

[11] Hentschel, *Ber.*, **18**, 1178 (1885). Lengfeld and Stieglitz, *Am. Chem. J.*, **16**, 71 (1894).

[12] Ref. 10, p. 346.

[13] α and γ are used arbitrarily to denote the lowest and highest index, respectively, when the indices remained constant. Exact orientation was not possible with the substances examined.

Optical Properties.—Habit, thin, rectangular plates; extinction, parallel, α parallel to elongation; interference figure, uniaxial; indices, $\alpha = 1.645$; $\gamma = 1.665$.

Methylation of ω-Phenyl-biuret.—One g. of phenyl-biuret was dissolved in 30 cc. of 2 *N* sodium hydroxide and the solution, cooled by running water, was shaken vigorously for a half hour. After about ten minutes methyl-phenyl-biuret commenced to separate. The solution was well cooled with ice before it was filtered; yield, 0.6 g. It crystallized from hot water in a mat-like mass of fine needles and melted after a second recrystallization, at 183°. It is very soluble in hot methyl or ethyl alcohol.

Anal. Subs., 0.1768: CO_2, 0.3613; H_2O, 0.0870. Subs., 0.1572, 0.1358: N, 29.8 cc. (23°, 767 mm.), 25.9 cc. (23°, 765 mm.). Calcd. for $C_9H_{11}O_2N_3$: C, 55.94; H, 5.74; N, 21.76. Found: C, 55.73; H, 5.50; N, 21.47, 21.54.

Optical Properties.—Habit, small, rect. plates; extinction, parallel, α parallel to elongation; indices, $\alpha < 1.445$, $\gamma = 1.725$.

ω'-Methyl-ω-Phenyl-Biuret.—A solution of 6.6 g. of ethyl N^{ω}-phenyl-allophanate in 66 cc. of an aqueous 33% methylamine solution was heated in a pressure flask in boiling water for half an hour. The cooled solution soon began to deposit large, well-formed crystals. It stood overnight and was then filtered; yield, 3 g. The substance melted at 133° when recrystallized once from methyl alcohol, from which it separated in thick, hexagonal prisms. It is slightly soluble in hot water and easily soluble in hot alcohol.

Anal. Subs., 0.1447, 0.1800: CO_2, 0.2971, 0.3681; H_2O, 0.0744, 0.0965. Subs., 0.1509, 0.1653; N, 29.2 cc. (23°, 771 mm.), 32.0 cc. (21°, 766.5 mm.). Calcd. for $C_9H_{11}O_2N_3$: C, 55.94; H, 5.74; N, 21.76. Found: C, 55.99; 55.76; H, 5.78, 5.99; N, 22.01, 22.12.

Optical Properties.—Habit, hexagonal plates; extinction, symmetrical, γ parallel to elongation; interference figure, uniaxial; indices, $\alpha = 1.595$, $\gamma = 1.671$.

Action of Aniline.—Finely powdered ω'-methyl-ω-phenyl-biuret was moistened with aniline and warmed for several minutes in an aniline bath just below the boiling point. It dissolved readily. After the solution had cooled, aqueous alcohol was added; crystals then separated which melted at 210° when recrystallized from alcohol. The substance was identified as ω,ω'-diphenyl-biuret by a mixed-melting-point determination and the optical properties: habit, plates; extinction, parallel, α parallel to elongation; interference figure, biaxial; indices, $\alpha = 1.591$, $\beta = 1.650$, $\gamma > 1.755$.

The methyl-phenyl-biuret which melts at 183° did not dissolve readily in aniline, and did not react under the same conditions, or even when the solution was boiled for a short time. The original material separated from the cool solution. When the solution was heated on a boiling aniline bath for 15 minutes, however and then cooled, it deposited fine needles of diphenyl-urea. It was recrystallized from alcohol, and then melted at 237–238°, either alone or mixed with a known sample. From the filtrate, on evaporating the aniline, some of the original material was regained.

Action of Phenyl Isocyanate on Methyl-Urea at 80–90°.—One g. of finely powdered methyl-urea, recrystallized from absolute alcohol, was dried for about two hours and then heated with 2.5 g. of pure phenyl isocyanate in a closed flask for one hour at 80–90°. As the clear, brown solution cooled, it became solid with crystals. Anhydrous ether was added, and the solid was filtered off and washed well with ether; yield, 1.2 g. It was recrystallized from methyl alcohol in which it is very soluble. Small, thick crystals were formed which melted at 132–133°. The substance was completely identified as ω'-methyl-ω-phenyl-biuret by comparison with that obtained above.

Attempts to Prepare Ethyl N^{ms}-Methyl-N^{ω}-Phenyl-Allophanate.—Chloro-formanilide (12 g.) and methyl-urethan[14] (8 g.) were heated in a test-tube closed with an air

---

[14] Adams, "Organic Chemical Reagents," III, *Bull. Univ. Illinois.*

reflux tube for half an hour at 100°; the solution turned brown and much gas was evolved. After it had stood for several hours, the solution became thick with crystals imbedded in a brown sirup. Ether was added to dissolve the sirup and the crystalline material was filtered off. The yield was about 4 g. It was purified by dissolving in alcohol and precipitating with ether. The shining flakes that formed proved to be only aniline hydrochloride, as the melting point (190°), a complete analysis and the deep violet coloration of the free base with bleaching powder showed.

Anal. Calcd.: C, 55.59; H, 6.2; N, 10.8; Cl, 27.36. Found: C, 55.69; H, 6.33; N, 10.84; Cl, 27.26.

When chloro-formanilide and methyl-urethan were heated at 50–60° for a half hour, an even larger yield of aniline hydrochloride resulted, and when they were left at room temperature for several hours, the same product slowly crystallized. At 150° the solution deposited only diphenyl-urea. This is undoubtedly due to the hydrolysis of phenyl isocyanate, into which chloro-formanilide decomposes at that temperature. Aniline hydrochloride may have resulted merely from the hydrolysis of chloro-formanilide alone, as it has been found that the latter substance, when exposed to the air for some time, slowly loses its odor, and a mass of the hydrochloride results.

Summary

1. The position of the phenyl group in ω-phenyl-biuret has been definitely proved.
2. Two new methyl-phenyl-biurets have been prepared. One is ω′-methyl-ω-phenyl-biuret. The other is probably *ms*-methyl-ω-phenyl-biuret.
3. Reasons are advanced for not assigning to Biltz' methyl-phenyl-biuret the structure $C_6H_5NHCONHCONHCH_3$ as he has recommended.
4. An unsuccessful attempt to synthesize ethyl N^{ms}-methyl-N^{ω}-phenyl-allophanate was made.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF YALE UNIVERSITY]

RESEARCHES ON PROTEINS. VII.[1] THE PREPARATION OF THE PROTEIN "SERICIN" FROM SILK[2]

BY ELBERT M. SHELTON[3] AND TREAT B. JOHNSON

RECEIVED JULY 8, 1924 PUBLISHED FEBRUARY 5, 1925

Silk occupies a very promient position among the organic resources of nature. Its commercial and economic importance is evidenced by the large amount of capital invested in manufacturing enterprises dependent upon it as a staple product of industry. From a scientific standpoint

---

[1] Previous publications in this series: Johnson and Kohman, THIS JOURNAL, **37**, 1863 (1915); **37**, 2164 (1915). Johnson, Hill and O'Hara, *ibid.*, **37**, 2170 (1915). Johnson, *ibid.*, **37**, 2598 (1915). Johnson and Hill, *ibid.*, **38**, 1392 (1916). Johnson and Daschavsky, *ibid.*, **41**, 1147 (1919).

[2] Constructed from part of a dissertation presented by Elbert M. Shelton to the Faculty of the Graduate School, Yale University, June, 1924, in candidacy for the degree of Doctor of Philosophy.

[3] Holder of the Cheney Organic Chemistry Research Fellowship, Yale, 1923–24.