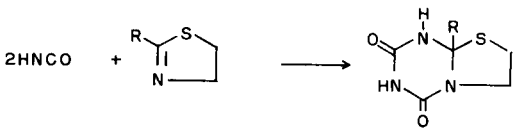
Department of Chemistry, Fisk University

Preparation of Some 2,3,5,6,7,8,8a-Heptahydrothiazolo[3,2-*a*]-*s*-triazine-5,7-diones (1)

H. P. Penner and Alfred R. Conklin, Jr.

A number of 2-substituted-2-thiazolines have been found to react readily with two moles of isocyanic acid in ethereal solution to give 2,3,5,6,7,8,8a-heptahydrothiazolo-[3,2-*a*]-*s*-triazine-5,7-diones (IIa-e). Preliminary reports indicate some activity of these compounds against Walker's carcinosarcoma 256 in rats.

As a result of attempts to prepare some bicyclic thiazolo derivatives of biological interest it was deemed important to investigate the reactions between isocyanic acid (2) and 2-substituted-2-thiazolines. We have found that two moles of isocyanic acid in ethereal solution react very readily with a number of 2-substituted thiazolines to form thiazolo-*s*-triazine derivatives as follows:



I II

a, R = CH_3

b, R = $CH(CH_3)_2$

c, R = $CH_2C_6H_5$

d, R = C_6H_5

e, R = C_4H_3O (2-furyl)

Lange and Hale (3) have described the reactions of Schiff bases with isocyanic acid. They found that when the nitrogen atom of the Schiff base contained an aliphatic group, two moles of isocyanic acid reacted to form a six membered ring; and if the substituent on nitrogen was an aromatic group, one mole of isocyanic acid reacted to give a four-membered cyclo-addition product. In their work isocyanic acid was presumed to form *in situ* with a solution of potassium cyanate in glacial acetic acid.

In our work all of the 2-substituted thiazolines tested reacted with two moles of isocyanic acid, even when a deficiency of the acid was present or the thiazoline substituents were rather widely varied as shown above (Ia-e). While the reactions appeared to be complete within a few minutes, the mixtures were usually kept for an overnight period before the products were collected. Isocyanic acid was prepared by depolymerization of cyanuric acid at 700° in a stream of nitrogen and collection in cold ether, which solvent appeared to give better results than tetrahydrofuran. In all of these reactions the only products isolated were the indicated triazine derivatives. Occasionally the crude products had melting points that were slightly higher than those of the pure products finally obtained. This may have been due to the presence of some repolymerized cyanuric acid, which decomposes slowly above 360°.

The infrared spectra of all of these compounds show similar patterns. All have a broad band in the region 3400 and 2700 cm^{-1} which is similar to the absorption of cyanuric acid in this region. There also are doublets near 1700 cm^{-1} characteristic of the carbonyl absorptions in *s*-triazine ring systems (4). In the case of the methyl-substituted product (IIa) there also appears a third band at 1670 cm^{-1} possibly indicating either some tautomerism or Fermi resonance of an overtone of a strong band in the 800 cm^{-1} region.

The thiazolines (Ia-e) were prepared by reported procedures (5,6) from the reaction of the corresponding *N*-(2-hydroxyethyl)amide and phosphorus pentasulfide. While the yields were generally low, 10-20% except for 40% for the benzyl derivative (Ic), the products were usually quite easily isolated. The 2-methyl-2-thiazoline (Ia) was also prepared from thioacetamide and 2-bromoethylamine hydrobromide according to the method of Gabriel (7), but this method did not appear to offer any advantage. The 2-(2-furyl)-2-thiazoline (Ie) and the picrate of 2-isopropyl-2-thiazoline (Ib) have not been previously reported.

Compounds IIa, IIb, and IIc are currently being

screened for activity against cancer under the auspices of the Cancer Chemotherapy National Service Center of the National Cancer Institute. Preliminary reports have shown that they have some activity against Walker's carcinosarcoma 256 (intramuscular) in Fischer 344 rats. For each test a dose of 400 mg. per kg. was administered intraperitoneally in saline for four consecutive days before sacrifice. Results are summarized in Table I.

TABLE I

Results of Cancer Screening Tests in Rats

Compound	Survivors	Av. tumor wt. (g.) Test	Control	Relative tumor wt., Test/Control
IIa	6 of 6	4.2	8.2	0.51
IIa	6 of 6	7.1	7.3	0.97
IIb	6 of 6	4.8	8.2	0.58
IIc	5 of 6	5.0	8.2	0.60

According to the screening procedure compound IIa in the original series passed stage 1 of the sequential screen (Test/Control is equal to or less than 0.53). A second series on IIa performed for confirmation showed no appreciable activity.

EXPERIMENTAL

Melting points are uncorrected and were determined either on a Mel-Temp (Laboratory Devices, Cambridge, Massachusetts) or on a modified Herschberg apparatus. Except as noted the infrared spectra were prepared from mulls with a Perkin-Elmer Model 337 Infracord. Nujol was used in the region of 1300 cm^{-1} to 600 cm^{-1}, and either halocarbon oil or hexachlorobutadiene was used between 4000 and 1300 cm^{-1}. Combustion analyses were by the Schwarzkopf Microanalytical Laboratory, Woodside, New York.

Preparation of the 2-Thiazolines (Ia-e).

The thiazolines were prepared according to the method described by Wenker (5), the 2-phenyl and 2-(2-furyl) derivatives (Id and Ie) with Sheehan's modification (6). It was found, however, that the best results were obtained and spontaneous reaction generally ensued when the phosphorus pentasulfide was added to the *N*-substituted amides at 40° rather than at lower temperatures. Yields were generally between 10 and 20% except for the 2-benzylthiazoline (Ic) which was obtained in 40% yield. The 2-(2-furyl)-2-thiazoline (Ie) has not been previously reported. It was prepared from 28.0 g. (0.25 mole) of 2-furoic acid (Aldrich) and 15.2 g. (0.25 mole) of 2-aminoethanol (Eastman white label). The mixture was heated to 200° and allowed to cool to 40° when 17.5 g. (0.078 mole) of phosphorus pentasulfide was added and the mixture warmed to initiate the reaction. The product isolated according to Sheehan's procedure boiled at 94° (4 mm.) and weighed 3.75 g. (9.8%). Redistillation (98-100° at 5 mm.) gave an analytical sample.

Anal. Calcd. for C_7H_7NOS: C, 54.88; H, 4.61; N, 9.14; S, 20.93. Found: C, 54.76; H, 4.57; N, 9.24; S, 21.19.

The picrate of 2-isopropyl-2-thiazoline (Ib) is also unreported. It was prepared in 72% yield, m.p. 116-119°, from ethereal solutions of the thiazoline and picric acid. The crude product was purified by five recrystallizations from 1:1:1 mixture of methanol, methyl ethyl ketone, and petroleum ether, m.p. 117.5-119°.

Anal. Calcd. for $C_{12}H_{14}N_4O_7S$: C, 40.22; H, 3.94; N, 15.64. Found: C, 40.28; H, 4.10; N, 15.58.

2-Methyl-2-thiazoline was also prepared by the method reported by Gabriel (7). Four grams (0.053) of thioacetamide and 10.0 g. (0.049 mole) of 2-bromoethylamine hydrobromide gave 0.8 g. (16%) of product.

Cyanuric Acid.

No detailed procedure for conversion of cyanuric chloride to cyanuric acid is given in the literature. The following method was found to be convenient. A sample of 185 g. of cyanuric chloride (American Cyanamid complimentary research sample or Eastman yellow label) was suspended in 300 ml. of glacial acetic acid and the mixture kept at reflux for an overnight period. Shorter periods of reflux did not always result in complete conversion. The product was separated by filtration and washed first with large volumes of water, then with methanol, and finally with acetone to remove any unreacted cyanuric chloride and to promote drying. The infrared spectrum was the same as that reported in the literature (4).

Isocyanic Acid.

The method used was based on the procedure of Close and Spielman (8). About 15 g. of cyanuric acid was added to a 40 by 200 mm. test tube equipped with a 6 mm. inlet tube extending to the bottom and a 10 mm. exit tube extending just through a cork stopper in the test tube. The exit tube led through the two electric furnaces of a Sargent No. S-21580 combustion apparatus and then into another 40 by 200 mm. test tube containing anhydrous ether cooled in an ice bath. The furnaces were heated to 700° while the system was flushed with dry nitrogen. The cyanuric acid was then strongly heated with a Paul Haack burner while the nitrogen flowed at the rate of about one bubble per second. It was found that slower flow rates and/or lower furnace temperatures resulted in clogging of the tubes before an appreciable amount of isocyanic acid was collected. The minimum concentration of the isocyanic acid in the ether was estimated by addition of aniline to an aliquot portion and weighing the amount of phenylurea formed. The solutions were usually 2 to 5 *M*.

2,3,5,6,7,8,8a-Heptahydro-8a-methylthiazolo[3,2-*a*]-*s*-triazine-5,7-dione (IIa).

To 0.41 g. (0.004 mole) of 2-methyl-2-thiazoline was added 1 ml. (0.004 mole) of ethereal isocyanic acid solution. The product which was collected after an overnight period weighed 0.22 g. and melted over a range around 180°. Yields of crude product from other runs ranged from 20 to 79%. Purification was effected by solution either in tetrahydrofuran or in dioxane and precipitation with petroleum ether (b.p. 30 to 60°), m.p. 190-191°; infrared cm^{-1}, 3300(f), (9), 3160(f), 2980(f), 2820(f), 1700(s), 1735(s), 1660(m), 1600(m), 1465(m), 1425(m), 1350(w), 1255(w), 1240(w), 1185(m), 1077(w), 1040(w), 970(w), 860(f), 770(f), 755(f), 790(m), 739(w), 725(w), 700(m).

Anal. Calcd. for $C_6H_9N_3O_2S$: C, 38.48; H, 4.85; N, 22.45. Found: C, 38.32; H, 4.97; N, 22.71.

2,3,5,6,7,8,8a-Heptahydro-8a-isopropylthiazolo[3,2-*a*]-*s*-triazine-5,7-dione (IIb).

To 3.7 g. (0.032 mole) of 2-isopropyl-2-thiazoline was added with stirring 10 ml. of ethereal isocyanic acid solution (0.063 mole) and the mixture allowed to stand overnight. Upon filtration 2.42 g. (47.4%) of product, m.p. 213-216°, was obtained. After five recrystallizations from ethyl acetate the compound melted at 216-218°; infrared cm^{-1}, 3345(f) (9), 3245(f), 3150(f), 3050(f), 2955(f), 2945(f), 2860(f), 1710(m), 1755(m), 1690(s), 1500(s), 1380(w), 1210(s), 1165(m), 1120(m), 1070(m), 1030(m), 970(m), 960(m), 870(f), 820(f), 770(f), 750(f), 725(f), 690(w), 670(w), 605(m).

Anal. Calcd. for $C_8H_{13}N_3O_2S$: C, 44.63; H, 6.08; N, 19.52. Found: C, 44.84; H, 6.03; N, 19.20.

2,3,5,6,7,8,8a-Heptahydro-8a-benzylthiazolo[3,2-*a*]-*s*-triazine-5,7-dione (IIc).

To 0.25 g. (0.0013 mole) of 2-benzyl-2-thiazoline was added 2 ml. (0.0026 mole) of ethereal isocyanic acid solution. The product collected after an overnight period weighed 0.28 g. and melted at 198-205°. The product was recrystallized five times from methyl ethyl ketone to give an analytical sample which melted at 220-222°; infrared cm^{-1}, 3240(f) (9), 3220(f), 3050(f), 2980(f), 2970(f), 2935(f), 1715(s), 1685(s), 1515(s), 1475(m), 1430(w), 1380(m), 1370(m), 1123(m), 1075(s), 1033(m), 975(s), 960(m), 930(w), 875(f), 820(f), 775(f), 750(f), 726(f), 690(m), 608(s), 565(s).

Anal. Calcd. for $C_{12}H_{13}N_3O_2S$: C, 54.74; H, 4.98; N, 15.96. Found: C, 54.98; H, 5.05; N, 15.77.

2,3,5,6,7,8,8a-Heptahydro-8a-phenylthiazolo[3,2-*a*]-*s*-triazine-5,7-dione (IId).

To 2.0 g. (0.012 mole) of 2-phenyl-2-thiazoline in 2 ml. of anhydrous ether was added 6 ml. (0.02 mole) of ethereal isocyanic acid solution. After an overnight period 1.5 g. of product was collected, m.p. 210-212°. The product was purified by solution in tetrahydrofuran and precipitation with petroleum ether, to give an ill-defined but reproducible melting point of 204.5-206.5°; infrared cm^{-1}, 3240(f) (9), 3175(f), 3030(f), 2925(f), 2860(f), 2790(f), 1700(s), 1650(s), 1470(s),

1340(s), 1285(s), 1270(s), 1195(s), 1129(s), 1070(m), 1022(m), 999(m), 905(s), 835(s), 780(f), 765(f), 740(f), 691(s), 651(s), 570(s), 550(s), 540(s), 510(w), 470(s), 405(m), (KBr).

Anal. Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.01; H, 4.45. Found: C, 53.07; H, 4.59.

2,3,5,6,7,8,8a-Heptahydro-8a-(2-furyl)-thiazolo[3,2-*a*]-*s*-triazine-5,7-dione (IIe).

To 0.30 g. (0.002 mole) of 2-(2-furyl)-2-thiazoline in 5 ml. anhydrous ether was added 1.5 ml. (0.005 mole) of ethereal isocyanic acid solution. After an overnight period 0.11 g. (20%) of product was collected, m.p. 175-185°. Purification was effected by solution in tetrahydrofuran and precipitation with petroleum ether, m.p. 196-197°; infrared cm^{-1} 3280(s), 3230(s), 3080(m), 2930(w), 2880(w), 1720(s), 1685(s), 1515(m), 1475(w), 1460(w), 1425(w), 1370(m), 1340(w), 1271(s), 1238(m), 1212(m), 1200(m), 1165(w), 1150(s), 1133(s), 1100(w), 1072(m), 1000(m), 960(w), 948(s), 910(m), 890(w), 880(m), 830(s), 763 (f) (9), 752(f), 740(f), 700(w), 658(m), 636(w), 592(s), 580(s), 548(s).

Anal. Calcd. for $C_9H_9N_3O_3S$: C, 45.18; H, 3.79; N, 17.56. Found: C, 45.39; H, 4.13; N, 17.33.

REFERENCES

(1) This work was supported in part by Grant No. GM-11974 of the U. S. Public Health Service, National Institutes of Health.

(2) This compound is presumed to react as HNCO, isocyanic acid. This term will therefore be used exclusively, although no claim of the absence of HOCN, cyanic acid, should be implied.

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(9) The (f) represents fine structure on broad absorption.

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