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Molecular Compound Formation between Substituted Biurets and Isocyanurates

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RECEIVED MARCH 14, 1953

It has been found that 1-substituted biurets form molecular compounds with similarly substituted isocyanurates. The complexes are generally nicely crystalline compounds with sharp melting points.

In an attempted preparation of *n*-amyl isocyanurate by heating urea with *n*-amylurea, a product was isolated which melted sharply at 178–179°, in disagreement with the value established for the same product obtained through the condensation of *n*-amylbiuret with ethyl carbonate.[1] Analytical data suggested an empirical formula of $C_{15}H_{28}N_6O_5$. It was felt that this might represent a stable molecular compound of *n*-amyl isocyanurate and the corresponding biuret in a 1:1 proportion. This fact was demonstrated by dissolving the two compounds in boiling alcohol and cooling; a product identical with the 178–179° material separated in 96% yield.

A survey of the literature revealed two other examples of biuret–isocyanurate complexes. Herzig[2] isolated a product during the preparation of biuret which was said to be a 1:1 molecular compound of biuret itself and cyanuric acid, but no melting point was given. We have been able to prepare what appears to be such a complex by dissolving cyanuric acid and an excess of biuret in hot water and cooling. The crystals obtained seemed to be homogeneous when examined under a microscope; however, completely satisfactory analyses could not be obtained. The product was unstable at elevated temperatures and had no distinct point of fusion. Furthermore, an attempt to prepare the complex using a 1:1 ratio of constituents gave only cyanuric acid. These data indicate that the bonding forces in this particular substance are relatively weak, and special conditions must be created to ensure its formation.

Moore and Gatewood[3,4] isolated a product melting at 196–198° from the oxidation of 9-phenyluric acid. They described the product as 3-phenylbiuret, but Blair[5] later showed that it was a molecular compound composed of phenylbiuret and phenyl isocyanurate in a 3:2 ratio. We have confirmed the existence of such a complex although we found the compound to melt at 210–211° and to have a 2:1 ratio of components.

It appeared to be of interest to determine whether complex formation is a general property of the isocyanurates. Consequently a number of other isocyanurates were mixed with biurets having corresponding substituents and dissolved in an appropriate solvent at the boiling point. Cooling precipitated a nicely crystalline molecular compound in all cases; most of the derivatives had sharp, reproducible melting points. Oddly enough, only the phenyl compound appears to exist in other than a simple 1:1 ratio of biuret to isocyanurate.

The methyl and isobutyl complexes, like the unsubstituted molecular compound discussed above, disintegrated before melting and their formation may be viewed with suspicion. That true molecular compounds exist is attested to by the fact that the constituents have a large differential solubility in the solvents employed and precipitation in a 1:1 ratio is, therefore, highly improbable.

Some preliminary work was carried on with mixed molecular compounds; *i. e.*, those prepared from biurets and isocyanurates dissimilarly substituted. There was evidence of some degree of association with those studied, but no sharply melting, clearly defined crystals were obtained.

Most of the products were tested for anticonvulsant activity, but were generally inactive or weakly active.[6] The *n*-amyl and benzyl derivatives provided exceptions. These compounds gave good protection against electroshock, Metrazol and psychomotor seizures at the rather high dose level of 800 mg./kg. The activity in neither case represented a summation of the effects of the constituents, and indicates that the complexes are sufficiently stable to survive intact the rigors of absorption into a biological system.

Acknowledgment.—The author wishes to express his appreciation to Mr. E. F. Shelberg and his staff for their coöperation in carrying out the large number of micro-analytical determinations required for this work. The author is also indebted to Drs. R. K. Richards and G. M. Everett for providing the pharmacological data.

Experimental

Preparation of Molecular Compounds.—With the exception of the phenyl derivative the complexes were prepared by dissolving 1.0 to 1.5 equivalents[7] of the substituted biuret[8] and a similarly substituted isocyanurate[1] in boiling water containing acetone, where necessary, to increase the solubility.[9] The products separated as leaflets or needles upon cooling the solution, and were recrystallized once for analysis. The yields ranged from 64 to 96%. The properties of the compounds prepared are given in Table I.

Demonstration of Biuret–Isocyanurate Ratio.—All of the compounds prepared by the above procedure appear to be 1:1 structures. This ratio is best indicated by the analytical results (Table I).

It is recognized that the analytical data provide a strong indication, but do not constitute proof, that the products are 1:1 molecular compounds. It was hoped that con-

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[1] W. J. Close, THIS JOURNAL, **75**, 3617 (1953).

[2] J. Herzig, *Monatsh.*, **2**, 410 (1881).

[3] F. J. Moore and E. S. Gatewood, THIS JOURNAL, **45**, 135(1923).

[4] E. S. Gatewood, *ibid.*, **45**, 146 (1923).

[5] J. S. Blair, *ibid.*, **56**, 904 (1934).

[6] For details of testing methods see J. E. P. Toman, G. M. Everett and R. K. Richards, *Texas Rpts. Biol. Med.*, **10**, 96 (1952).

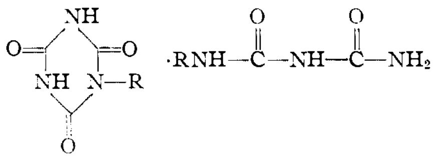
[7] Better results were often obtained by using an excess of biuret instead of a stoichiometric amount, probably because the products dissociate somewhat in the boiling solvents and unchanged isocyanurate tends to separate. Since the biuret is the most soluble component of the system it does not interfere with the isolation of a pure product.

[8] D. A. Dunnigan and W. J. Close, THIS JOURNAL, **75**, 3615 (1953).

[9] Some complexes were obtained in alcohol. It was found that a few which were unstable in alcohol formed easily in water. The phenyl derivative is an example.

TABLE I

MOLECULAR COMPOUNDS



					Analyses					
			Yield,			Calcd.			Found	
R	Solvent[a]	M.p., °C.	%	Formula[b]	C	H	N	C	H	N
H	A	Decomp.	87	$C_5H_8N_6O_5$	25.9	3.5	36.2	25.4 25.4	3.6 3.4	35.7 36.5
CH_3	B	Decomp.	64	$C_7H_{12}N_6O_5$	32.3	4.7	32.3	32.5	4.4	31.8
C_2H_5	A	172–173	87	$C_9H_{16}N_6O_5$	37.5	5.6	29.2	37.8	5.6	29.1
n-C_3H_7	A or C	173–175	85	$C_{11}H_{20}N_6O_5$	41.8	6.4	26.6	42.1	6.2	26.9
n-C_4H_9	A or C	181–182	93	$C_{13}H_{24}N_6O_5$	45.4	7.0	24.4	45.7	6.9	24.4
i-C_4H_9	B	Decomp.	85	$C_{13}H_{24}N_6O_5$	45.4	7.0	24.4	45.4	7.0	24.7
n-C_5H_{11}	A	178–179	96	$C_{15}H_{28}N_6O_5$	48.4	7.6	22.6	48.8	7.7	22.8
i-C_5H_{11}	B or C	177–178	90	$C_{15}H_{28}N_6O_5$	48.4	7.6	22.6	48.5	7.6	22.6
n-C_6H_{13}	B	180–181	94	$C_{17}H_{32}N_6O_5$	51.0	8.1	21.0	51.2	8.0	21.2
C_6H_5	A	209–211[c]	94	$C_{25}H_{25}N_9O_7$[d]	53.3	4.5	22.4	53.3	4.3	22.2
$C_6H_5CH_2$	B or C	185–186	84	$C_{19}H_{20}N_6O_6$	55.3	4.9	20.4	55.5	4.7	20.7

[a] The symbols refer to the following solvents: A = water; B = water + acetone; C = 95% alcohol. [b] Calculated on the basis of a 1:1 ratio of components. [c] Blair (ref. 4) records 197°. [d] Calculated on the basis of a 2:1 ratio of biuret to isocyanurate.

firmation could be obtained by dissolving the components in molecular proportions in a suitable solvent and evaporating to dryness. This technique failed to give material melting sharply enough to be definitive. Likewise, melting mixtures of the powdered reactants, as carried out successfully by Blair,[5] gave inconclusive results. This latter method suffers from the disadvantage that complete homogeneity of the powder mixture is difficult to obtain.

The yields obtained provide additional evidence of the 1:1 formulation. For the most part they are too high to permit any reasonable proportion in which the isocyanurate predominates. Since the biuret was often used in excess, the yields do not as easily rule out structures in which the biuret predominates. However, in the majority of cases the excess amounted to less than 25%, and any reasonable complex containing a biuret–isocyanurate ratio greater than 1:1 would leave a certain amount of isocyanurate unreacted. The isocyanurates are the least soluble materials in the system, and would be expected to appear as contaminants of the products. This has not been observed.

Molecular Compound of Phenylbiuret and Phenyl Isocyanurate.—This derivative has been described[5] as melting at 197° and having a 3:2 ratio of biuret to isocyanurate. Several preparations of this substance have consistently given crystals which melt at 209–211°. The product has a 2:1 ratio of components, as shown by the following experiments.

Phenylbiuret[8] (179 mg., 1 millimole) was mixed with 103 mg. (0.5 millimole) of phenyl isocyanurate[1] and dissolved in a minimum quantity of boiling water. Cooling precipitated 238 mg. of the molecular compound, m.p. 208–209°. A second crop of 12 mg., m.p. 199–203°, was obtained from the filtrate. Recrystallization of the product brought the m.p. to 209–211°.

The 250 mg. of product isolated corresponds to an 89% yield, based on a 2:1 ratio of biuret to isocyanurate. The yield is greater than the theoretical based on a 3:2 ratio.

Further confirmation of the 2:1 structure was obtained by setting up an experiment identical with that described above except that the components were mixed in a 3:2 ratio. The product separated in an 83% yield based on a 3:2 structure, or 94% based on a 2:1 ratio. Unchanged isocyanurate was isolated from the filtrate.

Finally, the neutral equivalent was determined by electrometric titration.[10] Calcd. for a 3:2 complex: 474. Calcd. for a 2:1 complex: 563. Found: 549.

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[10] Kindly carried out by Dr. William Brownell and Mr. Harvey Miller.