Urea–Formaldehyde Condensation Products. I. Urons[1]

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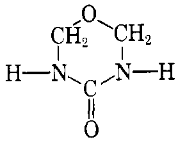
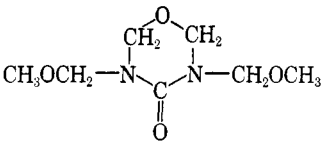
The synthesis of the parent member of the "Uron" class, tetrahydro-4*H*-1,3,5-oxadiazin-4-one, was effected by the acid-catalyzed hydrolysis of tetrahydro-3,5-bis(methoxymethyl)-4*H*-1,3,5-oxadiazin-4-one. A compound previously reported to be tetrahydro-3,5-dimethyl-4*H*-1,3,5-oxadiazin-4-one was shown to be 1,3-dimethyl-1-methoxymethylurea. The synthesis of tetrahydro-3,5-dimethyl-4*H*-1,3,5-oxadiazin-4-one was effected by the hydrogenolysis of tetrahydro-3,5-bis(methoxymethyl)-4*H*-1,3,5-oxadiazin-4-one in the presence of Raney nickel.

In 1936 Kadowaki[2] assigned the name "Uron" to a cyclic urea (I), tetrahydro-4*H*-1,3,5-oxadiazin-4-one, and described the preparation of N,N'-bis(methoxymethyl)uron (II), tetrahydro-3,5-bis(methoxymethyl)-4*H*-1,3,5-oxadiazin-4-one.



I



II

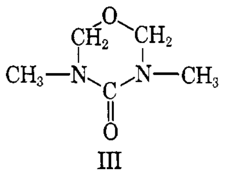
Until now there has been some uncertainty concerning the nature of the so-called "Urons" and in fact I itself has recently been referred to by Marsh[3] as a "hypothetical substance" presumably because it has never been reported.

We repeated Kadowaki's preparation and obtained, as he did, a product having the correct carbon, hydrogen, and nitrogen content for II; however, the methoxyl analysis was much too high and the total formaldehyde was much too low for this structure. In addition, the infrared absorption spectrum of this material had a strong NH band at 2.98 μ which remained even when the product was fractionated carefully. An examination of this product by vapor phase chromatography clearly showed that Kadowaki had a mixture of two major and several minor components.

By the use of a preparative vapor phase chromatographic column the isolation of pure II was easily effected since it came off the column last. The product was identified as II by elemental, methoxyl, and total formaldehyde analyses, and a molecular weight determination.

Since attempts to prepare I by the cyclization of 1,3-bis(hydroxymethyl)urea were unsuccessful, an attempt was made to cleave selectively the methoxymethyl groups of II by acid hydrolysis, using a dilute solution of dimedone since this reagent is acidic and will also tie up the released formaldehyde as methylenebisdimedone. After hydrolyzing, the insoluble methylenebisdimedone was filtered off and from the filtrate a colorless, crystalline solid melting at 170–171° was obtained. This material was identified as the long-sought parent "Uron," I, by elemental analysis, total formaldehyde, and molecular weight determinations.

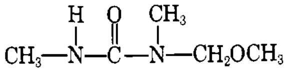
Kadowaki[2] also reported the preparation of a low-melting compound, N,N'-dimethyluron (III), tetrahydro-3,5-dimethyl-4*H*-1,3,5-oxadiazin-4-one, by the reaction of 1,3-dimethylurea with formaldehyde followed by cyclization; this claim was supported by excellent analytical data.



III

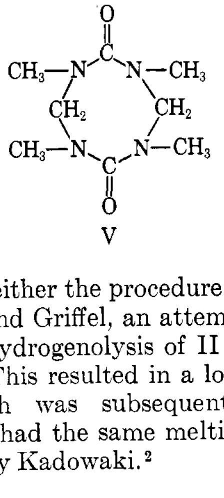
In 1958 Becher and Griffel[4] reported on the infrared absorption spectra of several compounds of the "Uron" class, citing Kadowaki's article and publishing a spectrum in the 6–15-μ region of a product which they assumed to be III. We repeated the preparation of Becher and Griffel and found that the infrared absorption spectrum of the product had a strong NH band at 2.99 μ. A comparison with the spectrum reported by Becher and Griffel showed that both spectra were identical in the 6–15-μ region. Elemental, methoxyl and total formaldehyde analyses showed that the compound obtained by Becher and Griffel was actually 1,3-dimethyl-1-methoxymethylurea (IV).

Numerous attempts were made to prepare III by Kadowaki's procedure but in every case the products were IV and the known compound tetramethyldimethylenediureid[2] (V).



$$CH_3-\overset{\text{H}}{\text{N}}-\overset{\text{O}}{\overset{\|}{\text{C}}}-\overset{\text{CH}_3}{\text{N}}-CH_2OCH_3$$

IV



V

Since III was not obtained by either the procedure of Kadowaki or of that of Becher and Griffel, an attempt was made to prepare it by the hydrogenolysis of II in the presence of Raney nickel. This resulted in a low-melting crystalline solid which was subsequently identified as III; compound III had the same melting point as that originally reported by Kadowaki.[2]

Experimental

All melting points are uncorrected.

Tetrahydro-4*H*-1,3,5-oxadiazin-4-one (I).—A mixture of 2.0 g. (0.0105 mole) of II, 5.70 g. (0.0407 mole) of dimedone and 600 ml. of water was maintained at boiling temperature for 20 min., then cooled to room temperature, and filtered to separate the methylenebis(dimedone). The filtrate was concentrated at 1 mm., while

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(1) Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September 1962.

(2) H. Kadowaki, *Bull. Chem. Soc. Japan*, **11**, 248 (1936).

(3) J. T. Marsh, *Textile Recorder*, **79**, 55 (July, 1961).

(4) H. J. Becher and F. Griffel, *Chem. Ber.*, **91**, 2032 (1958).

maintaining the temperature below 30°, to a volume of 20 ml. and filtered again to remove additional methylenebis(dimedone); the filtrate was again concentrated at 1 mm. to remove the remaining water. The residue (1.10 g.), a tacky solid, on trituration with an acetone–ethanol mixture gave a crystalline solid (0.30 g., m.p. 158–165°); recrystallization from acetonitrile gave colorless needles, m.p. 170–171°; infrared (Nujol mull): 3.15, 3.27, 3.45, 5.95, 6.50, 6.95, 7.15, 7.27, 7.57, 8.60, 8.80, 9.07, 9.55, 9.72, 10.07, 11.50, 12.35 μ.

Anal. Calcd. for $C_3H_6N_2O_2$: C, 35.3; H, 5.95; N, 27.40; CH_2O (total), 58.64; mol. wt., 102. Found: C, 35.06; H, 6.07; N, 27.11; CH_2O (total), 58.64; mol. wt., 104.6 ± 10.

Tetrahydro-3,5-bis(methoxymethyl)-4*H*-1,3,5-oxadiazin-4-one (II). A. Method of Kadowaki.[2]—This procedure gave a liquid which on distillation *in vacuo* through a 6-in. Vigreux column gave 101.7 g. of product. (54%), b.p. 127–137° at 4 mm., $n^{25}D$ 1.4675; infrared (film): 2.95, 3.42, 3.55, 6.02, 6.70, 6.87, 7.20, 7.50, 7.75, 8.57, 9.35, 9.80, 10.35, 10.75, 11.05, 11.87, 12.42, 12.95, 13.32, 14.27 μ.

Anal. Calcd. for $C_7H_{14}N_2O_4$: C, 44.20; H, 7.42; N, 14.74; CH_3O, 32.60; CH_2O (total), 63.05. Found: C, 44.05; H, 7.49; N, 14.61, CH_3O, 37.16; CH_2O (total), 57.8; CH_2O (free), none.

B. Isolation by Vapor Phase Chromatography.—Samples (50 μl.) of the reaction mixture prepared by the Kadowaki procedure were injected into an F&M Model 500 gas chromatograph containing a 12-ft. column packed with 20% silicon gum rubber on Chromosorb W, a flux calcined diatomaceous earth, while using a helium flow rate of 50 ml. per minute. The temperature conditions were maintained as follows: injection part, 270°, block, 300°, and column, 200°. Using these conditions it was found that pure II ($n^{25}D$ 1.4705) had a retention time of 15.4 min. (peak height); samples of II were collected in a tube cooled to −60°; infrared (film): 3.37, 3.50, 5.97, 6.66, 6.82, 7.20, 7.50, 7.75, 8.57, 9.32, 9.80, 10.32, 10.75, 11.05, 12.45, 13.35, 14.25 μ.

Anal. Calcd. for $C_7H_{14}N_2O_4$: C, 44.20; H, 7.42; N, 14.74; CH_3O, 32.60; CH_2O (total), 63.05. Found: C, 44.04; H, 7.39; N, 14.76; CH_3O, 32.49; CH_2O (total), 63.66.

Tetrahydro-3,5-dimethyl-4*H*-1,3,5-oxadiazin-4-one (III).—An amount of 95.1 g. (0.50 mole) of II was dissolved in sufficient methanol to make 400 ml. of solution. The solution was charged to a 1-l. stainless steel autoclave together with 15 g. of Raney nickel and shaken at 150–165° for 10 min. and at 200° for 8 hr.; the autoclave was then cooled to room temperature and vented.

The methanolic solution on concentration *in vacuo* gave 59.8 g. of crude product which on analysis by vapor phase chromatography showed three components; the last component was identified as starting material.

Distillation of the crude product under reduced pressure gave five fractions boiling over a range of 74–90° at less than 1 mm.; vapor phase analysis of each fraction showed that no clear-cut separation was obtained. However, the second fraction (6.4 g., b.p. 74–77° at less than 1 mm.) had the greatest concentration of the first component. When this fraction was cooled at −60° to induce crystallization and twice recrystallized from ether at −60°, the resulting solid (m.p. 36.4°, $n^{26}D$ 1.4808) was found to be chromatographically pure and identified as III; infrared (film): 3.40, 3.47, 6.05, 6.60, 6.82, 7.00, 7.15, 7.57, 7.95, 8.17, 9.05, 9.25, 9.65, 10.35, 12.40, 13.32 μ.

Anal. Calcd. for $C_5H_{10}N_2O_2$: C, 46.10; H, 7.74; N, 21.55; CH_2O (total), 46.1. Found: C, 45.90; H, 7.75; N, 21.45; CH_2O (total), 46.8.

The second component was not isolated; it is believed to be tetrahydro-1,3,5-trimethyl-4*H*-1,3,5-triazin-4-one because the addition of pure tetrahydro-1,3,5-trimethyl-4*H*-1,3,5-triazin-4-one to the crude product greatly increased the peak height of the second component.

Tetrahydro-1,3,5-trimethyl-4*H*-1,3,5-triazin-4-one.—An amount of 17.6 g. (0.20 mole) of 1,3-dimethylurea was dissolved in 33.2 g. (0.41 mole) of 37% formaldehyde and 31.0 g. (0.40 mole) of 40% aqueous methylamine was added dropwise while maintaining the temperature below 35°. The reaction mixture was refluxed for 18 hr. and concentrated at 15 mm. to remove the water. The residue (29.0 g.) was distilled at 0.30 mm. through a micro Vigreux column and the fraction (7.35 g.) boiling at 65–67° was collected and identified as tetrahydro-1,3,5-trimethyl-4*H*-1,3,5-triazin-4-one.

Anal. Calcd. for $C_6H_{13}N_3O$: C, 50.39; H, 9.09; N, 29.35. Found: C, 50.33; H, 9.09; N, 29.35.

1,3-Dimethyl-1-methoxymethylurea (IV).—The procedure used was that described by Becher and Griffel.[4] Distillation of the crude material through a 5-in. Vigreux column gave 75.3 g. (65%) of a colorless liquid (b.p. 99–100° at 1 mm., $n^{26}D$ 1.4626); infrared (film): 2.98, 3.40, 3.55, 6.10, 6.53, 7.10, 7.30, 7.73, 8.0, 8.15, 8.52, 8.70, 9.20, 9.35, 9.70, 10.32, 10.57, 11.06, 11.85, 12.55, 13.00 μ.

Anal. Calcd. for $C_5H_{12}O_2$: C, 45.4; H, 9.15; N, 21.2; CH_3O, 23.45; CH_2O (total), 22.7. Found: C, 46.1; H, 9.33; N, 21.64; CH_3O, 24.19; CH_2O (total), 23.2.

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Polyfunctional Aliphatic Compounds. IV. The Cyclization of Nitriles by Halogen Acids. A New Synthesis of Thiazoles

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α-Cyanoalkyl thiocyanates, prepared from α-chloroalkyl and α-(4-toluenesulfonyloxy)alkyl cyanides, are shown to undergo cyclization to derivatives of 2-bromo-4-aminothiazole by means of hydrogen bromide. Hydrogen chloride is unsatisfactory as a cyclizing agent whereas hydrogen iodide causes further reduction and leads directly to derivatives of the previously inaccessible 4-aminothiazoles. Attempts to apply this synthesis to the preparation of selenazoles were unsuccessful.

In earlier papers,[1,2] we have shown that the cyclization reaction of α,ω-dinitriles can be used effectively for the synthesis of pyridine and isoquinoline compounds. For example, 3-hydroxyglutaronitrile is cyclized to 2-amino-6-bromopyridine hydrobromide by hydrogen bromide and 2-cyanobenzyl cyanide with the same reagent leads exclusively to 3-amino-1-bromoisoquinoline hydrobromide.

All previous work[3] dealing with the action of anhydrous hydrogen halides on dinitriles of the type under discussion has been devoted largely to systems in which the two nitrile groups were joined by a carbon

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(1) Part II, F. Johnson, J. P. Panella, A. A. Carlson, and D. H. Hunneman, *J. Org. Chem.*, **27**, 2473 (1962).

(2) Part III, F. Johnson and W. A. Nasutavicus, *ibid.*, **27**, 3953 (1962).

(3) This has been summarized in part II (ref. 1).