Cyclization of 6-Hydrazinopurines to *s*-Triazolo[3,4-*i*]purines and Their Rearrangement to the Isomeric *s*-Triazolo[5,1-*i*]purines[1]

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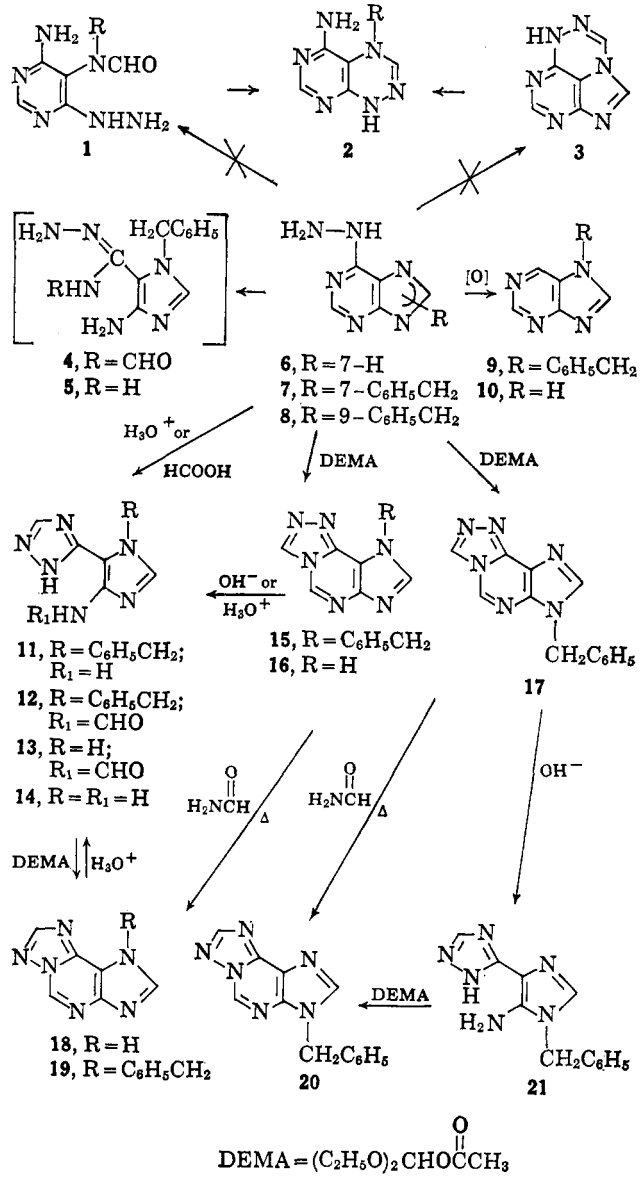
The reaction of 6-hydrazinopurine with diethoxymethyl acetate gave *s*-triazolo[3,4-*i*]purine (**16**), whereas reaction with formic acid gave N-[4(5)-*s*-triazol-3-ylimidazol-5(4)-yl]formamide (**13**). Treatment of **16** with formic acid and concentrated hydrochloric acid gave, respectively, **13** and 3-[4(5)-aminoimidazol-5(4)-yl]-*s*-triazole (**14**). Rearrangement of **16** was effected in formamide to give the isomeric *s*-triazolo[5,1-*i*]purine (**18**), which was also obtained by treatment of **14** with diethoxymethyl acetate. Similar reactions occurred with 7- and 9-benzyl-6-hydrazinopurines.

In a study of methods of synthesis of pyrimido-[5,4-*e*]-*as*-triazines (**2**),[2] the use of the readily available 6-hydrazinopurines (**6**)[3] as precursors of this ring system was investigated (routes **6** → **3** → **2** and **7** → **1** → **2**, Chart I).[4] Although the preparation of the desired ring system from the isomeric 6-hydrazinopurines was unsuccessful, some interesting and unreported reactions of the hydrazino group in this system were encountered. The preparation of some *s*-triazolo-[4,3-*i*]purines, their rearrangement to *s*-triazolo[5,1-*i*]-purines, and the isolation of the proposed intermediates in the isomerizations are the subject of this paper.[5]

When a solution of 7-benzyl-6-hydrazino-7H-purine (**7**) in aqueous sodium hydroxide was allowed to stand at room temperature, it was completely converted to 7-benzyl-7H-purine (**9**).[6] Although the rate of reaction was slower, **9** was also obtained from a solution of **7** in pH 7 phosphate buffer. Presumably, **7** is initially oxidized to a diazo intermediate,[7] which decomposes with loss of nitrogen to give **9**. Likewise, a solution of 6-hydrazinopurine (**6**) in aqueous sodium hydroxide was oxidized to give purine (**10**), and the rate of reaction was increased by passing oxygen through the solution. However, the product obtained by treatment of **7** with 1 *N* hydrochloric acid was identified (see below) as 3-(4-amino-1-benzylimidazol-5-yl)-*s*-triazole (**11**). This reaction was also observed in hot 3 *N* sulfuric acid. Thus, protonation of **7** appears to result in opening of the pyrimidine ring at the 2-position to give an amidrazone intermediate (**4**), followed by ring closure between the formamido and hydrazino groups to give **11**. However, the formation of **5** and formic acid, which recombine to give **11**, cannot be excluded.

On treatment of **7** with hot formic acid, the single product was identified as N-(1-benzyl-5-*s*-triazol-3-ylimidazol-4-yl)formamide (**12**) (see below), which on deformylation with methanolic hydrogen chloride gave **11**. Finally, a good yield of a tricyclic product, 9-benzyl-9H-*s*-triazolo[3,4-*i*]purine (**15**), was obtained by reaction of **7** with diethoxymethyl acetate[8a,b] at room temperature. **15** results from ring closure at

CHART I



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(4) J. A. Montgomery and C. Temple, Jr., *ibid.*, **79**, 5238 (1957).

(5) For similar rearrangements in triazolopyrimidines, see (a) G. W. Miller and F. L. Rose, *J. Chem. Soc.*, 5642 (1963); (b) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *J. Org. Chem.*, **28**, 2257 (1963); (c) D. Shiho, S. Tagami, N. Takahayashi, and R. Honda, *J. Pharm. Soc. Japan*, **76**, 804 (1956).

(6) The autoxidation of alkyl hydrazines is known to give a variety of products. For example, see L. E. Eberson and K. Persson, *J. Med. Pharm. Chem.*, **5**, 738 (1962).

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N-1,[9,10] and is the first reported example of this ring system. The pyrimidine ring of **15** was opened in either 0.1 *N* hydrochloric acid or 0.1 *N* sodium hydroxide at room temperature to give **12**, identical with the product obtained from the action of formic acid on **7**. That the formyl group was on the amino group and not on a triazole ring nitrogen was shown by the proton magnetic resonance spectrum of **12** in dimethyl-d_6 sulfoxide which exhibited proton signals (in parts per million on the τ scale) at 4.33 (CH_2); 2.78 (C_6H_5); 2.20, 1.37, and 1.13 (doublet, J = 11 c.p.s.) (CH); and 0.53 (doublet), −4.17 (NH). The spin–spin coupling observed between the CH and NH protons of the formamido group is only consistent with structure **12**. The formation of **12** from **7** and formic acid may involve either an initial formation of **11** (as with hydrochloric acid), followed by formylation or prior cyclization to **15**, with subsequent ring opening.

The cyclization of 9-benzyl-6-hydrazino-9H-purine (**8**) was also effected with diethoxymethyl acetate to give 7-benzyl-7H-*s*-triazolo[3,4-*i*]purine (**17**). On treatment with 2 *N* sodium hydroxide, **17** was converted directly to 3-(5-amino-1-benzylimidazol-4-yl)-*s*-triazole (**21**).

The cyclization of 6-hydrazinopurine (**6**) itself was studied with (a) formamide, (b) formic acid, (c) diethoxymethyl acetate, and (d) ethyl orthoformate–concentrated hydrochloric acid. In formamide at 180° the main product was purine (**10**) apparently resulting from the oxidation of **6** in this medium (see above). As expected from the results obtained with **7**, the action of formic acid on **6** provided N-[4(5)-*s*-triazol-3-ylimidazol-5(4)-yl]formamide (**13**). In both diethoxymethyl acetate[8a,b] and ethyl orthoformate–concentrated hydrochloric acid[8c,d] at room temperature, **6** gave *s*-triazolo[3,4-*i*]purine (**16**). Further treatment of **16** with hot formic acid gave the formamide **13**. In addition, the pyrimidine ring of **16** was opened in 2 *N* sodium hydroxide, but the product could not be obtained in pure form. However, in concentrated hydrochloric acid **16** gave a good yield of the dihydrochloride of 3-[4(5)-aminoimidazol-5(4)-yl]-*s*-triazole (**14**). Although the free base could not be isolated pure by neutralization of an aqueous solution of the dihydrochloride with aqueous sodium hydroxide, partial neutralization provided the pure monohydrochloride.

When the dihydrochloride of **14** was treated with diethoxymethyl acetate, the product was *s*-triazolo-[5,1-*i*]purine (**18**) instead of the isomeric *s*-triazolo-[3,4-*i*]purine (**16**). As with **16**, however, reaction of **18** with concentrated hydrochloric acid provided the dihydrochloride of **14**. The cyclization of **11** and **21** with diethoxymethyl acetate also gave the *s*-triazolo-[5,1-*i*]purines **19** and **20**, respectively. The direction of cyclization in these ring closures is attributed to the greater nucleophilicity of the hydrazino nitrogen over that of the lone nitrogen in the *s*-triazole ring.[11]

Furthermore, the *s*-triazolo[3,4-*i*]purines **15**, **16**, and **17** were rearranged in formamide at 180° to give, respectively, the corresponding *s*-triazolo[5,1-*i*]purines **19**, **18**, and **20**. Although **16** was found to rearrange in formamide at 150°, the isomerization reaction was unsuccessful when **16** was heated in the solid state at 200°, in anisole (150°), or in anisole containing either ammonium hydroxide or formic acid. Apparently the rearrangement reaction involves the initial formation of **13** as an intermediate. Support for this conclusion was provided by the ring closure of **13** to **18** in formamide at 180°. Although the conditions are more vigorous, these isomerization reactions are similar to those recently reported for the conversion of *s*-triazolo[4,3-*c*]pyrimidines to *s*-triazolo[1,5-*c*]pyrimidines.[8a]

The ultraviolet spectra and the bands in the range 1700–1500 cm.$^{-1}$ of the infrared spectra for the compounds prepared are summarized in Table I. At pH 7 the long wave length band of the *s*-triazolo[3,4-*i*]purines is consistently 7–8 mμ higher than the corresponding band in the *s*-triazolo[5,1-*i*]purines.

TABLE I

Compd.	Ultraviolet absorption spectra,[a] λ_{max}, mμ ($\epsilon \times 10^{-3}$) pH 1	pH 7	pH 13	Infrared absorption spectra, 1700–1500-cm.$^{-1}$ region
	s-Triazolo[3,4-*i*]purines			
16	258 (9.25)	257 (7.83)	263 (7.57)	1665
	264 (9.65)	263 (8.26)	272 (7.99)	1540
		284 (4.78)	301 (5.82)	1515
17	258 (9.16)	248 (5.44)	*b*	1645
	265 (9.95)	256 (7.14)		1530
		265 (7.65)		1500
		288 (5.29)		
15	259[b]	260 (9.85)	*b*	1650, 1540
	267[b]	268 (9.66)		1520, 1500
		285 (4.72)		
	s-Triazolo[5,1-*i*]purines			
18	261 (6.70)[c]	262 (6.16)	290 (9.00)	1640, 1560
	273 (7.10)	277 (7.57)		1520, 1505
20	276 (7.78)	280 (8.16)	*b*	1650, 1540
				1510, 1500
19	263[b]	264 (7.95)	264[b]	1680, 1530
	276[b]	278 (7.85)	277[b]	1500
	N-[4(5)-*s*-Triazol-3-ylimidazol-5(4)-yl]formamides			
13	248 (15.1)	251 (11.9)	251 (11.4)	1665, 1635, 1585
				1515, 1505
12	247 (13.7)	244 (9.85)	245 (10.3)	1675, 1625
				1550, 1500
	3-[4(5)-Aminoimidazol-5(4)-yl]-*s*-triazoles			
14[d]	244 (10.0)	265 (12.2)	262[b]	1665, 1605, 1575
	260 (10.0)			1535, 1505
21	246 (12.5)	263 (15.3)	*b*	1635, 1595
	261 (11.7)			1570, 1505
11	244 (8.33)	265 (9.1)	260 (8.73)	1620, 1545, 1535
	265 (7.43)[c]			1510, 1500

[a] These spectra were determined by dilution of a neutral solution with the appropriate solvent. [b] Unstable. [c] Shoulder. [d] Monohydrochloride.

Experimental Section

The melting points reported were determined on a Kofler Heizbank apparatus and are corrected. The ultraviolet and infrared spectra, respectively, were determined in aqueous solution with a Cary Model 14 recordng spectrophotometer and in pressed potassium bromide disks with a Perkin-Elmer Model 221 spectrophotometer.

***s*-Triazolo[3,4-*i*]purines. A. General Procedure.**—A suspension of the 6-hydrazinopurine (2.0 g.) in diethoxymethyl

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TABLE II

Compd.	Method	Reaction: Time, hr.	Reaction: Temp., °C.	Recrystn.[a] solvent	Yield, %	M.p., °C.	Formula	Calcd., %: C	Calcd., %: H	Calcd., %: N	Found, %: C	Found, %: H	Found, %: N
						s-Triazolo[3,4-*i*]purines							
16	A	27	*b*	A	89	>264	$C_6H_4N_6$	45.00	2.50	52.50	45.06	2.52	52.36
	B	118	*b*		64								
17	A	27	*b*	A + B	96	243–244	$C_{13}H_{10}N_6$	62.40	4.00	33.60	62.59	4.26	33.43
15	A	18	*b*	A + B	72	>264	$C_{13}H_{10}N_6$	62.40	4.00	33.60	62.62	4.17	33.53
						s-Triazolo[5,1-*i*]purines							
18	A	4	*b*	C	51	>264	$C_6H_4N_6$	45.00	2.50	52.50	44.77	2.64	52.19
	B	1.5	185		58								
	C	2	180		66[c]								
20	A	40	*b*	C	63	193–194	$C_{13}H_{10}N_6$	62.40	4.00	33.60	62.53	3.90	33.50
	B	2	180		61								
19	A	19	*b*	C	55	192–193	$C_{13}H_{10}N_6$	62.40	4.00	33.60	62.25	3.95	33.24
	B	2	180		69								
						N-[4(5)-*s*-Triazol-3-ylimidazol-5(4)-yl]formamides							
13	A	18	101	D	74	>264	$C_6H_6N_6O$	40.40	3.37	47.20	40.71	3.62	47.14
	B	26	101	C	66								
12	A	110	101	D	96	208–209[d]	$C_{13}H_{12}N_6O$	58.20	4.48	31.30	57.99	4.51	31.47
	C	20	*b*		71								
						3-[4(5)-Aminoimidazol-5(4)-yl]-*s*-triazoles							
14	A	70	*b*		92	>264[d]	$C_5H_6N_6 \cdot 2HCl$	26.90	3.58	37.70	27.07	3.35	37.62
				e	55	>264[d]	$C_5H_6N_6 \cdot HCl$	32.15	3.75	45.00	32.33	3.66	45.22
	B	4	*b*		79								
21	C	25	*b*	B	57	219–220	$C_{12}H_{12}N_6$	60.00	5.00	35.00	60.16	5.15	34.91
11	D	*e*	80	*e*	40	223–224	$C_{12}H_{12}N_6$	60.00	5.00	35.00	60.17	4.96	35.23
	E	1.5	*b*		64								

[a] A, N,N-dimethylformamide; B, water; C, ethanol; D, neutralization of an aqueous solution of the sodium salt with 1 *N* hydrochloric acid. [b] Room temperature. [c] Crude yield. [d] With decomposition. [e] See Experimental Section.

acetate (25 ml.) was stirred at room temperature, and the solid was collected by filtration. The reaction conditions, yields and properties are summarized in Tables I and II.

B.—A suspension of 6-hydrazinopurine (**6**, 88 mg.) in ethyl orthoformate (10 ml.) containing 1 drop of concentrated hydrochloric acid was stirred at room temperature for 118 hr. Additional ethyl orthoformate (2 ml.) was added at the end of 88 hr. to complete the reaction (as indicated by thin layer chromatography). Evaporation of the suspension to dryness and treatment of the residue as in A gave the product (60 mg.).

***s*-Triazolo[5,1-*i*]purines. A. General Procedure.**—A solution of the 3-[4(5)-aminoimidazolyl]-*s*-triazole (1.0 g.) in diethoxymethyl acetate (25 ml.) was stirred at room temperature and evaporated to dryness *in vacuo*. The reaction conditions, yields, and properties are summarized in Tables I and II.

B. General Procedure.—A solution of the *s*-triazolo[3,4-*i*]-purines (500 mg.) in formamide (10 ml.) was heated at 180–185° and evaporated to dryness *in vacuo*. The reaction conditions, yields, and properties are summarized in Tables I and II.

C.—A solution of N-[4(5)-*s*-triazol-3-ylimidazol-5(4)-yl]formamide (**13**, 50 mg.) in formamide (5 ml.) was heated at 180° for 2 hr. and evaporated to dryness *in vacuo*, and the residue was washed with ethanol to give impure product (33 mg.) (see Table II).

N-[4(5)-*s*-Triazol-3-ylimidazol-5(4)-yl]formamides. A. General Procedure.—A solution of the 6-hydrazinopurine (360 mg.) in formic acid (10 ml.) was heated at reflux and evaporated to dryness *in vacuo*. The reaction conditions, yields, and properties are summarized in Tables I and II.

B.—A solution of *s*-triazolo[3,4-*i*]purine (**16**, 450 mg.) in formic acid (10 ml.) was heated at reflux and evaporated to dryness *in vacuo* (see Table II).

C.—A suspension of 9-benzyl-9H-*s*-triazolo[3,4-*i*]purine (**15**, 735 mg.) in water (50 ml.) and ethanol (10 ml.) containing 1 *N* sodium hydroxide (6 ml.) was stirred at room temperature. The resulting solution was neutralized with 1 *N* hydrochloric acid, and the solid that deposited was collected by filtration (see Table II).

3-[4(5)-Aminoimidazol-5(4)-yl]-*s*-triazoles. A and B.—A suspension of either *s*-triazolo[3,4-*i*]purine (**16**, 1.5 g.) (method A) or *s*-triazolo[5,1-*i*]purine (**18**, 50 mg.) (method B) in concentrated hydrochloric acid was stirred at room temperature, and the dihydrochloride of **14** was collected by filtration. An aqueous solution of the dihydrochloride was partially neutralized with 1 equiv. of 1 *N* sodium hydroxide and refrigerated to give the monohydrochloride. The reaction conditions, yields, and properties are summarized in Tables I and II.

C.—A suspension of 7-benzyl-7H-*s*-triazolo[3,4-*i*]purine (**17**, 2.0 g.) in 2 *N* sodium hydroxide (30 ml.) was stirred at room temperature. The resulting solution was acidified with 12 *N* hydrochloric acid to pH 1, and after filtration the filtrate was neutralized to pH 6 with 1 *N* sodium hydroxide. Initially an oil deposited which slowly crystallized to give a slightly gummy solid which was collected by filtration (see Table II).

D.—A solution of 7-benzyl-6-hydrazino-7H-purine (**7**, 1.0 g.) in 1 *N* hydrochloric acid (12 ml.) was stirred at room temperature for 94 hr., then heated at 75–80° for 1 hr. After standing for an additional 7 days at room temperature, the solution was evaporated to dryness under reduced pressure, and the residue was washed with methanol (10 ml.). The hygroscopic solid obtained by evaporation of the methanol was dissolved in water (10 ml.), and the solution was neutralized with 1 *N* sodium hydroxide. The product that precipitated was collected by filtration and dried *in vacuo* over phosphorus pentoxide (see Table II).

E.—A solution of N-(1-benzyl-5-*s*-triazol-3-ylimidazol-4-yl)-formamide (**12**, 200 mg.) in 20% methanolic hydrogen chloride (5 ml.) was stirred at room temperature. The hydrochloride that deposited was collected by filtration, and treated as described in D.

7-Benzyl-7H-purine (**9**).—A solution of 7-benzyl-6-hydrazino-7H-purine (**7**, 1.0 g.) in methanol (100 ml.) and pH 7 phosphate buffer (85 ml.) was allowed to stand at room temperature for about 2 weeks and concentrated *in vacuo* to 20 ml., and the solid that deposited recrystallized from water: yield 310 mg. (35%), m.p. 145–146° (lit.[3b] m.p. 145–146°). This oxidation was complete in 12 hr. by passing a slow stream of oxygen through the solution.

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