161. *Some Properties of Urea, Biuret, and Triuret.*

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Urea reacts with thionyl chloride to give biuret and triuret, and with sulphuryl chloride and chlorosulphonic acid to give biuret, triuret, or cyanuric acid according to the conditions employed : thiourea does not give similar reactions. The reaction with thionyl chloride affords the best method for the preparation of biuret and triuret, the properties and structure of which are briefly discussed.

Fenton (J., 1882, **41**, 262) has shown that a mixture of urea and metallic sodium when gently heated undergoes a violent reaction, forming sodium cyanamide (unrecorded yield). Moureu (*Bull. Soc. chim.*, 1894, **11**, 1069) claimed that urea when heated with thionyl chloride undergoes dehydration with formation of cyanamide; he isolated the latter as its silver derivative but did not record the yield. Werner * (" Chemistry of Urea," 1923, p. 92) stated that urea is only slowly attacked by thionyl chloride under Moureu's conditions, and gives a yield of cyanamide of only 0·11% of the theoretical. It is noteworthy that Fenton (*loc. cit.*) failed to dehydrate urea with phosphoric oxide, and that Walther (*J. pr. Chem.*, 1909, **79**, 126) found that zinc chloride at 220° converted urea into cyanuric acid.

We have reinvestigated Moureu's work and find that urea when heated with thionyl chloride undergoes solely deamination, and a mixture of biuret and triuret [or carbonyldiurea, $CO(NH{\cdot}CO{\cdot}NH_2)_2$] is thus obtained, the proportion of triuret increasing with that of thionyl chloride employed. No indication of cyanamide formation could be detected. The mixture of biuret and triuret can be readily separated into its pure constituents by crystallisation from water, and this action of thionyl chloride provides the best known method for the preparation of both these compounds. Previous methods for the preparation of triuret, *e.g.*, by the action of carbonyl chloride on urea or oxamide (Schmidt, *J. pr. Chem.*, 1872, **5**, 39, 56; Schiff, *Annalen*, 1896, **291**, 374) or of hydrogen peroxide on uric acid (Schittenhelm and Wiener, *Z. physiol. Chem.*, 1909, **62**, 103; Ohta, *Biochem. Z.*, 1913, **54**, 442; Walters and Wise, *J. Amer. Chem. Soc.*, 1917, **39**, 2476; Venable, *ibid.*, 1918, **40**, 1100), are either troublesome or give only low yields. The formation of biuret by the interaction of urea and thionyl chloride was briefly noted, but without quantitative details, by Warren and Wilson (*Ber.*, 1935, **68**, 957), who considered that Moureu (*loc. cit.*) mistook biuret for cyanamide.

Sulphuryl chloride has, as expected, a more vigorous action than thionyl chloride when heated with urea. By carefully controlling the reaction, however, we have isolated from the reaction product a colourless crystalline *substance* of composition $C_4H_{16}O_7N_8S$. A cold aqueous solution of this substance does not furnish sulphate ions; it is, however, very readily hydrolysed by hot dilute mineral acids to biuret and sulphuric acid. Consequently, it can be extracted from the crude reaction product only if the latter is first neutralised by ammonia or trimethylamine : direct extraction with hot water liberates sufficient acid from traces of unchanged sulphuryl chloride to cause complete hydrolysis, and only biuret then separates when the aqueous

* A paper entitled " The Action of Thionyl Chloride on Urea " by E. A. and A. E. A. Werner (*Sci. Proc. Royal Dublin Soc.*, 1943, **23**, No. 13) has recently been announced, but we have not been able to obtain a copy.

extract is cooled. The constitution of this intermediate compound is unknown. It may be a trihydrate, $C_4H_{10}O_4N_8S,3H_2O$; it is, however, stable indefinitely in a vacuum at room temperature, but when heated at 130°/15 mm. undergoes slow progressive decomposition, and no definite anhydrous derivative could be obtained. No analogous compound could be isolated from the urea–thionyl chloride reaction product.

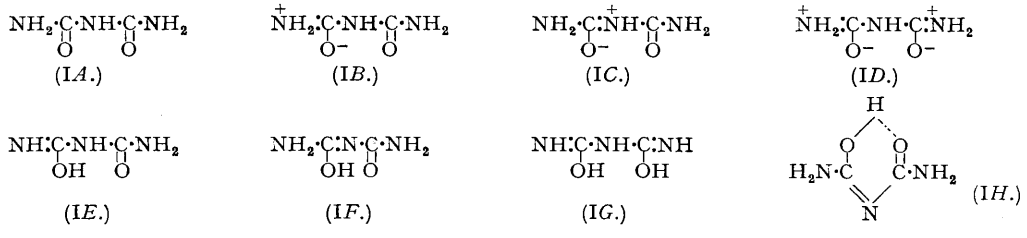
If the interaction of urea and sulphuryl chloride is promoted by direct heating, and the violent reaction then allowed to proceed unchecked, the above compound is not formed, but cyanuric acid is the main product.

Chlorosulphonic acid reacts vigorously with powdered urea even in the cold. When only 0·5 mol. of the acid is used, biuret is again formed, but 1 mol. of the acid gives either cyanuric acid or aminosulphonic acid, $NH_2{\cdot}SO_3H$, with a trace of triuret, according to the conditions employed.

The properties of urea are thus the direct converse of those of thiourea in two important respects. Whereas water cannot normally be abstracted from the urea molecule, hydrogen sulphide can readily be eliminated from thiourea by the action of various metallic oxides, with the consequent formation of cyanamide or (by spontaneous polymerisation) of dicyandiamide. On the other hand, whereas urea readily loses ammonia to give biuret and triuret, no similar reaction occurs with thiourea. We find that boiling thionyl chloride does not react with thiourea; sulphuryl chloride gives only traces of sulphur (being otherwise unchanged); chlorosulphonic acid liberates considerable sulphur, but no other product could be isolated.

Considerable further work is required to elucidate the mechanism by which biuret, triuret, and cyanuric acid are formed by the action of the above acid chlorides on urea. It is clear that the biuret may arise from the hydrolysis of sulphur compounds derived from the acid chlorides used, but there is no definite evidence of the source of the triuret. The cyanuric acid may possibly arise by one or both of two means: (*a*) cyclisation and consequent deamination of triuret, (*b*) polymerisation of cyanic acid formed by direct dissociation of the urea. The likelihood of cyanic acid thus formed reacting with unchanged urea by a " Wöhler rearrangement " to give biuret has been disproved by Davis and Blanchard (*J. Amer. Chem. Soc.*, 1929, **51**, 1806). Biuret undergoes no further deamination when treated with boiling thionyl or sulphonyl chloride.

Certain points concerning the structure of biuret deserve brief discussion, although this structure, like that of urea, must be affected strongly by the environment of the compound. It is clear, however, that biuret may exist as a resonance hybrid between the conventional form (I*A*) and several " zwitterion " forms such as (I*B*), (I*C*), or (I*D*); furthermore, it may exist as partly or fully enolised tautomerides such as (I*E*), (I*F*), or (I*G*). Finally, there is a strong possibility that the structure, particularly in the crystalline state, will be deeply modified by hydrogen bonds, giving cyclic structures, of which one of the simplest is (I*H*) but which may be very much more complex. (The possible structures of triuret are of course far more numerous still.)



(I*A*.) (I*B*.) (I*C*.) (I*D*.)

(I*E*.) (I*F*.) (I*G*.) (I*H*.)

Dr. A. Hargreaves and Dr. W. H. Taylor, of the Physics Department of the Manchester College of Technology, have kindly investigated the structure of crystalline anhydrous biuret; unfortunately this proves to have 8 molecules per unit cell, and this complexity, combined with its space-group, makes elucidation of its molecular structure exceedingly difficult.

Three properties of the biuret structure are noteworthy. (*a*) Some unknown factor in this structure apparently prevents the replacement of both oxygen atoms by sulphur unless other substituents are present to stabilise the molecule. Monothiobiuret, $NH_2{\cdot}CS{\cdot}NH{\cdot}CO{\cdot}NH_2$, and several mono- and di-substituted dithiobiurets, $RNH{\cdot}CS{\cdot}NH{\cdot}CS{\cdot}NH_2$, $RNH{\cdot}CS{\cdot}NH{\cdot}CS{\cdot}NHR$, and $R_1R_2N{\cdot}CS{\cdot}NH{\cdot}CS{\cdot}NH_2$, are known, but the parent dithiobiuret has not been prepared (cf. Wunderlich, *Ber.*, 1886, **19**, 452; Hecht, *Ber.*, 1892, **25**, 749; Fromm *et al.*, *Annalen*, 1893, **275**, 20; 1906, **348**, 161; *Ber.*, 1895, **28**, 1096; 1899, **32**, 835; 1922, **55**, 804).

(*b*) Biuret in alkaline solution usually acts as a dibasic acid, and hence forms a complex bivalent anion with certain heavy metals; *e.g.*, $Na_2[Cu(C_2H_3O_2N_3)_2]$, $Tl_2[Cu(C_2H_3O_2N_3)_2]$, $Ba[Cu(C_2H_3O_2N_3)_2]$, $Tl_2[Ni(C_2H_3O_2N_3)_2]$, and $Ba[Ni(C_2H_3O_2N_3)_2]$ are known, although some of these have water of crystallisation (Schiff, *Annalen*, 1898, **299**, 253; Rising *et al.*, *J. Biol. Chem.*, 1930, **89**, 1; Traube *et al.*, *Ber.*, 1927, **60**, 43; 1930, **63**, 2094; 1935, **68**, 1399).

(*c*). Attention has not previously been directed to the remarkable alternation in properties shown by biuret, triuret, tetrauret, and the next higher homologue, carbonyldibiuret, $CO(NH{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NH_2)_2$: this alternation appears in the m. p., solubility in cold water, and in ability to give the biuret reaction:

	M. p.	Solubility in cold water.	Biuret reaction.
$NH(CO{\cdot}NH_2)_2$	190° (decomp.)	Moderately soluble	Deep red colour
$CO(NH{\cdot}CO{\cdot}NH_2)_2$	231 ,,	Slightly soluble	Very faint colour
$NH(CO{\cdot}NH{\cdot}CO{\cdot}NH_2)_2$	186 ,,	Readily soluble	Intense violet colour
$CO(NH{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NH_2)_2$	235 ,,	Almost insoluble	No coloration

Only qualitative data for solubility in cold water are available. (For general properties of these compounds, see Schmidt, *loc. cit.*; Schiff, *loc. cit.*; Thiele and Uhlfelder, *Annalen*, 1898, **303**, 106.) Our knowledge of the true structure of these compounds is meagre, but it is clear that some unknown factor causes a profound but apparently similar modification in the structure of alternate members.

Since cyanuric acid can be obtained by the action of sulphuryl chloride on urea, a possible route to the preparation of melamine becomes open, because Beilstein (*Annalen*, 1860, **116**, 357) has shown that cyanuric acid is converted by phosphorus pentachloride into cyanuric chloride, and this is readily converted into melamine by heating with ammonia (Hofmann, *Ber.*, 1885, **18**, 2765). Since Beilstein's preparation of cyanuric chloride is both costly and inefficient, we investigated the action of sulphuryl chloride and of chlorosulphonic acid on cyanuric acid, but there was no apparent reaction, for even after several hours' heating treatment with ammonia under Hofmann's conditions gave ammonium cyanurate and not melamine.

The possibility of converting cyanuric acid directly into melamine by the action of ammonia has also been investigated. When the acid was heated in an autoclave with zinc chloride previously saturated with ammonia, ammonium cyanurate was again formed: calcium chloride similarly saturated with ammonia gave calcium cyanurate. These attempts were therefore abandoned.

Experimental.

Interaction of Urea and Thionyl Chloride.—The following are the optimum conditions for the preparation of pure biuret and triuret.

(*a*) *Biuret.* A mixture of dried, finely powdered urea (30 g.) and pure thionyl chloride (13·5 c.c., 0·38 mol.), in a flask having a reflux condenser closed by a calcium chloride tube, was heated on a water-bath for 2·5 hours with occasional vigorous shaking. The flask, whilst still warm, was then evacuated with a water-pump to remove excess chloride, etc. The almost solid product was recrystallised from water (150 c.c.), an undissolved residue of triuret (1 g.; m. p. 225°, efferv.) being collected. The filtrate on cooling deposited monohydrated biuret, which in a vacuum desiccator gave anhydrous biuret, m. p. 186° (efferv.); yield, 14·5 g., 56%. Further recrystallisation from alcohol (*ca.* 400 c.c.) removed a trace of undissolved triuret and gave pure biuret, m. p. 190° (efferv.); yield, 9·7 g., 38% (Found: C, 22·9; H, 4·95; N, 40·5. Calc. for $C_2H_5O_2N_3$: C, 23·3; H, 4·85; N, 40·8%).

(*b*) *Triuret.* A mixture of urea (40 g.) and thionyl chloride (50 c.c., 1 mol.) was treated as in (*a*), and after evacuation the residue was neutralised with a few drops of aqueous ammonia (*d* 0·880) and then recrystallised twice from very dilute aqueous ammonia. Colourless crystals of triuret, m. p. 227° (efferv.), were obtained: 4·8 g., yield 15% (Found: C, 24·6; H, 4·3; N, 38·3. Calc. for $C_3H_6O_3N_4$: C, 24·7; H, 4·1; N, 38·4%). Schiff (*loc. cit.*) gives m. p. 231—232°. The triuret can be obtained by treatment with water alone, but the use of ammonia, by retaining in solution a trace of cyanuric acid, gives a purer product.

Interaction of Urea and Sulphuryl Chloride.—(*a*) When dry powdered urea (10 g.) was added to sulphuryl chloride (13·5 c.c., 1 mol.), almost complete dissolution resulted, accompanied by a marked fall in temperature. This solution was heated at 90° for 1 hour, and the excess of chloride then pumped off in a vacuum from the warm product. The crude product, recrystallised from water, furnished biuret (2·6 g.), m. p. 188°, mixed and unmixed.

(*b*) Experiment (*a*) was repeated on a 6-fold scale. The crude product after the vacuum treatment was now, however, neutralised with cold aqueous ammonia (*d* 0·880), and then dissolved by addition of boiling water. The white crystals (9·1 g., m. p. 152° decomp.) obtained on cooling were then recrystallised from 8N-ammonia (300 c.c.). The crystalline product was dried in a vacuum over phosphoric oxide for several days; 6·5 g., m. p. 159° (efferv.) (Found: C, 15·0; H, 4·7; N, 34·8; S, 10·0. $C_4H_{10}O_4N_8S,3H_2O$ requires C, 15·0; H, 5·0; N, 35·0; S, 10·0%). Although this *compound* was thus stable in a vacuum at room temperature, yet when heated at 130°/15 mm. it slowly formed a glassy mass and then an amorphous powder, and its weight fell slowly during many hours: progressive decomposition occurred and it was impossible to prove the presence of water of crystallisation. The function of the ammonia was apparently solely to neutralise sulphuric and hydrochloric acids which would otherwise have been formed during aqueous extraction of the original crude product and would subsequently have caused hydrolysis. The use of aqueous trimethylamine instead of ammonia in this preparation gave ultimately the same product, m. p. 160° (efferv.), unchanged by admixture with the previous sample (Found: C, 15·9; H, 5·2; N, 34·6%).

A cold aqueous solution of this substance gave no immediate precipitate with barium chloride and hydrochloric acid, but on warming, barium sulphate was rapidly precipitated. A mixture of the compound (1 g.) and 1% hydrochloric acid (20 c.c.) was boiled for 10 mins. and was then clear; after 5 mins.' further boiling, the solution was cooled and deposited biuret, 0·2 g., m. p. after dehydration 188—189° (mixed and unmixed) (Found: N, 41·1%).

When the sulphuryl chloride in experiment (*b*) was increased to 6 mols. and the other conditions left unchanged, the same substance was isolated.

(*c*) Experiment (*a*) was repeated, but the original mixture was now heated directly on a sand-bath. Immediately the vigorous initial reaction subsided, the flask was lifted so that it was just not in contact with the sand, and the heating continued for a further 15 mins., an almost solid product being obtained. After the usual evacuation, the product was leached with cold water; the residue (4·4 g.), twice recrystallised from much hot water, gave cyanuric acid, unaffected by heating to 550° (Found: C, 28·0; H, 2·5; N, 32·6. Calc. for $C_3H_3O_3N_3$: C, 27·9; H, 2·3; N, 32·6%).

(*d*) Experiment (*c*) was repeated, but the product after evacuation was treated with excess of aqueous ammonia (*d* 0·880) and then dissolved by addition of boiling water. Cooling gave a white deposit, which when collected and boiled with water evolved ammonia, the solution ultimately depositing cyanuric acid (Found: C, 28·1; H, 2·4; N, 32·9%) on cooling.

(*e*) Experiment (*c*) was repeated, but the reaction mixture was removed from the sand-bath immediately the reaction started. The product became almost solid on cooling, and after the usual evacuation, direct recrystallisation from water gave pure triuret, m. p. 232° (Found: C, 24·8; H, 4·3; N, 38·9%).

Interaction of Urea and Chlorosulphonic Acid.—(*a*) When urea (5 g.) and chlorosulphonic acid (2·7 c.c., 0·5 mol.) were mixed, a vigorous reaction ensued and the mixture became semi-solid. The product was heated on a water-bath for 2·5 hours, excess of chlorosulphonic acid removed, and the residue recrystallised from a small quantity of water, giving biuret, m. p. 188° (mixed and unmixed). (*b*) Experiment (*a*) was repeated, but with 1 mol. of chlorosulphonic acid. The residue was mixed with water, set aside for 12 hours, and the undissolved fraction recrystallised from water; aminosulphonic acid, m. p. 207° (mixed and unmixed), was obtained (Found: N, 14·4. Calc. for H_3O_3NS: N, 14·4%). The original aqueous extract, taken to dryness and then recrystallised, gave a very small quantity of triuret, m. p. 230° (decomp.), unchanged by admixture with an authentic sample. (*c*) Experiment (*b*) was repeated, the reaction

mixture being heated at 170° for 1 hour. The final residue, recrystallised from much water, gave cyanuric acid, which, when thoroughly dried, was unaffected by heating to 300° (Found: N, 32·4%). Baumgarten (*Ber.*, 1936, **69**, 1929) has shown that urea and sulphuric acid under suitable conditions also give aminosulphonic acid.

Biuret was recovered unchanged after it had been heated (*a*) with thionyl chloride (6 mols.) on a water-bath for 2·5 hours, and (*b*) with sulphuryl chloride (3 mols.) at 90° for 1 hour. When biuret (4 g.) and chlorosulphonic acid (12 c.c., 5 mols.) were mixed in the cold, a vigorous reaction occurred. The mixture, when heated at 100° for 2 hours, became semi-solid. Treatment with cold water gave a crystalline residue of aminosulphonic acid, m. p. 204° (mixed and unmixed), and a further crop was obtained from the aqueous extract. Since no organic compound could be isolated, the biuret had apparently been broken down, carbon dioxide being the main product.

Reactions of Thiourea.—Thiourea was also recovered unchanged after it had been heated at 100° for 2·5 hours with (*a*) thionyl chloride (3 mols.), (*b*) sulphuryl chloride (3 mols.); a trace of elementary sulphur was also obtained in the latter experiment. When, however, powdered thiourea (5 g.) and chlorosulphonic acid (4·4 c.c., 1 mol.) were mixed, a vigorous reaction ensued; the mixture, which became yellow, was allowed to cool spontaneously, and after the usual vacuum treatment was extracted with boiling water. Sulphur (1·5 g., representing 70% of that originally in the thiourea) remained, and the filtrate deposited a small quantity of unchanged thiourea. The experiment was repeated but with 3 mols. of chlorosulphonic acid, the mixture being heated on a water-bath for 30 mins. After the usual treatment, extraction with boiling water gave a considerable residue of sulphur; evaporation of the filtrate caused a further minute deposit of sulphur, but no organic residue could be isolated.

Dicyandiamide from Thiourea.—A mixture of thiourea (100 g.), powdered litharge (600 g., 2·05 mols.), and hot water (500 c.c.) was boiled under reflux for 3 hours and then rapidly filtered, the residual lead oxide and sulphide being washed on the filter with hot water. The united filtrate and washings were evaporated to *ca.* 120 c.c., and on cooling deposited colourless crystals of dicyandiamide, m. p. 205—206° (mixed and unmixed), 43 g.; a further 3 g. were recovered from the solution. Total yield, 83% of theoretical.

Molecular Weights of Biuret and Triuret.—These were determined ebullioscopically. Biuret: *M*, in 0·480% alcoholic solution, 113; in 1·28% solution, 112; in 1·65% solution, 115; in 1·60% aqueous solution, 100; in 3·03% solution, 111; in 4·07% solution, 113; in 5·19% solution, 114 (Calc. for $C_2H_5O_2N_3$: *M*, 103). Triuret: *M*, in 0·55% aqueous solution, 160; in 0·71% solution, 180 (Calc. for $C_3H_6O_3N_4$: *M*, 146). The low solubility of triuret even in boiling water made accurate determinations impossible.

When a solution of triuret (0·50 g.) in boiling water (80 c.c.) was refluxed for 2 hours, no odour of ammonia was detected, and the solution on cooling deposited pure triuret (0·39 g.; m. p. 228°, efferv.): cyclisation to ammonium cyanurate therefore does not occur in these conditions.

Dr. Hargreaves and Dr. Taylor report: "*Biuret.* Rectangular plates have been selected from material recrystallised once from water and twice from alcohol. With light transmitted normally through the plate face and between crossed Nicols straight extinction is observed. An incomplete biaxial optic figure is observed when the crystals are examined in convergent light transmitted normally through the plate face. The density of the crystals, measured by flotation in a mixture of benzene and bromoform, is $1{\cdot}45_2$. *X*-Ray rotation and oscillation photographs show that the crystals are monoclinic, with the symmetry axis parallel to the length of the rectangular plates. The *C* face of the crystal being chosen as the plate face, the unit cell dimensions are as follows: $a = 9{\cdot}20$ A., $b = 6{\cdot}6$ A., $c = 15{\cdot}4$ A., $\beta \sim 90°$. With 8 molecules in the unit cell the calculated density is 1·44.

"Indexing of the oscillation photographs indicates that reflections $\{hkl\}$ are present only when $(h + l)$ is even, and $\{h0l\}$ reflections are present only when h is even and l is even. These halvings limit the space-group to either C_{2h}^6 or C_s^4. The eight molecules in the unit cell lie in completely general positions in lattices with either of these space-groups, and both space-groups are of low symmetry. It would be difficult therefore to proceed any further with the investigation of this compound.

"*Triuret.* The crystals of triuret provided are too small for *X*-ray examination by single crystal methods. Attempts to grow larger crystals have not been successful."

Reactions of Cyanuric Acid.—(1) *With sulphuryl chloride.* A mixture of anhydrous cyanuric acid (2 g.) and sulphuryl chloride (5 c.c., 3 mols.) was heated at 90° for 1 hour. The excess of chloride was removed in a vacuum, and the residue boiled with concentrated ammonia solution. The hot clear solution deposited only ammonium cyanurate, which, boiled in hot aqueous solution, ultimately by hydrolysis deposited cyanuric acid (Found: N, 32·1%). No melamine could be detected.

(2) *With chlorosulphonic acid.* A mixture of cyanuric acid (2 g.) and chlorosulphonic acid (6 c.c., 6 mols.) was heated at 160—170° for 2 hours and then treated as in (1). Ammonium cyanurate, giving cyanuric acid (Found: N, 32·4%), was again obtained.

(3) *With zinc chloride–ammonia.* This reagent was prepared by passing dry hydrogen chloride through molten zinc chloride at 280° to remove any basic chloride, then dry hydrogen to remove acid fumes, and finally ammonia, which was passed through for 30 mins. at 280° and then continued as the product cooled. A mixture of this pulverised reagent (40 g.) and cyanuric acid (2 g.) was heated in a sealed tube at 300° for 5 hours. The product on extraction with hot water gave only crude ammonium cyanurate, which afforded cyanuric acid as in (1).

(4) *With calcium chloride–ammonia.* Anhydrous calcium chloride was heated at 160° in a current of hydrogen chloride, which was then replaced by dry air. The salt was then chilled in ice-water, and dry ammonia passed through until absorption ceased. A mixture of this product (27 g.) and anhydrous cyanuric acid (2 g.) was heated in an autoclave at 240° for 8 hours, and when cold was extracted with boiling water (500 c.c.). The solution deposited large crystals, which were recrystallised from water and placed in a vacuum, where they underwent decrepitation and partial dehydration. The residue was apparently calcium cyanurate *tetrahydrate*, but it underwent no further dehydration during 6 hours' exposure to a vacuum at 140° [Found: C, 19·9; H, 3·35; N, 22·7; Ca, 10·7. $(C_3H_2O_3N_3)_2Ca,4H_2O$ requires C, 19·6; H, 3·3; N, 22·8; Ca, 10·9%].

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