Synthesis of a 1,2,3-Triazolo[1,5-*a*]-1,3,5-triazine. A New Heterocyclic System (1)

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The synthesis of 3-methyl-7-oxo-5-thioxo-4*H*,6*H*-1,2,3-triazolo[1,5-*a*]-1,3,5-triazine (a new bicyclic system) is described. The key step involves reaction of 4-amino-5-methyl-1,2,3-triazole with carbethoxyisothiocyanate followed by cyclization with alkali.

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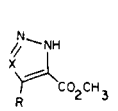
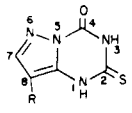
As part of our program of synthesis of *C*-nucleosides, we have utilized 4-ribosylated-3-carbomethoxy pyrazole **1** (2) for the preparation of the new *C*-nucleoside 8-(β-D-ribofuranosyl)pyrazolo[1,5-*a*]-1,3,5-triazine **3** (3). The corresponding 1,2,3-triazolo derivative **2** (2) should similarly lend itself to the synthesis of the *C*-3-ribosylated 1,2,3-triazolo[1,5-*a*]-1.3,5-triazine **4**. Since this particular heterocyclic system, to the best of our knowledge, has never been reported, we describe herein the first synthesis of a 1,2,3-triazolo[1,5-*a*]-1,3,5-triazine, as part of model studies in our laboratory for the synthesis and transformations of forthcoming *C*-nucleosides such as **4**.



1 X = CH
2 X = N



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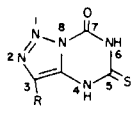

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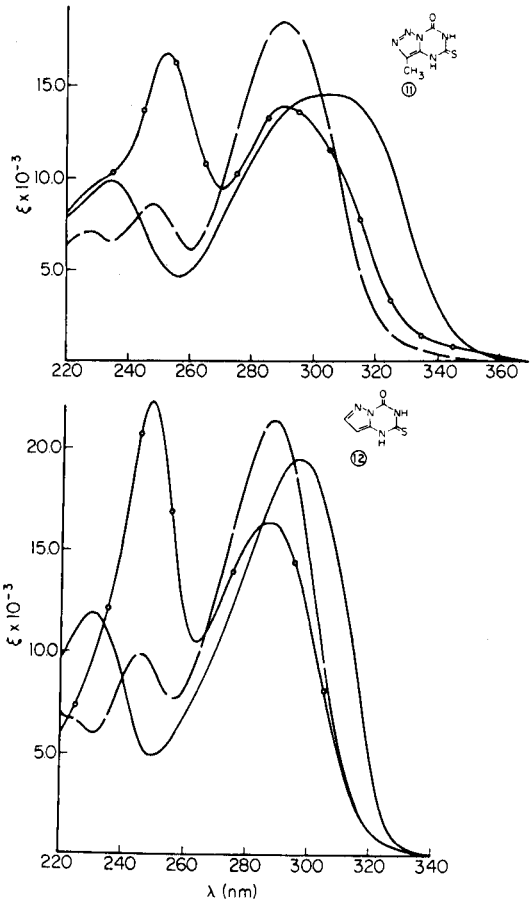
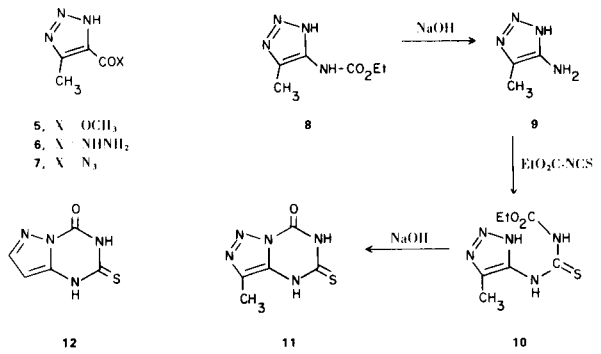
R = β-D-Ribofuranosyl

The starting material, 4-carbomethoxy-5-methyl-1,2,3-triazole **5**, was obtained in good yield by the 1,3-dipolar cycloaddition of trimethylsilylazide to methyl tetrolate. Conversion of **5** to the corresponding amino triazole **9** was accomplished essentially by a method described by Yamada and co-workers (4). Thus treatment of triazole ester **5** with hydrazine in methanol afforded in very good yields the hydrazide **6** which was nitrosated to the corresponding acyl azide **7**. This compound underwent a Curtius rearrangement in refluxing ethanol to afford the ethyl carbamate **8**. Hydrolysis of **8** in 10*N* sodium



Legend for Figure 1.

Uv spectra of Compound **11** and **12** at *p*H 0.1 (neutral species – – –), *p*H 7 (monoanion ———), and *p*H 14 (dianion –o–o–).



hydroxide at reflux temperature afforded the amino triazole **9** in good yields.

Access to the 1,2,3-triazolo[1,5-*a*]-1,3,5-triazine system was envisaged by reaction of **9** with ethoxycarbonyl isothiocyanate (5) according to the method utilized for the synthesis of **2** from the corresponding aminopyrazole (3,6). When applied to 3-aminopyrazoles, the method normally proceeds by monoacylation of the exocyclic amino group (3,4,7) which is also accompanied by formation of some of the product diacylated at both the 3-amino group and the *N*-1 endocyclic nitrogen (6). Other amino azoles, however, might react differently. Thus 3-amino-1,2,4-triazole appears to undergo monoacylation at the endocyclic *N*-2 (8) while the method fails altogether when applied to 5-amino tetrazole (7).

Reaction of **9** with ethoxycarbonyl isothiocyanate afforded in good yield a single product which was identified as **10**. Proof that reaction of the amino group had occurred with the isothiocyanate function was obtained from an examination of the pmr spectrum of **10** which showed the absence of the exocyclic amino (present in **9** at δ 4.70) and the presence of a low field signal at δ 14.49 (exchangeable with deuterium oxide) indicative of the presence of the NH in the triazole ring (9). A similar low field signal can be observed for compounds **5-9** in Table I. The pmr spectrum of **10** also exhibits signals for the two imido NH's at δ 11.05 and 11.45, and for the carbethoxy group (δ (CH_3) = 1.26 and δ (CH_2) = 4.22). Such data are fully consistent with structure **10**.

Treatment of ω-ethoxycarbonylthioureido-1,2,3-triazole **10** with dilute aqueous sodium hydroxide at room temperature led to immediate cyclization to the crystalline 1,2,3-triazolo[1,5-*a*]-1,3,5-triazine **11**, which analyzed for the monohydrate.

Assignation of structure **11** to the product of cyclization is, of course, based on the identity of its synthetic precursor **10** as well as on a comparison of the pmr and uv spectral properties of both **11** and its known (6,7) pyrazolo[1,5-*a*]-triazine isostere **12** obtained by the same general procedure. Thus the pmr spectra of both **11** and **12** exhibit signals for the two triazine-NH protons with very similar chemical shifts (**11**, δ = 13.04 and **12**, δ = 13.06). A comparison of the uv spectral curves of both **11** and **12** (see Figure 1 and Table II) shows a striking similarity for their neutral and anionic forms. Furthermore, the difference in the pK_a of **11** (pK_a 4.06 and 9.41)(10) and **12** (pK_a 5.21

Table I

Pmr Data (a) for Compounds **5-12** in DMSO-d_6 at 100 MHz

Compound	δ Triazole Ring NH	δ CH_3	Others
5	15.36	2.47	δ 3.83 (s, 3, $COOCH_3$)
6	14.66	2.45	δ 9.48 (broad s, 1, NH), δ 4.54 (broad s, 2, NH_2)
7	15.50	2.50	
8	14.35	2.13	δ 9.21 (s, 1, N*H*CO), δ 4.05 (q, 2, CO_2CH_2), δ 1.21 (t, 3, CH_2CH_3)
9	13.09	2.05	δ 4.70 (broad s, 2, NH_2)
10	14.99	2.14	δ 11.45 and 11.05 (two s, 2, NH-CS-NH), δ 4.22 (q, 2, CO_2CH_2), δ 1.26 (t, 3, CH_2CH_3)
11		2.30	δ 13.04 (broad s, 2, NH), δ 3.35 (H_2O of crystallization)
12			δ 13.06 (broad s, 2, NH), δ 7.87 (d, 1, H-7, $J_{7,8}$ = 1.9 Hz), δ 5.90 (d, 1, H-8)

Table II

Uv Data for **11** and **12**

1,2,3-Triazolo[1,5-*a*]-1,3,5-triazine **11**			Pyrazolo[1,5-*a*]-1,3,5-triazine **12**		
*p*H	λ max (nm)	ε	*p*H	λ max (nm)	ε
0.1	227	7060	0.1	225	6620
	248	8560		246	9995
	290	18570		287.5	21660
7.08	235	9880	7.08	230	12040
	305	14630		296	19750
14	252	16790	14	248	22360
	291	13920		286	16340

and 10.57) is consistent with the weaker basic character of the 1,2,3-triazole ring present in **11** (11) as compared with that of the pyrazolo ring in **12** (12).

The application of this study to the synthesis of triazolotriazine *C*-nucleosides is in progress.

EXPERIMENTAL

General.

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. The pmr spectra were obtained on a Jeol PS-100 spectrometer with TMS as internal standard. Ultraviolet absorption data were determined with a Cary recording spectrophotometer, Model 15, using buffers and techniques previously described (13). The apparent pK_a values are accurate to ± 0.05 *p*H unit and were determined spectrophotometrically by methods previously employed (13,14). Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan. Thin layer chromatography (tlc) was performed on microscope slides coated with Merck silica gel GF_{254} and substances were visualized either by uv absorption or iodine vapor.

5-Methyl-1,2,3-triazole-4-carboxylic Acid Methyl Ester (**5**).

A mixture of 19.6 g. (0.2 mole) of methyl tetrolate and 57.5 g. (0.5 mole) of trimethylsilylazide was heated at 105° in a sealed vessel for 75 hours. After cooling and treatment with 100 ml. of methanol, a white solid precipitated. Evaporation of the mixture to dryness and crystallization of the remaining solid from methanol-ethyl ether afforded 24.0 g. (85%) of **5**, m.p. 209-210°.

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.77. Found: C, 42.70; H, 4.94; N, 29.85.

5-Methyl-1,2,3-triazole-4-carboxylic Acid Hydrazide (**6**).

A solution of 16.0 g. (0.133 mole) of compound **5** in 20 ml. of methanol and 10 ml. of anhydrous hydrazine (technical grade) was stirred overnight at room temperature. Evaporation of solvent and excess reagent *in vacuo* (3 co-evaporations with ethanol) afforded **6** as a crystalline residue (16.0 g.). Recrystallization from methanol afforded 12.19 g. of analytically pure product, m.p. 211-212°. Another 2.68 g. was obtained by crystallization of the residue (after evaporation of the methanolic mother liquor) from water, total yield 93%.

Anal. Calcd. for $C_4H_7N_5O$: C, 34.04; H, 5.00; N, 49.62. Found: C, 34.37; H, 4.97; N, 49.38.

5-Methyl-1,2,3-triazole-4-carbonyl Azide (**7**).

To an efficiently stirred solution of **6** (2.82 g., 20 mmoles) in 15 ml. of water and 3 ml. of concentrated hydrochloric acid at 0° was added dropwise a cold solution of sodium nitrite (1.4 g.) in 4 ml. of water. After 10 minutes, the white crystalline product was filtered, washed with water and dried over phosphorus pentoxide at room temperature. This afforded 2.42 g. (79.5%) of analytically pure azide **7**, m.p. 139-140° dec.

Anal. Calcd. for $C_4H_4N_6O$: C, 31.58; H, 2.65; N, 55.25. Found: C, 31.81; H, 2.70; N, 55.10.

4-Amino-5-methyl-1,2,3-triazole (**9**).

A solution of 2.00 g. of **7** (13.14 mmoles) in 20 ml. of ethanol was heated to reflux for 3.5 hours. Evaporation of the mixture to dryness afforded 5-methyl-1,2,3-triazole-4-carbamic acid methyl ester, **8**, as a syrup. Without further purification, **8** was hydrolyzed in 20 ml. of 10*N* sodium hydroxide by heating the solution to reflux for 3 hours. After cooling, the solution was passed through a column of Amberlite IRC-50 (H^+) resin (150 ml. bed volume) and the eluent was evaporated to dryness to afford the crude amino triazole **9** as a syrup which crystallized slowly on standing.

For characterization purposes the solid was converted to its hydrochloride salt by treatment with ethanolic hydrogen chloride. Evaporation of the solvent and of the excess hydrogen chloride followed by crystallization of the residue from ethanol-ethyl ether afforded 1.26 g. (71%) of the hydrochloride salt of **9**. Recrystallization from 2-propanol gave the analytical sample, m.p. 158-160°.

Anal. Calcd. for $C_3H_7ClN_4$: C, 26.77; H, 5.24; N, 41.63; Cl, 26.34. Found: C, 26.76; H, 5.26; N, 41.62; Cl, 26.25.

An analytically pure sample of **9** as the free base (m.p. 102-104°) was also obtained by sublimation at 100° (0.02 mm Hg) of the crude product.

Anal. Calcd. for $C_3H_6N_4$: C, 36.73; H, 6.16; N, 57.11. Found: C, 36.91; H, 6.12; N, 57.18.

The crude material was found to be of sufficient purity for its conversion to **10** and was therefore used in subsequent steps (*vide infra*) without further purification.

4-(3-Ethoxycarbonylthioureido)-5-methyl-1,2,3-triazole (**10**).

The crude aminotriazole **9** (1 g., ~10 mmoles) was added to an acetonitrile solution of carbethoxy isothiocyanate which was prepared *in situ* from 1.36 g. of potassium thiocyanate (14 mmoles) and 1.52 g. of ethyl chloroformate (14 mmoles) in 12 ml. of acetonitrile. After a slightly exothermic initial reaction, the mixture was stirred for 30 minutes at room temperature. Some

inorganic insoluble material was filtered and the clear solution was evaporated to dryness. The product was recrystallized from ethanol to afford (after drying over phosphorus pentoxide *in vacuo*) 1.50 g. (65%) of analytically pure **10**, m.p. 149-151°; λ max (water): 264 nm (ε, 12,300).

Anal. Calcd. for $C_7H_{11}N_5SO_2$: C, 36.67; H, 4.84; N, 30.54; S, 13.98. Found: C, 36.68; H, 4.82; N, 30.37; S, 14.05.

3-Methyl-7-oxo-5-thioxo-4*H*,6*H*-1,2,3-triazolo[1,5-*a*]-1,3,5-triazine (**11**).

The thioureido triazole **10** (250 mg., 1.09 mmoles) was dissolved in 2 ml. of 1*N* sodium hydroxide and after standing for 5 minutes at room temperature the solution was acidified with 1*N* hydrochloric acid. The mixture was left at 5° overnight and the crystalline product that precipitated was filtered, washed with water and dried over phosphorus pentoxide to give 144 mg. (70%) of analytically pure **11**, m.p. 219° dec. The pmr spectrum of **11** showed the presence of 1 molecule of water of crystallization.

Anal. Calcd. for $C_5H_3N_5OS \cdot H_2O$: C, 29.85; H, 3.50; N, 34.80; S, 15.93. Found: C, 29.94; H, 3.49; N, 34.88; S, 16.03.

REFERENCES AND NOTES

(1) This investigation was supported in part by funds awarded by the National Cancer Institute, DHEW (Grants No. CA-08748, CA-17085, and CA-18856); by the Fellowship from "Program of Cultural Cooperation between U. S. A. and Spain" (F. G. D. L. H.) and by the Hearst Fund (S. Y-K. T.).

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(10) The pK_a of 4.06 probably represents the dissociation to the monoanion and that of 9.41 to the dianion.

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