[CONTRIBUTION FROM NITROGEN DIVISION, ALLIED CHEMICAL CORP.]

Isocyanurates. I. Some Condensation Reactions of Cyanuric Acid[1]

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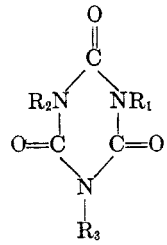
Received March 28, 1960

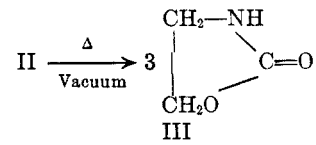
New cyanuric acid derivatives in which side chains contain functional groups have been synthesized. Specific condensations of cyanuric acid have been obtained with ethylene oxide, allyl chloride, ethyl chloroacetate, and acrylonitrile, respectively. All resulting compounds have been shown to exist in the isocyanurate form.

Three general methods are useful for the preparation of isocyanurates (derivatives of *s*-triazine-2,4,6-[1H, 3H, 5H]trione): thermal rearrangement of cyanurates,[3] trimerization of certain alkyl or aryl isocyanates,[4] and condensation of alkyl halides with certain salts of cyanuric acid.[5] Little has been done using the cyanuric acid nucleus as a site for condensation reactions where side chains containing functional groups are formed. We have found that a variety of isocyanurates can be formed under alkaline conditions.



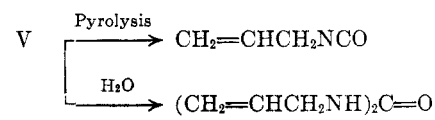
I. R_1, R_2, R_3 = —H
II. R_1, R_2, R_3 = —CH_2CH_2OH
IV. R_1 = —H; R_2, R_3 = —$CH_2CH{=}CH_2$
V. R_1, R_2, R_3 = —$CH_2CH{=}CH_2$
VI. R_1, R_2, R_3 = —$CH_2COOC_2H_5$
VII. R_1 = —H; R_2, R_3 = —CH_2CH_2CN
VIII. R_1, R_2, R_3 = —CH_2CH_2CN
IX. R_1 = —H; R_2, R_3 = —CH_2CH_2COOH
X. R_1, R_2, R_3 = —CH_2CH_2COOH
XI. R_1, R_2, R_3 = —$CH_2CH_2COOC_2H_5$
XII. R_1 = —H; R_2, R_3 = —$CH_2CH_2CH_2NH_2$
XIII. R_1, R_2 = —H; R_3 = —$CH_2CH_2CH_2NH_2$

Ethylene oxide and cyanuric acid (I) in dimethylformamide containing sodium hydroxide catalyst reacted in a 3:1 molar ratio to form tris(2-hydroxyethyl) isocyanurate (II). The isomeric tris(2-hydroxyethyl) cyanurate has been reported[6] from the transesterification of trimethyl cyanurate and ethylene glycol. The iso structure was assigned to our product on the bases of infrared peaks in the carbonyl region, hydrolysis of II to ethanolamine and vacuum pyrolysis of II to 2-oxazolidone (III). The transformation of II to



III, possibly through the hydroxyethyl isocyanate intermediate, offers a convenient synthetic route to III not involving phosgene.

Triallyl isocyanurate (V) has been prepared from the reaction of allyl chloride and potassium cyanate under pressure.[7] We have found that allyl chloride reacts easily with an aqueous solution of cyanuric acid maintained at *p*H 10–10.5 and catalyzed by a small amount of cuprous ion. Both diallyl isocyanurate (IV) and V were isolated from the reaction mixture. The assignment of the iso structure to the products was made on the basis of a comparison with an authentic sample of triallyl cyanurate,[8] which did not show infrared absorption in the carbonyl region shown by our compound. A vacuum pyrolysis of V, containing caustic, gave a small amount of allyl isocyanate. This conversion is similar to the formation of III from II. The identity of the allyl isocyanate was established by its conversion to allylurea and *N*-allyl-*N'*-phenylurea. *N,N'*-diallylurea was also isolated from the pyrolysis residue. A similar reaction has been observed with triethyl isocyanurate. The latter compound forms ethyl isocyanate and *N,N'*-diethylurea under stringent conditions.[9]



The synthesis of tris(2-carbethoxymethyl) isocyanurate (VI) from potassium cyanate and ethyl chloracetate has been reported.[10] Our attempts to repeat this work failed. Subsequently, it was found VI could be prepared in a 60% yield by heating trisodium cyanurate and ethyl chloroacetate at 150–200° for several hours. An attempt to prepare

(1) Presented before the Division of Organic Chemistry at the Southeastern Regional meeting of the American Chemical Society, Richmond, Va., November 5–7, 1959.

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(3) E. Bilmann and J. Bjerrum, *Ber.*, **50**, 506 (1917); A. Hofmann, *Ber.*, **19**, 2061 (1886).

(4) F. Gal, *Compt. rend.*, **61**, 527 (1865); A. Hofmann, *Ber.*, **18**, 765 (1885).

(5) A. Hofmann, *Ber.*, **18**, 2796 (1885); J. Ponomarew, *Ber.*, **18**, 3271 (1885); E. Fisher, *Ber.*, **30**, 2616 (1897).

(6) J. Dudley, *et al.*, *J. Am. Chem. Soc.*, **73**, 2999 (1951).

(7) D. Kaiser and D. Holm-Hansen, U. S. Patent **2,536,-849** (1951).

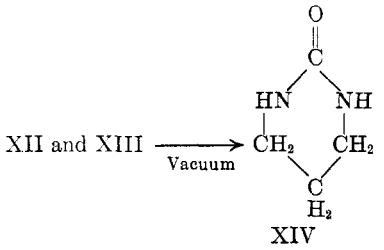
(8) Sample obtained from Monomer-Polymer, Inc.

(9) M. Nencki, *Ber.*, **9**, 1008 (1876).

(10) Ger. Patent **812,312** (1949).

this material under conditions described for triallyl isocyanurate did not yield VI. This can be explained by the rapid hydrolysis of VI to urea derivatives.

Tris(2-cyanoethyl) isocyanurate (VIII) and bis-(2-cyanoethyl) isocyanurate (VII) can be prepared by allowing acrylonitrile and I to react in dimethylformamide containing a quaternary ammonium base catalyst. These new nitriles are readily hydrolyzed by aqueous mineral acid to the corresponding carboxylic acids. The triscarboxylic acid (X) is easily esterified to XI. Catalytic pressure hydrogenation of VIII in ammonia resulted in the loss of one or two of the cyanoethyl groups to give bis(3-aminopropyl) isocyanurate (XII) and mono(3-aminopropyl) isocyanurate (XIII). The ease of decyanoethylation of VIII was shown by its transformation to VII in liquid ammonia at 80°. Tetrahydropyrimidinone-2 (XIV) was isolated



XIV

from a vacuum distillation of mixtures obtained in the above hydrogenations. The latter reaction once again illustrates the apparent ease with which certain alkyl isocyanurates form alkyl isocyanates.

EXPERIMENTAL[11]

Cyanuric acid (I). A three kilogram-sample of urea was melted in a three-l. round bottom flask and immersed in a molten lead bath heated to above 300°. A vigorous evolution of ammonia began and continued for about 1 hr. During this time the flask contents were at about 225°; at the end of the period the contents of the flask had solidified. The pot temperature was maintained at about 250° for an additional hour. The flask was removed from the bath, allowed to cool, and then broken to recover the solid product. The crude product (1900 g.) was ground and refluxed for 2 hr. with 6*N* nitric acid using 3.5 g. of pyrolyzate per 100 ml. of acid. On cooling this solution, long needle-like crystals precipitated, were filtered, washed with water and dried, to give 1600 g. of product (yield 75%). Recrystallizing this material from water gave I of at least 99% purity.

Anal. Calcd. for $C_3H_3N_3O_3$: C, 27.90; H, 2.33; N, 32.56. Neut. equiv., 129.0. Found: C, 28.00; H, 2.57; N, 32.58. Neut. equiv., 128.6.

Tris(2-hydroxyethyl) isocyanurate (II). To 2000 ml. of dimethylformamide in a three-necked flask equipped with submerged gas inlet, stirrer, thermometer, and Dry Ice cooled condenser was added 175 g. I and 3 g. sodium hydroxide. The reaction mixture was heated to 130° and 175 g. gaseous ethylene oxide fed in at a rate to maintain the temperature at 135–140°. On completion of the oxide addition the insoluble sodium cyanurate was removed by filtration and the excess solvent evaporated at reduced pressure. The solid crude product remaining was recrystallized from methanol to give 275 g. of II, m.p. 134–136°.

Anal. Calcd. for $C_9H_{15}N_3O_6$: C, 41.38; H, 6.0; N, 16.09. Found: C, 41.40; H, 5.9; N, 16.08.

Hydrolysis of II in strong sodium hydroxide gave 3 moles of carbon dioxide and ethanolamine. The latter was identified by its index of refraction, boiling point, and infrared spectra. Infrared scan of II in potassium bromide showed absorption at 5.93 μ for the carbonyl group.

Conversion of tri-(2-hydroxyethyl) isocyanurate (II) *to oxazolidone* (III). The vacuum pyrolysis of II (127 g.) was effected by slowly heating to 180° while maintaining the pressure at 1–2 mm. III distilled as a liquid at 130–140° and quickly solidified in the receiver to give 114 g. of product (yield 90%), m.p. 85–87°. The product was further purified by crystallization from chloroform and melted 89–90° (lit.,[12] m.p. 88–90°).

Triallyl isocyanurate (V). To a three-necked flask fitted with addition funnel, stirrer, Dry Ice-acetone cooled reflux condenser, and thermometer was added 65 g. I, 60 g. sodium hydroxide, and 800 ml. water. The solution was heated to 50° and 0.5 g. cuprous chloride catalyst was added. Allyl chloride (250 g.) was introduced dropwise during a 15 min. interval and heating was continued for 15 min. Sufficient 50% sodium hydroxide was added as needed to maintain the *p*H at 10–10.5 throughout the run. The crude product was removed by benzene extraction, washed with water, dried and distilled to remove the benzene solvent. Residual crude V weighed 107.6 g. (yield 86%), b.p. 100–110°/0.2–0.5 mm., m.p. 19–22°, n_D^{30} 1.5110.

Anal. Calcd. for $C_{12}H_{15}N_3O_3$: C, 57.84; H, 6.06; N, 16.86. Found: C, 57.85; H, 6.40; N, 16.86.

Diallyl isocyanurate (IV). The aqueous residue from triallyl isocyanurate synthesis was acidified to *p*H 1–2 with sulfuric acid. The diallyl isocyanurate (IV) was collected by filtration; yield 12.4 g. (11.9%), m.p. 143–145°.

Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.65; H, 5.27; N, 20.10. Found: C, 51.87; H, 5.39; N, 19.90.

Tris(carbethoxymethyl) isocyanurate (VI). Trisodium cyanurate (65.0 g.) and ethyl chloroacetate (122.5 g.) were placed in a 320 cc. stainless steel autoclave and heated at 190–195° for 6 hr. The contents were washed from the cooled autoclave with ethanol and filtered to remove the unchanged sodium cyanurate. The filtrate was distilled under vacuum to remove ethanol and excess ethyl chloroacetate leaving 78.0 g. of crude product (yield 60%), b.p. 200–240°, 0.4–1.0 mm. Redistilling this product gave a fraction boiling at 210–220°/0.45 mm. This liquid crystallized on standing, m.p. 71–78° after recrystallization from ethanol.

Anal. Calcd. for $C_{15}H_{21}N_3O_9$: C, 46.51; H, 5.4; N, 10.85. Found: C, 46.65; H, 5.89; N, 10.72.

Attempted saponification of VI in 100 ml. of 5% sodium hydroxide at reflux resulted in ring rupture with the formation of *N,N*,-dicarbethoxymethyl urea, m.p. 148–150° (from ethanol). An authentic sample prepared by the reaction of ethyl glycinate and phosgene[13] failed to depress the melting point of the solid hydrolysis product.

Cyanoethyl isocyanurates. A slurry of I (43 g.) in 250 ml. dimethylformamide containing 12 ml. of "Triton B" (trimethylbenzyl ammonium hydroxide, 38% in water) was prepared. Acrylonitrile (53 g.) was added dropwise over a period of 1 hr. The slurry was refluxed at 120–130° for 2.5 hr. A clear solution formed which on cooling gave 31.8 g. (yield 33%) of tris(2-cyanoethyl) isocyanurate (VIII), m.p. 220–230°; recrystallized from dimethylformamide, m.p. 228–230°.

Anal. Calcd. for $C_{12}H_{12}N_6O_3$: C, 50.00; H, 4.17; N, 29.18. Found: C, 50.01; H, 4.26; N, 29.10.

Evaporation of the dimethylformamide solution from the synthesis of VIII above at reduced pressure gave 56.4 g. (yield 67%) of bis(2-cyanoethyl) isocyanurate (VII),

(11) Temperatures and melting points reported are uncorrected.

(12) S. Frankel and M. Cornelius, *Ber.*, **51**, 1654 (1918).

(13) E. Fisher, *Ber.*, **34**, 440 (1901).

m.p. 190–210°; recrystallized from ethanol, m.p. 216–218°.

Anal. Calcd. for $C_9H_9N_5O_3$; C, 46.00; H, 3.83; N, 29.80. Found: C, 46.13; H, 3.68; N, 30.02.

A mixture of VIII (15 g.) and 150 cc. concd. hydrochloric acid heated at reflux for 4 hr. gave 17.9 g. (yield 99%) of tris(2-carboxyethyl) isocyanurate (X), m.p. 226–230°; recrystallization from water, m.p. 228–229°.

Anal. Calcd. for $C_{12}H_{15}N_3O_9$; C, 41.75; H, 4.35; N, 12.17. Neut. equiv., 115.0. Found: C, 41.87; H, 4.39; N, 12.10. Neut. equiv., 115.2.

Hydrolysis of VII (7.9 g.) as described above gave 9.0 g. (yield 99%) of bis(2-carboxyethyl) isocyanurate (IX), m.p. 287–289° after recrystallization from water.

Anal. Calcd. for $C_9H_{11}N_3O_7$: C, 39.57, H, 4.03; N, 15.38. Neut. equiv., 136.5 and 91.0. Found: C, 39.69; H, 3.91; N, 15.25. Neut. equiv., 135.7 and 91.5.

Tris(2-carboxyethyl) isocyanurate (X) (34.5 g.) refluxed with 200 ml. of 5*N* absolute ethanolic hydrogen chloride for 2 hr. gave 40.0 g. (yield 93%) of tris(2-carbethoxyethyl) isocyanurate (XI), m.p. 50–52° after recrystallization from ethanol.

Anal. Calcd. for $C_{18}H_{27}N_3O_9$: C, 50.35; H, 6.33; N, 9.80. Found: C, 50.16; H, 6.33; N, 9.78.

Hydrogenation of tris(2-cyanoethyl) isocyanurate (VIII). A stainless steel autoclave containing 50.0 g. of VIII, 17.1 g. Raney nickel and 61.3 g. anhydrous ammonia was pressurized to 1400 p.s.i.g. with hydrogen and heated to 80–82° for 5 hr. Additional hydrogen was added as the reaction proceeded until theoretical uptake was realized.

The autoclave was cooled, vented, and the product washed from the bomb with absolute ethanol and filtered from the catalyst. Evaporation of the alcohol solution gave a sirupy mass practically free of ammonia. Extraction of the sirupy mass with ethanol gave 23.9 g. of bis(3-aminopropyl) isocyanurate (XII), m.p. 212–215°; crystallized from water and then from *N*-methylpyrrolidone, m.p. 205–207°.

Anal. Calcd.: Mol. wt., 243. Neut. equiv., 121.5 and 243. Found: Mol. wt. by freezing point depression of water: 236. Neut. equiv., 126 and 252.

Reaction with dilituric acid gave a didilituric salt.

Anal. Calcd. for $C_{17}H_{23}N_{11}O_{13}$: C, 34.62; H, 3.90; N, 26.15. Found: C, 34.64; H, 3.77; N, 25.93.

A mixture of 43.0 g. of VIII, 100 ml. of ethanol, 15.6 g. of wet W-2 Raney nickel and 18.1 g. of ammonia was placed in a 320 ml. autoclave and heated to 155–160° for 3 hr. at 2000 p.s.i.g. hydrogen pressure. The autoclave was cooled, vented, and the contents washed out with ethanol. The catalyst was filtered and the solution concentrated to give 15.0 g. mono(3-aminopropyl) isocyanurate (XIII).

Anal. Calcd. for $C_6H_{10}N_4O_3$: C, 38.75; H, 5.38; N, 30.10. Neut. equiv., 186. Found: C, 39.05; H, 5.64; N, 30.08; Neut. equiv., 187.

Attempted isolation of the above amines *via* vacuum distillation gave appreciable quantities of tetrahydropyrimidinone-2 (XIV), m.p. 263–265° (lit.,[14] m.p. 263–265°). The identity of the pyrimidone-2 was established by hydrobromic acid hydrolysis to 1,3-diaminopropane and comparison of the dihydrochloride and the picrate salts of the latter with authentic materials. The known and the unknown salts gave identical infrared spectra.

Conversion of tris(2-cyanoethyl) isocyanurate (VIII) *to bis(2(cyanoethyl) isocyanurate* (VII). Heating VIII (50 g.) and 70 g. of anhydrous ammonia in a 320-ml. autoclave for 4 hr. at 80° gave 39.1 g. of VII (yield 96%), m.p. 216–218°. A mixed melting point with an authentic sample of bis(2-cyanoethyl) isocyanurate gave no depression. Infrared spectra of the compounds were identical.

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(14) E. Fisher and H. Koch, *Ann* **232**, 224 (1886).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XXXIX. An Alternative Synthesis of 9-(2′,3′-Anhydro-β-D-ribofuranosyl)adenine

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Received March 30, 1960

A seven-step synthesis of 9-(2′,3′-anhydro-β-D-ribofuranosyl)adenine (VIII) from 9-(β-D-xylofuranosyl)adenine (I) was accomplished. The direct coupling route to VIII using 2-*O*-acetyl-5-*O*-benzoyl-3-*O*-(*p*-tolylsulfonyl)-D-xylofuranosyl chloride (XIb) was explored but proved less satisfactory than the use of the 5-*O*-methoxycarbonyl analog (XIa) of XIb.

In a previous paper[2] from these laboratories, the synthesis of the anhydronucleoside (VIII) from 1,2-di-*O*-acetyl-5-*O*-methoxycarbonyl-3-*O*-tosyl-D-xylofuranose (X) was described. The over-all yield of this versatile intermediate (VIII) from X was only 8.9% with essentially all of the low yield being attributable to difficulties in the coupling reaction between the chlorosugar (XI) and chloromercuri-6-benzamidopurine. It was felt that better over-all yields of X might be obtainable by carrying out the necessary transformations on a suitable and more readily accessible preformed nucleoside. The coupling reaction between 2,3,5-tri-*O*-benzoyl-D-xylofuranosyl bromide and chloromercuri-6-benzamidopurine has been reported to give approximately 45% of 9-(β-D-xylofuranosyl)adenine (I)[3] and this nucleoside (I) appeared to be a suitable starting material for an alternative synthesis of VIII.

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, *cf.* W. A. Skinner, K. A. Hyde, H. F. Gram, and B. R. Baker, *J. Org. Chem.*, in press.

(2) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 3967 (1959).

(3) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).