not identified any further. While it is true that the hydrazoic acid could arise by alkaline ring opening of III to II, the data nevertheless, indicate that structure II cannot be precluded from consideration.

Accordingly, the simplest and most decisive method of making a choice between II and III would be to examine the infrared spectrum of the thiosemicarbazide–nitrous acid product for the presence of the azido group, since this latter group, if present in a molecule, is easily detected by such means.[5] The infrared spectrum of a specimen, having a nitrogen and sulfur content corresponding to the theoretical of II or III, showed no absorbance in the 4.5- to 5-micron range, the range characteristic of the azido group.[5] Thus, structure II can be eliminated from consideration.[6] This datum, however, is not offered as complete proof of structure III, although the compound can now provisionally be assigned this structure.

During the course of this study on the preparation of III it was found advantageous to control the thiosemicarbazide–nitrous acid ratio by adding a standard solution of sodium nitrite from a buret to a cooled aqueous solution of thiosemicarbazide containing one equivalent of hydrochloric acid and removing the product as it precipitates. The crude product, so obtained, is substantially pure, and is not improved by further recrystallization.

EXPERIMENTAL[7,8]

5-Amino-1,2,3,4-thiatriazole. To an ice cold solution of 20 g. (0.21 mole) of thiosemicarbazide in 95 cc. of 2.2*N* hydrochloric acid (0.21 mole), was added from a buret, with stirring, three 50-ml. portions of sodium nitrite solution containing a total of 14.7 g. (0.21 mole) of sodium nitrite. After each 50-ml. portion was added the product was collected and washed with 10 ml. of ice water, the filtrate being returned to the reaction vessel. For analysis, the crude product was vacuum dried. Yield 18.4 g. (82%).

Anal. Calcd. for CH_2N_4S: N, 54.87; S, 31.39. Found: N, 55.58; S, 31.08.

Recrystallization from methanol yielded fine, colorless needles which decomposed with a slight explosion at 136° in a capillary tube. On a hot plate the decomposition point was 128–130° (reported,[2] 128–130° dec.).

Anal. Calcd. for CH_2N_4S: N, 54.87; S, 31.39. Found: N, 55.39; S, 31.00.

The decomposition of III depends on the rate of heating. This was studied by placing a small quantity of recrystallized III on a Parr-Block preheated to a specific temperature. The following represents temperature and time required for decomposition, in minutes: 120°, 10; 110°, 20; 100°, 60; 95°, 150.

Infrared spectrum of III. The infrared absorption spectrum was obtained on a Perkin-Elmer spectrometer, Model 12-C. The sample consisted of 15 mg. of III mulled in 10 drops of white mineral oil for 5 to 10 min. The spectrum was taken over the range of 2 to 15 microns, using an automatic slit-drive and a scanning rate of 30 min. The following absorption peaks were observed, after subtraction of the white mineral oil background (in microns): 2.99, 3.12, 3.28, 6.14, 6.64, 7.48, 7.69, 7.84, 8.11, 8.61, 9.00, 10.60.

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(5) E. Lieber, D. R. Levering, and L. Patterson, *Anal. Chem.*, **23**, 1594 (1951).

(6) A more complete investigation and analysis of the ultraviolet and infrared absorption spectra of the products of the reaction of one mole of nitrous acid with a series of 4-substituted thiosemicarbazides is in progress. We are indebted to one of the referees for the comment that the band at 6.14 microns, which is the result of C=N group vibration, provides further evidence for structure III in preference to II, since C=S does not absorb in this region.

(7) Melting points are uncorrected.

(8) Microanalyses by Dr. C. Weiler and Dr. F. B. Strauss, Oxford, England.

Improved Procedure for Preparing 3-, 5-, or 3,5-Substituted Hydantoins[1]

ALBERT C. SMITH, JR., AND CORNELIUS C. UNRUH

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Hydantoin and its substituted derivatives are frequently prepared by the cyclization of the corresponding ureidoacetic esters, amides, or acids. Various methods have been employed to prepare the latter derivatives, often involving the preparation of difficultly accessible reagents. A convenient method of preparation of these hydantoic acid esters and amides which is capable of wide application, is described.

As a general preparative method, an α-isocyanato ester was allowed to react with ammonia or a primary amine to give the hydantoic ester in good yield. In some instances, the corresponding amide was obtained. Cyclization of these esters or amides by mineral acids in the conventional manner gave the corresponding 3-, 5-, or 3,5-substituted hydantoins.

Hydantoin, or a 3-substituted hydantoin, was obtained by cyclizing the hydantoic ester (or amide) obtained by the reaction of ammonia or a primary amine with ethyl isocyanatoacetate. This ester, readily prepared in high yield by the reaction of carbonyl chloride with glycine ester hydrochloride, was first described by Morel,[2] and later by Siefken,[3] whose preparative procedure was used in this work. α-Amino-acid ester hydrochlorides other than glycine produced substituted α-isocyanatoacetic esters which, when allowed to react with

(1) Communication No. 1803 from the Kodak Research Laboratories.

(2) A. Morel, *Compt. rend.*, **143**, 119 (1906).

(3) W. Siefken, *Ann.*, **562**, 105 (1949).

TABLE I
HYDANTOIC ESTERS

R_1	R_2	Product	Empirical Formula	Yield, %	M.P., °C	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	H	Ethyl ureidoacetate	$C_5H_{10}O_3N_2$	95	135–137	41.0	6.8	19.2	41.0	6.6	19.1
CH_3	H	N-Methylureido-(N-methylacetamide)[a]	$C_5H_{11}O_2N_2$	..	184.5–185.5	41.3	7.6	29.0	41.1	7.6	29.5
H	$CH_3{\cdot}CH_2$	Ethyl α-ureidobutyrate	$C_7H_{14}O_3N_2$	..	96–98	48.3	8.05	16.1	48.6	8.1	16.0
$CH_3(CH_2)_{10}CH$	H	N-Laurylureidoacetamide	$C_{17}H_{34}O_3N_2$	..	..	65.0	10.8	8.9	65.5	10.9	8.8
$HOCH_2CH_2$	H	Ethyl N-(β-hydroxyethyl)-ureidoacetate	$C_7H_{14}O_4N_2$	91	71–73	44.2	7.4	14.7	43.8	7.5	14.4
H	$(CH_2)_6$	Dimethyl α,α′-diureidosebacate	$C_{14}H_{26}O_6N_4$	..	176–180	48.5	7.5	16.2	49.5	7.5	16.2

[a] The methylamide was formed instead of the ester.

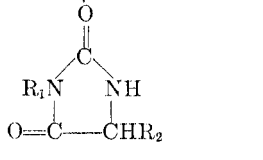
TABLE II
HYDANTOINS

R_1	R_2	Product	Empirical Formula	Yield, %	M.P., °C	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	H	Hydantoin	$C_3H_4O_2N_2$	58	220–222	36.0	4.0	28.0	36.4	4.1	28.1
CH_3	H	3-Methylhydantoin	$C_4H_6O_2N_2$	..	..	..	..	..	..	..	..
H	$CH_3{\cdot}CH_2$	5-Ethylhydantoin	$C_5H_8O_2N_2$	..	119.5–120.5	48.4	6.4	19.3	47.2	6.1	21.4
$CH_3(CH_2)_{10}CH$	H	3-Laurylhydantoin	$C_{15}H_{28}O_2N_2$	..	97–100	67.2	10.5	10.5	67.1	10.2	10.0
$HOCH_2CH_2$	H	3-(β-Hydroxyethyl)hydantoin	$C_5H_8O_3N_2$	..	98–101	41.6	5.5	19.4	42.0	5.7	19.5
H	$(CH_2)_6$	Hexamethylene-bis-(5-hydantoin)	$C_{12}H_{18}O_4N_4$	..	>250	51.1	6.4	19.8	51.3	6.2	20.3

ammonia, produced the corresponding 5-substituted hydantoin.

$$R_1NH_2 + OCN{\cdot}CHR_2{\cdot}COOC_2H_5 \longrightarrow R_1NH{\cdot}CO{\cdot}NHCHR_2{\cdot}COOC_2H_5$$
$$(\text{or } R_1NH{\cdot}CO{\cdot}NHCHR_2{\cdot}CONH_2)$$

conc. HCl



EXPERIMENTAL

Ethyl isocyanatoacetate. The procedure described by Siefken[3] was employed.

Ethyl α-isocyanatobutyrate. Fifty-five g. (0.33 mole) of ethyl α-aminobutyrate hydrochloride was refluxed in 250 ml. of dry toluene, with stirring, and a lively stream of phosgene was introduced through a gas-diffusion tube. At the end of 8⅓ hr., the product was vacuum-distilled, giving 38–39 g. (75%) of a product distilling at 64–67°/4 mm.

Anal. Calcd. for $C_7H_{11}NO_3$: C, 53.5; H, 7.0; N, 8.9. Found: C, 53.4; H, 6.9; N, 8.7.

Dimethyl α,α′-diaminosebacate dihydrochloride. To a suspension of 175 g. of α,α′-diaminosebacic acid[4] in 2 l. of methanol was added dry hydrogen chloride under anhydrous conditions, without cooling the vessel. As soon as the amino acid was in solution, the warm product was evaporated down to a syrup by a current of dried air. The residue was further evaporated down in a vacuum desiccator over phosphoric anhydride. To the viscous, brown residue was added 500 ml. of ethanol, and the solution was treated with charcoal to give a pale yellow solution. Ether was added in small portion to this solution (1 l.), with stirring and scratching the walls of the container. A permanent haze developed when 700 ml. of ether had been added. Crystallization commenced, and a further 300 ml. of ether was added cautiously. The crystalline precipitate was rapidly filtered off by suction, and was redissolved in 800 ml. of warm ethanol. On cooling to 0°, a white crystalline paste was formed which was rapidly filtered off, and was dried over phosphoric anhydride in a vacuum. Yield, 80 g.

Anal. Calcd. for $C_{12}H_{26}Cl_2N_2O_4$: C, 43.2; H, 7.8; N, 8.4; Cl, 21.3. Found: C, 43.0; H, 8.2; N, 8.3; Cl, 21.1.

Dimethyl α,α′-diisocyanatosebacate. A mixture of 32.5 g. of dimethyl α,α′-diaminosebacate dihydrochloride and 250 ml. of toluene was heated to reflux and a lively stream of phosgene was bubbled through the refluxing suspension until a homogeneous solution was obtained. This occurred after several hours. The product was vacuum-distilled and the fraction distilling at 192–194° at 1 mm. was collected. Yield, 13.7 g.

Anal. Calcd. for $C_{14}H_{20}N_2O_6$: C, 53.8; H, 6.4; N, 9.0. Found: C, 54.5; H, 6.8; N, 8.9.

Preparation of hydantoic esters. In general, ammonia or the amine was allowed to react with the isocyanato ester in dry benzene, the reaction vessel being cooled to moderate the reaction. The hydantoic ester, as a rule, crystallized out. It could then be filtered off, dried, or recrystallized from

(4) Prepared by the amination of α,α′-dibromosebacic acid. H. R. Le Sueur, *J. Chem. Soc.*, **91**, 1367 (1907). C. Neuberg and E. Neimann, *Hoppe-Seyler's Z. physiol. Chem.*, **45**, 104 (1905).

alcohol, if necessary. Table I indicates the results obtained.

Preparation of the hydantoins. In general, the hydantoic ester was mixed with 3 to 5 times its weight of 6*N* hydrochloric acid and heated for 15–20 min. to a temperature just below the boiling point of the mixture. On cooling, the hydantoin usually crystallized out, although, in some cases, the solution had to be evaporated down further before cooling afforded the crystalline product. The yields varied considerably, depending upon the amount of hydrochloric acid used in the reaction mixture.

In Table II are listed the various hydantoins obtained from the hydantoic esters shown in Table I.

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sym-Triazinetriphosphonic Acid Esters[1]

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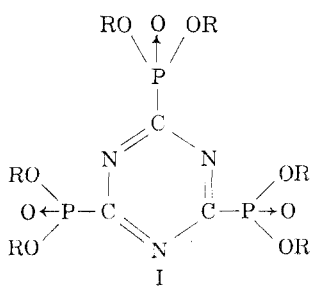
Cyanogen iodide and triethyl phosphite have been shown to interact forming diethyl cyanophosphate.[2] In the present work, the reaction of the trimeric cyanuric chloride with trialkyl phosphites was studied in the hope that the halogen would be active enough to permit the Arbusov rearrangement to occur. This was found to be the case, and 3 moles of the phosphite ester were observed to react easily with 1 mole of the cyanuric halide. The triazine ring system is apparently maintained in the products, which can be formulated as *sym*-triazine triphosphonic acid esters (I).



I

These esters are stable substances but show some tendency to hydrolyze in moist air, the hexamethyl ester being most reactive in this respect. The methyl, ethyl and β-chloroethyl esters were prepared, in addition to a crude *n*-propyl ester. Hydrolysis of the esters by long boiling with water gave a high-melting phosphonic acid which probably still contained ester groups as analysis gave high carbon values.[3]

The compounds, particularly the hexachloroethyl ester, were of interest in cancer chemotherapy due to the large number of alkylating groups present.

EXPERIMENTAL

Melting points are uncorrected.

sym-Triazenetriphosphonic acid esters (I). The reaction was carried out by adding powdered cyanuric chloride, in portions, to the warmed (about 60°) phosphite ester (3.1–3.5 molar equivalents). With the two lower esters, the product formed a paste on cooling. The preparation could also be done using benzene as solvent for the phosphite. Cyanuric acid, if present in the mixture, was removed by extraction of the product with chloroform, filtration and evaporation. The description of the synthesis of the ethyl ester only is given as the others were prepared similarly. Constants and analyses are listed in Table I.

TABLE I

sym-TRIAZINETRIPHOSPHONIC ESTERS

Ester	Yield, %	M.P., °C	C		H	
			Calcd.	Found	Calcd.	Found
Methyl	89.4	123–124.5	26.67	26.89	4.44	4.70
Ethyl	98.9	94–95	36.81	36.81	6.14	6.12
β-Chloroethyl	76.1	51.5–54	25.86	25.59	3.45	3.38

Triethyl phosphite (15 ml., 0.0877 mole) was treated gradually with 4.6 g. of cyanuric chloride (0.025 mole) at 50–60°. Considerable heating occurred and some evolution of ethyl chloride was noticed. The addition was completed in 15 min., whereupon the mixture was kept at 100° for 15 min. After standing for 1 hr. at room temperature, the paste was ground and extracted thoroughly with petroleum ether. The dried product weighed 12.1 g. or 98.9% yield. It gave well formed crystals from ether. The ester was recrystallized three times from this solvent and vacuum-dried for analysis. The ethyl ester is readily soluble in water to yield a neutral solution, from which it separates on warming as an oil which redissolves again on cooling.

The methyl ester was recrystallized from acetone-petroleum ether.

The β-chloroethyl ester was obtained first as an oil, which slowly crystallized during 2 to 5 days. When crystallization was complete, the mass was ground with 15 to 20 portions of ether (with some loss) and dried *in vacuo*. The product was pure but could be recrystallized from acetone-ether.

A crude *n*-propyl ester was prepared as an oil, part of which crystallized slowly on keeping at 0°.

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(1) The work described in this paper was carried out under a research grant (No. C-327) to Prof. D. M. Greenberg from the National Cancer Institute, United States Public Health Service.

(2) Saunders, Stacey, Wild, and Wilding, *J. Chem. Soc.*, 699 (1948).

(3) This acid showed weak chelating power for cupric ion in alkaline solution.