Triazines from Formaldehyde and Nitriles[1]

By Thomas L. Gresham and Thomas R. Steadman

The recent publication of a description[2] of the reaction of nitriles with formaldehyde (I) to yield hexahydro-1,3,5-tris-acyl-*s*-triazines prompts us to record such of our own independently performed experiments as will supplement those of Gradsten and Pollock.

We found that the reactions were best conducted in the presence of an excess of the nitrile, employing either α-polyoxymethylene or trioxane as the source of I. In the case of the preparation of hexahydro-1,3,5-tris-acrylyl-*s*-triazine (II), Gradsten and Pollock emphasized the need for freshly distilled acrylonitrile. We found in a series of five experiments that better yields and more easily controlled reactions consistently resulted from using commercially available acrylonitrile.[3] We believe this finding may be explained by the tendency of the impurities in the acrylonitrile to inhibit polymerization, since reactions involving freshly distilled acrylonitrile occasionally became uncontrollably violent, with consequent loss of material through polymerization and charring. Evidence for the identity of the products beyond that furnished by Gradsten and Pollock[2] was obtained by hydrolysis to recognizable fragments and molecular weight determinations.

The triazines described in this note are under study at the Sloan-Kettering Institute for Cancer Research. A preliminary report from Dr. C. Chester Stock has indicated that the results with hexahydro-1,3,5-tris-isobutyryl-5-triazine against mouse leukemia and sarcoma 180 have been encouraging enough to make this class of compounds worthy of further investigation. A full description of these chemotherapeutic studies will be published elsewhere.

Experimental

Hexahydro-1,3,5-tris-acrylyl-5-triazine (II).—In a two-liter three-necked flask fitted with a Hershberg tantalum wire stirrer, a reflux condenser and a dropping funnel, was placed 150 ml. of commercial acrylonitrile and 15 ml. of concentrated sulfuric acid. This solution was heated to 70° and a slurry of 90 g. of α-polyoxymethylene in 350 ml. of acrylonitrile was added over a period of an hour, during which time the temperature of the reaction mixture remained at 80° without further heating. After all of the slurry had been added, the reaction mixture was allowed to cool and the crystalline product filtered from the ice-cold mother liquors. These crystals were washed with 500 ml. of 1% sodium hydroxide and then with 500 ml. of water. The dried, crude product weighed 148 g. Recrystallization from ethanol gave 129.5 g. of II (52% yield). It should be noted that II polymerized quite readily, even in boiling alcohol or chloroform. Rapid cooling of clarified, saturated solutions of II ensured the absence of polymer in the product.

Anal. Calcd. for $C_{12}H_{15}N_3O_3$: C, 57.81; H, 6.07; mol. wt., 249.2. Found[4]: C, 57.70, 57.87; H, 6.17, 6.17; mol. wt.[5] (cryoscopic in acetic acid), 236, 228.

Hydrogenation of 1.50 g. of II in ethanol over Adams catalyst required 93 minutes at 30°, yielding 1.3 g. of hexahydro-1,3,5-tripropionyl-*s*-triazine (III), m. p. 149–150° (cor.) (in a sealed tube) after one recrystallization from ethanol. When crystals of III were held in a sealed tube for a few minutes at a temperature a little above the melting point, the melt resolidified and melted subsequently at 170–171° (cor.). Comparison of the infrared absorption curves[6] showed that the substances melting at these two temperatures were identical. In other experiments, the higher melting form was isolated directly as fluffy white needles.

Anal. Calcd. for $C_{12}H_{21}N_3O_3$: C, 56.45; H, 8.29; N, 16.46; mol. wt., 255. Found[7]: C, 56.65, 56.63; H, 8.21, 8.28; N, 16.37, 16.49; mol. wt. (ebullioscopic, benzene), 265, 261.[5]

Hydrolysis of 1.8 g. of III by 50 ml. of 10% sulfuric acid gave formaldehyde, which was identified as the 2,4-dinitrophenylhydrazone (m. p. 163° after one recrystallization from alcohol), and propionic acid, which was converted to the *p*-toluidide for identification, m. p. 124.5–125.5°. A mixed melting point showed no depression. Ammonia was liberated from the acid hydrolysis residue when it was made alkaline.

Hexahydro-1,3,5-trimethacrylyl-*s*-triazine.—To a solution of 90 g. of trioxane in 201 g. of inhibited methacrylonitrile[8] was added 10 ml. of concentrated sulfuric acid. The temperature of the reaction rose to 90°, and some formaldehyde was lost from the reaction vessel. After one hour at 90° (using external heating as necessary), a solution of 8 g. of sodium hydroxide in 200 ml. of water was added to the reaction mixture. The oily product crystallized on cooling and scratching to give 122 g. of crude product (41.9% yield). Recrystallization from ethanol resulted in 113.5 g. of crystals, m. p. 149.5–151° (cor.). In contrast with II this substance showed no signs of undergoing thermally induced polymerization at temperatures as high as its melting point.

Anal. Calcd. for $C_{15}H_{21}N_3O_3$: C, 61.83; H, 7.27; N, 14.42; mol. wt., 291.3. Found: C, 61.80, 61.83; H, 7.24, 7.38; N, 14.41, 14.47[4]; mol. wt., 292 ± 2 (ebullioscopic, benzene).[5]

From the hydrogenation of 2 g. of hexahydro-1,3,5-trimethacrylyl-*s*-triazine in ethanol over Adams catalyst there was isolated 1.5 g. of hexahydro-1,3,5-tris-isobutyryl-*s*-triazine (IV), m. p. 149–150° (cor.).

Anal. Calcd. for $C_{15}H_{27}N_3O_3$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.81, 60.82; H, 9.15, 9.28; N, 14.04, 14.05.[4]

Hydrolysis of 7.5 g. of IV with 10% sulfuric acid gave formaldehyde, ammonium sulfate and isobutyric acid, which was identified as the *p*-toluidide, m. p. 108–109°. A mixed melting point with an authentic specimen showed no depression.

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[1] Presented before the Division of Organic Chemistry at the 114th Meeting of the American Chemical Society, St. Louis, Missouri, September 6, 1948.

[2] Gradsten and Pollock, This Journal, **70**, 3079 (1948).

[3] American Cyanamid Co., New York 20, N. Y.

[4] Analysis by J. R. Kubik.

[5] Determination by D. M. Kurtz.

[6] Data by J. J. Shipman.

[7] Huffman Microanalytical Laboratories, Denver 2, Colorado.

[8] Shell Development Co., Emeryville, California.

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Dearrangement of Nitroaminoguanidine in a Solution of Ammonium Carbonate

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Nitroguanidine dearranges rapidly in hot, aqueous ammonium carbonate solution with the evolution of nitrous oxide and the formation of guanidine carbonate in practically quantitative yield.[1] Under the same conditions of hydrolysis the N-alkyl-N′-nitroguanidines yield nitrous oxide, the alkylamine, and guanidine carbonate; small quantities of alkylguanidine also have been isolated.[2] In connection with some other work, the hydrolysis of nitroaminoguanidine[3] in a solution of ammonium carbonate was investigated and found to be analogous to these other reactions. The following products were isolated and identified: hydrazine, guanidine, nitroguanidine, aminoguanidine and diaminoguanidine. The dearrangement mechanism for nitroguanidine derivatives, as proposed by Davis and co-workers,[1,2] satisfactorily accounts for the formation of these compounds

$$\mathrm{NH_2NHC(NH)NHNO_2}\left\{\begin{array}{ll} \rightleftarrows \mathrm{NH_2NH_2 + N{\equiv}C{-}NHNO_2} & (1) \\ \rightleftarrows \mathrm{NH_2NO_2 + N{\equiv}C{-}NHNH_2} & \\ \quad\;\downarrow & \\ \quad\mathrm{N_2O + H_2O} & (2) \end{array}\right.$$

$$\mathrm{N{\equiv}CNHNO_2 + NH_3 \rightleftarrows NH_2C(NH)NHNO_2} \quad (3)$$

$$\mathrm{N{\equiv}CNHNH_2 + NH_3 \rightleftarrows NH_2C(NH)NHNH_2} \quad (4)$$

$$\mathrm{N{\equiv}CNHNH_2 + NH_2NH_2 \rightleftarrows NH_2NHC(NH)NHNH_2} \quad (5)$$

$$\begin{array}{l} \mathrm{NH_2{-}C(NH)NHNO_2 \rightleftarrows N{\equiv}C{-}NH_2 + NH_2NO_2} \\ \hspace{13em}\downarrow \\ \hspace{11em}\mathrm{N_2O + H_2O} \quad (6) \end{array}$$

$$\mathrm{N{\equiv}C{-}NH_2 + NH_3 \rightleftarrows NH_2C(NH)NH_2} \quad (7)$$

Experimental

Twelve grams of nitroaminoguanidine (96% purity), 15.1 g. of ammonium carbonate, and 50 ml. of water were heated at 60–65° for twenty-five minutes. Gas was evolved vigorously and the solution developed an orange-red color. The reaction was completed by raising and holding the temperature at 75–80° for ten minutes. After adding 25 ml. of water, the solution was cooled to 30°, acidified with concentrated nitric acid, and finally chilled overnight at 0°. The white, fluffy solid (A) was recovered by filtration and washed with two 15-ml. portions of ice-cold water. The yield of dried product amounted to 2.4 g.; m. p. 170–185° (dec.). The filtrate and washings were combined and saved (B).

I. **Separation and Identification of Nitroguanidine and Nitroaminoguanidine in Fraction (A).**—The crude solid material was dissolved in 75 ml. of boiling water containing 1.0 ml. of glacial acetic acid. One ml. of benzaldehyde was added with stirring. A white precipitate formed immediately and was removed by filtration from the hot solution. The yield was 0.3 g.; m. p. 180–181°. Recrystallization from 95% ethyl alcohol gave hair-like needles, m. p. 185–186°; a mixed m. p. with the nitroguanyl hydrazone of benzaldehyde[4] was the same. From the filtrate, there was recovered after evaporation and cooling, 1.7–1.8 g. of material melting with decomposition at 232–235°. A mixed m. p. with nitroguanidine was 235–236°; an X-ray powder pattern on this material was identical with that obtained on a known specimen of nitroguanidine. The recovery corresponded to an 18–19% conversion to nitroguanidine.

II. **Isolation and Identification of Hydrazine, Aminoguanidine, and Diaminoguanidine in Filtrate (B).**—The filtrate and washings were heated to 60° and shaken for fifteen minutes with 15 ml. of benzaldehyde. After the solution remained at 0° for several hours, the precipitate was removed by filtration. The filtrate again was retained (C). The yield of dry hydrazones was 19.9 g. By extraction with four 50-ml. portions of boiling petroleum ether (b. p. 65–75°), 5.2 g. of crude benzalazine, m. p. 70–75°, was recovered. Recrystallization from either petroleum ether or ethyl alcohol raised the m. p. to 92–93°; a mixed m. p. with an authentic sample of benzalazine was the same. The yield of crude azine corresponded to a 27% conversion of the nitroaminoguanidine to free hydrazine.

The benzalazine-free hydrazones were extracted next with one 1500-ml. portion and four 200-ml. portions of boiling water. There was 0.5 g. of insoluble residue; m. p. 182–183°; a mixed m. p. with the nitroguanyl hydrazone of benzaldehyde was 183°.

The aqueous extract was cooled slowly to room temperature and the solid material removed. The yield of dried product was 5.2 g.; m. p. 154–156°. Several attempts to purify this fraction as the nitrate salt were unsuccessful. However, when it was converted into the free base and recrystallized from ethyl alcohol, yellow plates and needles, melting sharply at 180–181°, were obtained. A mixed m. p. with a known sample of dibenzaldiaminoguanidine was 181°; with benzalaminoguanidine, 153–157°. This crude nitrate also gave a sparingly soluble picrate from hot 95% ethyl alcohol, that melted at 242° without further purification; a mixed melting point with a pure specimen of dibenzaldiaminoguanidine picrate was 242–243°. The yield of diaminoguanidine was approximately 17%.

The 2300 ml. of mother liquor left after removing the dibenzaldiaminoguanidine nitrate were evaporated to 250 ml. and cooled for several days at 0°. Ultimately, 6.7 g. of crude benzalaminoguanidine nitrate (32% yield) were recovered; m. p. 155°. After repeated recrystallizations from water, the product melted at 167°; a mixed m. p. with benzalaminoguanidine nitrate was 170–171°. The picrate from alcohol decomposed at 253–254°; a mixed melting point with a known specimen was not depressed.

III. **Isolation of Guanidine in Filtrate (C).**—The aqueous filtrate from which the hydrazones had been separated was evaporated to dryness on the water-bath. By fractionally crystallizing this residue from 95% ethyl alcohol, most of the ammonium nitrate was separated from the small quantity of guanidine nitrate that remained in the last mother liquor. Final isolation of the guanidine as a reasonably pure derivative was made by preparing and fractionating the picrates from ethyl alcohol. The yield was 0.5 g.; m. p. 314–318° with decomposition (Davis[5] reports a melting point of 318.5–319.5° for guanidine picrate).

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[1] Davis and Abrams, *Proc. Am. Acad. Arts and Sciences*, **61**, 437 (1926).

[2] Davis and Elderfield, THIS JOURNAL, **55**, 731 (1933).

[3] Phillips and Williams, *ibid.*, **20**, 2465 (1928).

[4] Whitmore, Revukas and Smith, *ibid.*, **57**, 706 (1935).

[5] Davis, "Chemistry of Powder and Explosives," John Wiley & Sons, Inc., New York, N. Y., 1943, p. 168.

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Small-Angle Scattering of X-Rays and the Micellar Structure in Cellulose Fibers

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In a previous communication[1] it was shown that different cellulose fibers produce different

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[1] A. N. J. Heyn, THIS JOURNAL, **70**, 3138 (1948); comp. also *Text. Res. J.*, **19**, 163 (1949).