# Pyrimido[5,4-*e*]-*as*-triazines. VI. The Preparation of Some 5-Substituted 7-Aminopyrimido[5,4-*e*]-*as*-triazines[1]

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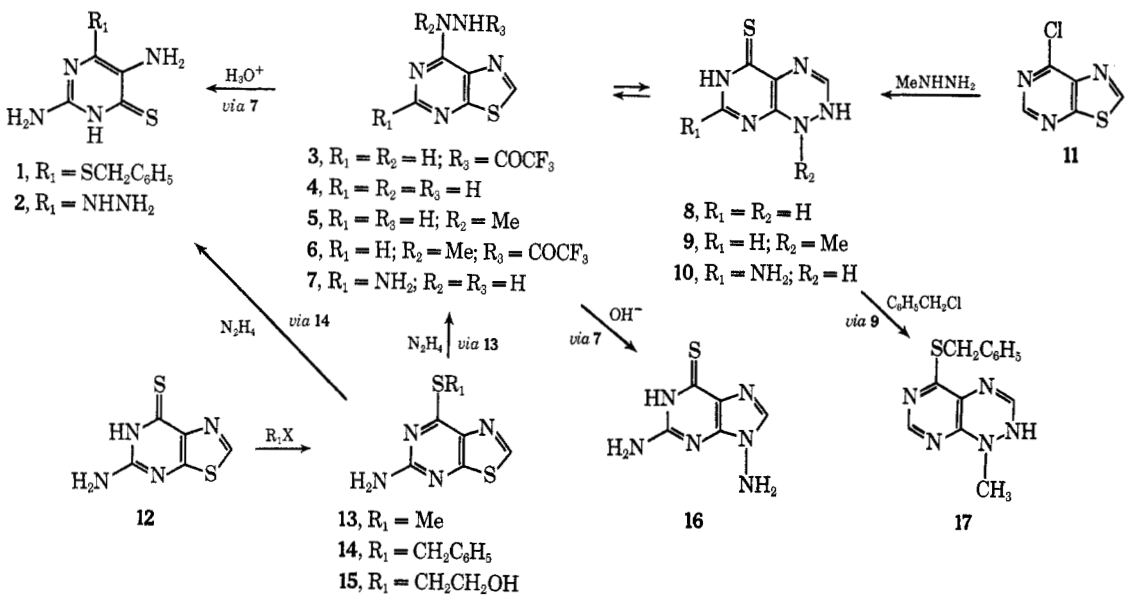
*Received June 1, 1971*

The rearrangement of one thiazolo[5,4-*d*]pyrimidine to a pyrimido[5,4-*e*]triazine and another to a 9-aminopurine is described. Reaction of methyl 6-amino-*as*-triazine-5-carboxylate (**18**) with guanidine to give 7-aminopyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one (**21**) was unsuccessful. The successful route to 7-amino compounds of this type involved the preparation and cyclization of 2,5-diamino-6-(benzylthio)-4-hydrazinopyrimidine (**30**) to give 7-amino-5-(benzylthio)pyrimido[5,4-*e*]-*as*-triazine (**31**). Nucleophilic displacement of the 5-(benzylthio) group of **31** gave the corresponding 1,2-dihydro-5(6*H*)-thione (**10**), 5(6*H*)-one (**21**), and 5-amino (**32**) derivatives. Air oxidation of **10** appeared to give mainly the corresponding hetreoaromatic 5(6*H*)-thione (**33**).

## Part A

This paper is concerned with the development of synthetic methods for the preparation of the potentially biologically interesting 5-substituted derivatives of 7-aminopyrimido[5,4-*e*]-*as*-triazines (2-amino-7-azapteridines).[2] The investigation of both pyrimidine and *as*-triazine routes to this type of compound are described.




Previously, the rearrangement of **8** to **3** in $CF_3CO_2D$ and of **4** to **8** in DMSO-$d_6$ was observed.[3] Reaction of **11**[4] with methylhydrazine gave a product that was shown by its elemental analyses and pmr spectrum in $CF_3CO_2D$ to be a mixture of **5** and **9**. This product was converted to **9** on heating at 78°. A solution of the latter in $CF_3CO_2D$ on standing for 72 hr showed the presence of **5** and a new component, presumably **6**. When this product was isolated and heated at 78°, the pmr spectrum of the resulting solid showed the presence of **9** containing only a trace amount of **5**. The structure of **9** was confirmed by benzylation to give the benzylthio derivative **17**. Our attention was now directed toward the preparation of **7**. The alkylation of **12**[5] with $CH_3I$, $C_6H_5CH_2Cl$, and $HOCH_2CH_2Br$ gave, respectively, **13**, **14**, and **15**. Treatment of **13** with hydrazine gave a 20% yield of **7**. None of **7** was isolated from the reaction of **14** and **15** with hydrazine, although the $HOCH_2CH_2S^-$ group of **15** was expected to be a better leaving group than the $CH_3S^-$ group of **13**.[6] The major product from **14** was purified and identified as the pyrimidine **1**, which results from cleavage of the thiazolo ring. Ultraviolet spectral data indicated that the corresponding pyrimidines were also obtained in the reactions of both **13** and **15** with hydrazine. Similarly, the hydrochloride salt of **7** was refluxed in $H_2O$ to open the thiazolo ring to give **2**, identified by comparison of its uv spectrum with that of 2,4,5-triaminopyrimidine-6(1*H*)-thione.[7]

The rearrangement of **7** to **10** was unsuccessful in DMSO. However, treatment of a DMSO solution of **7** with aqueous NaOH gave, not **10**, but a mixture of **7** and a compound identified as the 9-aminopurine **16** by comparison of its uv spectrum with that of thioguanine.[8] Presumably **16** results from anion formation at the 1

(1) This investigation was supported by funds from the C. F. Kettering Foundation and Chemotherapy, National Cancer Institute, National Institutes of Health, Contract NIH-71-2021.

(2) For a key reference to the pyrimido[5,4-*e*]-*as*-triazine antibiotics, see E. C. Taylor and F. Sowinski, *J. Amer. Chem. Soc.*, **91**, 2143 (1969).

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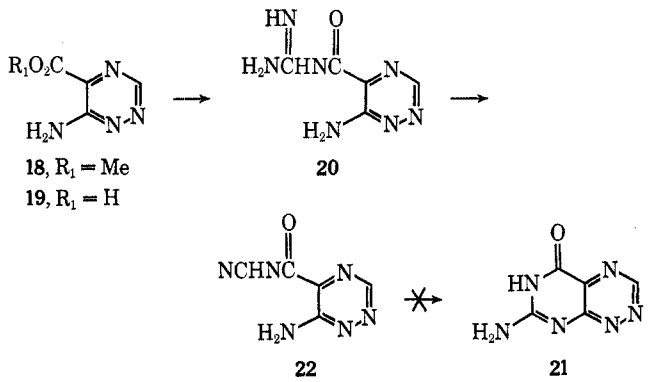
nitrogen of an intermediate hydrazinopyrimidine.[9] In contrast, the rearrangement of **4** to **8** in a neutral medium involved the 2 nitrogen of an intermediate hydrazinopyrimidine.[3]

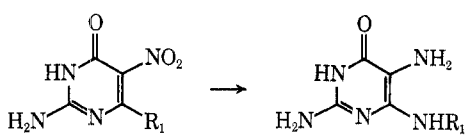
Reaction of **18**[10] with guanidine gave **20**, which was heated at 120° and then refluxed in 2-methoxyethanol to give a sample that was tentatively assigned the structure of either **21** or **22** based on elemental analyses. The tlc of this sample was similar to that of **21** described below; however, the pmr spectrum showed two CH peaks which were attributed to two tautomeric forms of **22**. Support for the latter was provided by the ir and



**18**, $R_1$ = Me
**19**, $R_1$ = H
**20**
**22**
**21**

uv spectra. The former exhibited two CN bands (2185, 2150 $cm^{-1}$), and the latter was similar to other *as*-triazines in an acidic medium in that the high wavelength uv peak decreased with time because of covalent hydration of the *as*-triazine ring.[10,11] Also, the conversion of **20** to **21** was unsuccessful when either **20** was heated at 160° or a suspension of **20** in toluene was refluxed. The guanidino group of **20** was hydrolyzed to give the corresponding carboxylic acid **19**[12] in either hot $H_2O$ or PrOH.

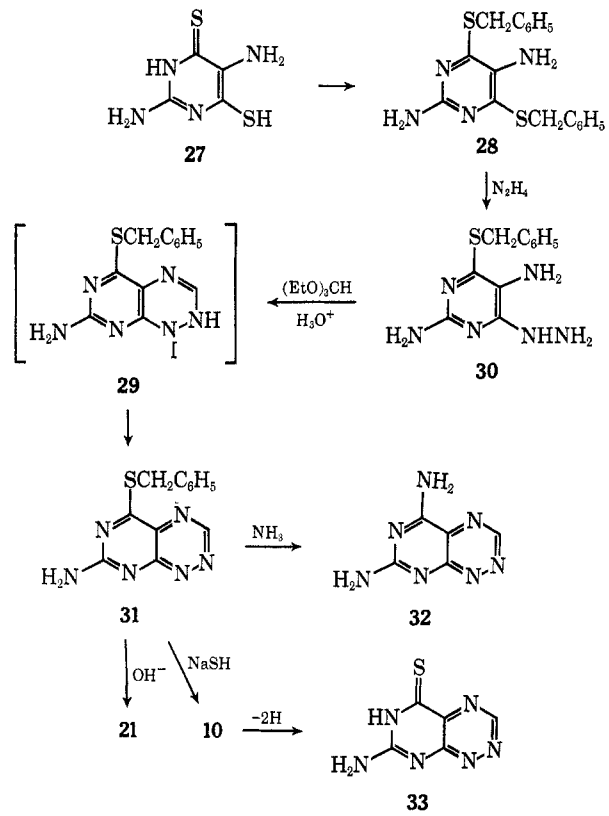
The preparation and cyclization of **25** to give the dihydro derivative of **21** was also unsuccessful. The hydrazinopyrimidine **24** was prepared by treatment of **23**[13] with hydrazine. Reduction of the nitro group of



**23**, $R_1$ = Cl
**24**, $R_1$ = $NHNH_2$
**25**, $R_1$ = $NH_2$
**26**, $R_1$ = H

**24** was effected with $Na_2S_2O_4$, but this reagent also cleaved the hydrazino group to give **26**.[14] The catalytic hydrogenation of **24** with either a palladium or rhodium catalyst resulted in the absorption of more than the theoretical amount of hydrogen, presumably also to give **26**.

To circumvent the difficulties encountered with the 5-nitropyrimidine **24**, the 5-aminopyrimidine **27**[5] was used as an intermediate. The benzylation of **27** with benzyl chloride in DMF in the presence of $K_2CO_3$ gave **28** which was treated with anhydrous hydrazine at 65° to give **30**. The cyclization of **30** was effected with ethyl orthoformate in the presence of hydrochloric acid to give **31**.[9] Presumably **31** was formed by air oxidation of the dihydro intermediate **29**. The cyclization of **30** to either an 8-amino-*s*-triazolo[4,3-*c*]pyrimidine[15]



**27**
**28**
**29**
**30**
**31**
**32**
**21**
**10**
**33**

or a 9-aminopurine[9,16] was excluded by the integrated intensities of the peaks in the pmr spectrum of **31**. Reaction of **31** with aqueous sodium hydroxide in dioxane at 60° replaced the benzylthio group to give **21**. Similarly, treatment of **31** with 10% ethanolic ammonia gave the diamino compound **32**. The interaction of **31** with sodium hydrosulfide not only replaced the benzylthio group but also reduced the *as*-triazine ring to give **10**. The air oxidation of **10** to **33** was attempted by recrystallization of **10** from $H_2O$. The pmr spectrum indicated that the recovered material was a mixture of **33** and an unidentified compound. The presence of **33** was shown by alkylation of the mixture with $C_6H_5CH_2Cl$ to again give **31**. The oxidation of **10** in DMSO containing aqueous NaOH appeared to give mainly **33**, but the pmr spectrum (overlapping CH peaks) and elemental analyses suggested that hydrolysis of the amino group might have occurred.

The uv and pmr spectra and selected bands in the ir spectra for the new compounds are presented in Table I. The uv spectra of the 7-aminopyrimido[5,4-*e*]-*as*-triazines and the corresponding 2-aminopteridines[17] are dissimilar in that the long wavelength band in the

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TABLE I

| Compd | Uv absorption[a] spectra at pH 7, $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$) | Ir absorption[b] spectra in KBr, selected bands, $cm^{-1}$ | Pmr spectral assignments,[c] chemical shift, $\delta$ (rel area) | Formula | Calcd, % C | Calcd, % H | Calcd, % N | Found, % C | Found, % H | Found, % N |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 261 (16.1), 382 (18.8)[d] | 1620, 1550 | | $C_{11}H_{12}N_4S_2$ | 49.98 | 4.56 | 21.19 | 50.06 | 4.58 | 21.12 |
| 5 | | | 4.25 (3, $CH_3$), 8.83, 9.33 (1, 1, CH)[e] | $C_6H_7N_5O \cdot 0.5H_2O$[f] | 37.88 | 4.24 | 36.83 | 37.77 | 3.86 | 36.92 |
| | | | | $C_6H_7N_5O$[f] | 39.77 | 3.89 | 38.64 | 40.01 | 4.07 | 38.51 |
| 7 | 286 (12.5) | 1615, 1610, 1570 | 4.5 br (2, $NH_2$), 6.3 br (2, $NH_2$), 8.62 (1, CH), 8.8 m (1, NH) | $C_5H_6N_6S$ | 32.95 | 3.32 | 46.12 | 33.03 | 3.35 | 46.35 |
| 9 | 252 (10.4), 354 (6.91)[d] | 1630, 1585, 1560 | 3.12 (3, $CH_3$), 6.78, 7.73 (1, 1, CH)[e] | $C_6H_7N_5S$ | 39.77 | 3.89 | 38.64 | 39.47 | 4.10 | 38.92 |
| 10 | 343 (4.13), 440 (5.66)[d] | 1615, 1580 | 6.28 d, 6.4, ~6.7 br (4, CH, $J_{23}$ = 3.6 Hz, $NH_2$, 2-NH), 8.58, 10.42 (1, 1, NH)[g] | $C_5H_6N_6S \cdot 0.12\text{-}C_2H_6O$ | 33.53 | 3.61 | 44.76 | 33.87 | 3.52 | 44.89 |
| 13 | 220 (18.5), 256 (14.1), 282 (8.05), 316 (9.45) | 1640, 1540, 1515 | 2.58 ($CH_3$),[h] 6.90 br (2, $NH_2$), 8.86 (1, CH) | $C_6H_6N_4S_2$ | 36.34 | 3.05 | 28.26 | 36.41 | 3.13 | 28.43 |
| 14 | 258 (13.5), 285 sh (8.66), 317 (10.4) | 1610, 1600, 1535 | | $C_{12}H_{10}N_4S_2$ | 52.53 | 3.67 | 20.42 | 52.31 | 3.80 | 20.61 |
| 15 | 255 (13.5), 285 sh (8.14), 316 (9.18) | 1625, 1540, 1515 | | $C_7H_8N_4OS_2$ | 36.83 | 3.53 | 24.54 | 36.72 | 3.46 | 24.35 |
| 16[i] | 264, 341[d] | 1645, 1635, 1560 | 5.8, 6.7, ~11 ($NH_2$, NH), 7.72 (CH), 8.62 (CH, 7) | $C_5H_6N_6S$ | 32.95 | 3.32 | | 32.87 | 3.32 | |
| 17 | 241 sh (10.1), 358 (4.55) | 1640, 1560, 1515 | 2.75 (3, $CH_3$), 4.30 (2, $CH_2$), 6.28 d (1, CH, $J_{23}$ = 3.6 Hz), 7.31 (5, $C_6H_5$), 7.7 m, 7.77 (2, NH, CH) | $C_{13}H_{13}N_5S$ | 57.54 | 4.83 | 25.82 | 57.34 | 4.92 | 25.51 |
| 20 | 237 (9.28), 363 (2.65) | 1695, 1670, 1640 | 4.9 br (4, $NH_2$), 7.17 (1, CH), 7.6 br (2, NH) | $C_5H_7N_7O$ | 33.15 | 3.89 | 54.12 | 33.06 | 4.08 | 54.15 |
| 21 | 261 (19.3), 313 sh (1.75), 384 (4.14)[d] | 1720, 1660 | 7.2 br (2, $NH_2$), 9.55 (1, CH), ~11.7 br (1, NH) | $C_5H_4N_6O$ | 36.59 | 2.46 | 51.20 | 36.70 | 2.42 | 51.22 |
| 22 | 257 sh (4.12), 345 (1.65) | 2185, 2150, 1650 | 7.4 br (NH, $NH_2$), 8.92 br, 9.31 br (CH) | $C_5H_4N_6O$ | 36.59 | 2.46 | 51.20 | 36.75 | 2.35 | 51.26 |
| 24 | 221 (15.6), 333 (10.2) | 1685, 1630, 1540 | | $C_4H_6N_6O_3 \cdot H_2O$ | 23.50 | 3.92 | 41.20 | 23.18 | 3.92 | 41.67 |
| | | | | $C_4H_6N_6O_3$ | 25.80 | 3.23 | | 25.63 | 3.32 | |
| 26 | 262 (14.6)[j] | | | $C_4H_7N_5O \cdot H_2SO_4$ | 20.05 | 3.76 | 13.40[k] | 19.32 | 3.88 | 13.62[k] |
| 28 | 251 (17.5), 350 (13.3) | 1635, 1595, 1520 | | $C_{18}H_{18}N_4S_2$ | 60.99 | 5.12 | 15.81 | 60.80 | 5.29 | 15.43 |
| 30 | 319 (8.04) | 1620, 1600, 1540 | | $C_{11}H_{14}N_6S$ | 50.36 | 5.38 | 32.03 | 50.64 | 5.38 | 31.77 |
| 31 | 268 (12.4), 352 sh (3.55), 414 (7.15) | 1650, 1630, 1565 | 4.55 (2, $CH_2$), 7.4 m (5, $C_6H_5$), 8.0 br (2, $NH_2$), 9.63 (1, CH) | $C_{12}H_{10}N_6S$ | 53.32 | 3.73 | 31.09 | 53.13 | 3.86 | 31.22 |
| 32 | 263 (16.7), 315 (2.09), 395 (4.07)[d] | 1670, 1630, 1580 | 7.0 br, 8.1 br (2, 2, $NH_2$), 9.48 (1, CH) | $C_5H_5N_7$ | 36.81 | 3.09 | 60.10 | 36.65 | 3.12 | 59.87 |

[a] Cary Model 14 and 17 spectrophotometers. [b] Perkin-Elmer Model 521 and 621 spectrophotometers. [c] Pmr spectra of samples were determined on DMSO-$d_6$ solutions (3–10% w/v), unless otherwise noted, on a Varian A-60A spectrometer with TMS as an internal reference; peak positions quoted in the case of multiplets are measured from the approximate center, and the relative peak areas are given to the nearest whole number. [d] Solvent contains 0.8% DMSO, 9.2% MeOH, and 90% pH 7 buffer. [e] Determined from the spectrum of a mixture of **5** and **9** in $CF_3CO_2D$ (10% w/v). [f] Mixture of **5** and **9**, see Experimental Section. [g] This spectrum also exhibited a weak peak near $\delta$ 1.2, which was attributed to the $CH_3$ of EtOH. [h] This peak overlapped the DMSO-$d_5$ peak. [i] Determined on a sample that contained both **7** and **16**. [j] Determined in 0.1 *N* HCl in the presence of cysteine. [k] Sulfur.

pyrimidotriazines is more than 25 nm higher than the corresponding band in the pteridines.

## Part B

## Experimental Section[18]

**2,5-Diamino-4-(benzylthio)pyrimidine-6(1*H*)-thione (1).**—A solution of **14** (1.0 g) in dioxane (50 ml) containing 95+% hydrazine (1.0 ml) was refluxed for 16 hr. The mixture was filtered, and the filtrate was evaporated to dryness *in vacuo*. The resulting residue was washed with $Et_2O$ (40 ml), then 0.2 *N* HCl (17 ml), and recrystallized from EtOH: yield 0.26 g (27%); mp ~247° dec and presoftening.

**7-(1-Methylhydrazino)thiazolo[5,4-*d*]pyrimidine (5) and 1,2-Dihydro-1-methylpyrimido[5,4-*e*]-*as*-triazine-5(6*H*)-thione (9).**—A cold solution of **11** (1.0 g)[4] in MeOH (30 ml) was added to a cold solution of methylhydrazine (0.70 ml) in MeOH (10 ml). The mixture was stirred in an ice bath for 1.5 hr, and the solid that deposited was collected by filtration and dried *in vacuo* over $P_2O_5$, yield 0.42 g. The pmr spectrum in $CF_3CO_2D$ indicated that this product was a mixture of **5** (57%) and **9** (43%). This sample analyzed as the one-half hydrate (see Table I). The filtrate from above was refrigerated for 18 hr to give a second crop, yield 0.16 g. The pmr spectrum indicated that this sample contained both **5** (80%) and **9** (20%). Elemental analyses indicated that an anhydrous mixture was obtained (see Table I). A second run was carried out in ethanol at room temperature. The mixture of **5** (61%) and **9** (39%) was stirred in 1 *N* HCl for 0.5 hr and then dried *in vacuo* over $P_2O_5$ at 78° for 18 hr to give an 84% yield of anhydrous **9**, mp >264°.

**5-Amino-7-hydrazinothiazolo[5,4-*d*]pyrimidine (7).**—A solution of **13** (500 mg) and 95+% hydrazine (0.4 ml) in PrOH (20 ml) was refluxed for 2 hr. The solid that deposited was collected by filtration, washed with hot petroleum ether (bp 85–105°), and dried *in vacuo* over $P_2O_5$, yield 92 mg (20%), mp >264°.

**Reactions with 5-Amino-7-hydrazinothiazolo[5,4-*d*]pyrimidine (7).**—A solution of **7** (100 mg) in DMSO (20 ml) containing 1 *N* NaOH (0.15 ml) was stirred at room temperature for 18 hr, neutralized with 1 *N* HCl (0.15 ml), and evaporated to dryness *in vacuo*. The resulting residue was washed with $H_2O$ and dried *in vacuo* over $P_2O_5$ at 78° for 4 hr to give a 1:3 mixture of **7** and **16**, yield 65 mg, mp >264°.

Solid **7** (25 mg) was added to concentrated HCl (2 ml), and the mixture was stirred at room temperature for 18 hr. The HCl salt of **7**, identified by its uv spectrum, was collected by filtration and refluxed in water (10 ml) for 4 hr. After filtration the residue (11 mg) obtained from the filtrate was identified as **2** by comparison of its uv spectrum (0.1 *N* HCl, 310 nm) with that of 2,4,5-triaminopyrimidine-6(1*H*)-thione (0.1 *N* HCl, 310 nm).[7] No reaction was observed when a solution of **7** in 4:1 DMSO–$H_2O$ was heated at 75° for 5 hr.

**7-Amino-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine-5(6*H*)-thione (10).**—A mixture of **31** (1.0 g) and hydrated NaSH (1.0 g) in $H_2O$ (40 ml) was heated with stirring at 80° for 2.5 hr. After filtration the filtrate was extracted with $Et_2O$ (discarded) and acidified with 1 *N* HCl. The solid that deposited was collected by filtration, washed with $C_6H_6$ and then with warm EtOH (25 ml), and dried *in vacuo* over $P_2O_5$ at 140°, yield 0.29 g (43%), mp >264°.

**Reactions with 7-Amino-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine-5(6*H*)-thione (10).**—A sample of **10** (180 mg) was recrystallized from a large volume of $H_2O$ and dried *in vacuo* over $P_2O_5$ at 140°, yield 90 mg, mp >264°.

*Anal.* Calcd for $C_5H_6N_6S$: C, 32.96; H, 3.32; N, 46.12. Found: C, 32.79; H, 3.38; N, 46.33.

Although this sample analyzed correctly for **10**, the pmr spectrum showed that this product was about a 2:1 mixture [$\delta$ 9.6 and 7.8 (CH)] of **33** and an unidentified component. The presence of **33** was confirmed by alkylation of the mixture (50 mg) with $C_6H_5CH_2Cl$ in 0.1 *N* NaOH to deposit **31**, yield 44 mg, mp 225° dec.

When a solution of **10** in $H_2O$ was refluxed for 18 hr, the pmr spectrum of the product showed weak CH peaks at $\delta$ 9.6 and 7.8 and a strong unidentified peak at $\delta$ 9.37.

Treatment of a DMSO solution of **10** (50 mg) with aqueous NaOH gave a mixture (32 mg) that appeared to contain **33** and another unidentified component [$\delta$ 9.6, 9.7 (CH)]. Elemental analyses suggested that the second component resulted from hydrolysis of the 7-amino group.

**5-Amino-7-(methylthio)thiazolo[5,4-*d*]pyrimidine (13).**—A mixture of **12** (1.0 g),[5] $CH_3I$ (0.38 ml), and $K_2CO_3$ (1.0 g) in DMF (20 ml) was stirred at room temperature for 4 hr, then diluted with 0.1 *N* HCl (90 ml), and evaporated to dryness *in vacuo*. The residue was washed with $H_2O$ (25 ml) and recrystallized from petroleum ether (bp 85–105°), yield 0.64 g (59%), mp 146°.

**5-Amino-7-(benzylthio)thiazolo[5,4-*d*]pyrimidine (14)** was similarly prepared by stirring a mixture of **12** (1.0 g),[5] $K_2CO_3$ (0.75 g), and $C_6H_5CH_2Cl$ (0.65 ml) in DMF (30 ml) at room temperature for 18 hr. The resulting residue was extracted with hot $CHCl_3$ (three 60-ml portions); the solid obtained from the combined extracts was recrystallized from benzene–petroleum ether (bp 85–105°), yield 0.69 g (46%), mp 145–146°.

**5-Amino-7-[2-(hydroxyethyl)thio]thiazolo[5,4-*d*]pyrimidine (15)** was similarly prepared by stirring a mixture of **12** (1.0 g),[5] 2-bromoethanol (0.38 ml), and anhydrous $K_2CO_3$ (0.75 g) in DMF (10 ml) at room temperature for 18 hr. The resulting residue was extracted with hot $C_6H_6$ (200 ml), which was cooled to deposit the product in two crops, yield 0.48 g (39%), mp 118–119°.

**5-(Benzylthio)-1,2-dihydro-1-methylpyrimido[5,4-*e*]-*as*-triazine (17).**—A mixture of **9** (1.6 g), $C_6H_5CH_2Cl$ (1.1 ml), and anhydrous $K_2CO_3$ (1.3 g) in DMF (20 ml) was stirred at room temperature for 18 hr. The mixture was evaporated to dryness *in vacuo*, and the residue was extracted with ether (three 100-ml portions). The solid obtained from the combined extracts was recrystallized from petroleum ether (bp 85–105°), yield 1.47 g (59.5%), mp 131° dec.

***N*-Amidino-6-amino-*as*-triazine-5-carboxamide (20).**—A mixture of **18** (2.0 g),[10] guanidine HCl (1.4 g), and NaOMe (0.76 g) in MeOH (25 ml) was stirred at room temperature for 18 hr. The solid was collected by filtration, washed with EtOH, and dried *in vacuo* over $P_2O_5$ at 56°, yield 1.7 g (72%), mp >264°.

***N*-Cyano-6-amino-*as*-triazine-5-carboxamide (22).**—Solid **20** (146 mg) was heated at 120° for 1 hr and then dissolved in 2-methoxyethanol (10 ml). The resulting solution was refluxed for 7 hr and evaporated to dryness *in vacuo*. This hygroscopic residue was washed with ether to give **22**, yield 127 mg (96%), melting point indefinite.

**7-Aminopyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one (21).**—A solution of **31** (1.1 g) in 1:2 dioxane–$H_2O$ (60 ml) containing 1 *N* NaOH (8.0 ml) was heated with stirring at 60° for 2 hr. The reaction mixture was filtered, and the filtrate was neutralized with 1 *N* HCl (8.0 ml). The precipitate that deposited was collected by filtration and washed with $Et_2O$ (two 50-ml portions). This solid was recrystallized twice from HOAc and dried *in vacuo* over $P_2O_5$ at 100° for 4 hr, yield 0.20 g (30%), mp >264°.

**2-Amino-4-hydrazino-5-nitropyrimidin-6(1*H*)-one (24).**—Anhydrous hydrazine (0.1 ml) was added to a suspension of **23** (200 mg)[13] in MeOH (10 ml), and the mixture was stirred at room temperature for 2.5 hr. The solid was collected by filtration, washed with MeOH, and dried *in vacuo* over $P_2O_5$ to give the hydrate, yield 200 mg (93%), mp >264°. This material was reprecipitated from DMSO with EtOH and dried at 100° to give anhydrous **24**.

**Reduction of 24.**—Solid $Na_2S_2O_4$ (4 g) was added with stirring over a 10-min period to a refluxing suspension of **24** (1.0 g) in $H_2O$ (30 ml). The hot mixture was filtered directly into cold 4 *N* $H_2SO_4$. After 1.5 hr the solid that deposited was collected by filtration and recrystallized from 2 *N* $H_2SO_4$ to give **26**·$H_2SO_4$, yield 0.26 g (20%), mp >264°.

**2,5-Diamino-4,6-bis(benzylthio)pyrimidine (28).**—A mixture of the semisulfate hydrate of **27** (9.0 g),[5] $K_2CO_3$ (16 g), and $C_6H_5CH_2Cl$ (8.7 ml) in DMF (180 ml) was stirred at room temperature for 18 hr and then diluted with $H_2O$ (900 ml). The oil that deposited was extracted with ether (three 1000-ml portions). The combined extracts were dried ($MgSO_4$), evaporated to dryness *in vacuo*, and the resulting oil stirred vigorously in ice–water to give a pink solid, yield 9.0 g (68%), mp ~73°. The analytical sample was obtained by recrystallization from hexane, mp 75°.

**2,5-Diamino-4-(benzylthio)-6-hydrazinopyrimidine (30).**—A solution of **28** (3.0 g) in 95+% hydrazine (30 ml) was heated with stirring at 65° for 18 hr and evaporated to dryness *in vacuo*. This residue was washed with hot petroleum ether (three 100-ml portions) and then extracted with $CHCl_3$ (300 ml). The extract was evaporated to dryness *in vacuo* to give practically pure **30**, yield 1.4 g (63%). For analyses a sample (390 mg) was recrys-

(18) Melting points were determined in a Kofler–Heizbank apparatus.

tallized from $H_2O$, yield 145 mg (50% recovery), mp 144° dec with presoftening from 139°.

**7-Amino-5-(benzylthio)pyrimido[5,4-*e*]-*as*-triazine (31).**—To a suspension of **30** (5.0 g) in $H_2O$ (250 ml) containing 1 *N* HCl (2.5 ml) was added $(EtO)_3CH$ (75 ml) with vigorous stirring. The mixture became oily and then resolidified. After 3 hr the crude product was collected by filtration and dried *in vacuo* over $P_2O_5$, yield 4.4 g (85%). For analyses a sample (860 mg) was recrystallized from MeCN, yield 650 mg (76% recovery), mp 226° dec.

**5,7-Diaminopyrimido[5,4-*e*]-*as*-triazine (32).**—Solid **31** (2.0 g) was added with stirring to 10% ethanolic ammonia (40 ml), which was cooled in an ice bath. After 30 min the ice bath was removed, and the reaction mixture was stirred at room temperature for 18 hr. The solid was collected by filtration, recrystallized from a large volume of $H_2O$, and dried *in vacuo* over $P_2O_5$ at 78°, yield 0.50 g (41%), mp >264°.

**Registry No.**—**1**, 31739-65-8; **5**, 31739-66-9; **7**, 31739-67-0; **9**, 31739-68-1; **10**, 31791-00-1; **13**, 31739-69-2; **14**, 31739-70-5; **15**, 31739-71-6; **16**, 31739-72-7; **17**, 31791-01-2; **20**, 31736-42-2; **21**, 31791-02-3; **22**, 31736-43-3; **24**, 31736-44-4; **26**, 23706-18-5; **28**, 31736-46-6; **30**, 31736-47-7; **31**, 31736-48-8; **32**, 31736-49-9.

**Acknowledgments.**—The authors are indebted to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Research Institute, who performed most of the microanalytical and spectral determinations reported.

# Bridgehead Nitrogen Heterocycles. I. The 2*H*(and 4*H*)-Pyrimido[1,2-*b*]pyridazin-2(and 4)-one, 3*H*-Imidazo[1,2-*b*]pyridazin-2-one, and 7*H*-1,3,4-Thiadiazolo[3,2-*a*]pyrimidin-7-one Systems

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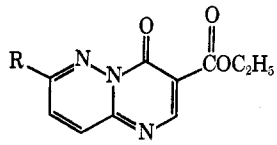
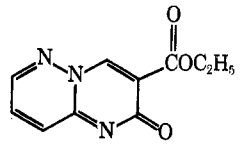
*Received April 26, 1971*

The title compounds have been synthesized by condensation of 3-amino-6-chloropyridazine and 2-amino-1,3,4-thiadiazole with several 3-chloroacrylic and atropic acids (and acid chlorides). Nucleophilic replacement reactions of some chloro-substituted 2*H*-pyrimido[1,2-*b*]pyridazin-2-ones are reported. Structural assignments are based on chemical evidence, ir, nmr, and mass spectral data. A brief analysis of the results is reported.

Of the isomeric pyrimido[1,2-*b*]pyridazinone and the 1,3,4-thiadiazolo[3,2-a]pyrimidone systems, only representatives of 4*H*-pyrimido[1,2-*b*]pyridazin-4-one[2] and 4*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-4-one[3,4] are known. The first report of the synthesis of the pyrimido[1,2-*b*]-pyridazinone ring system appeared in 1968 and came to our attention during the course of our own investigations. The condensation of 3-aminopyridazine with ethyl ethoxymethylenemalonate was reported by Stanovnik and Tišler[2] to afford ethyl 3-pyridazinylaminomethylenemalonate, which cyclized in refluxing diphenyl ether to give 3-ethoxycarbonyl-4*H*-pyrimido-[1,2-*b*]pyridazin-4-one (**1a**). The corresponding intermediate was prepared from 3-amino-6-chloropyridazine, but efforts to cyclize it to **1b** were unsuccessful. Structure **2**, resulting from initial condensation of 3-aminopyridazine with the ester carbonyl of ethyl ethoxymethylenemalonate, was rejected on the basis of the evidence for the intermediate and upon examination of spectroscopic data. An earlier report[3] describes a similar route to the 4*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-4-one system starting with 2-amino-5-methyl-1,3,4-thiadiazole and ethyl ethoxymethylenemalonate. Levin, *et al.*,[4] described these two reactants as yielding ethyl 5-methyl-1,3,4-thiadiazol-2-ylaminomethylenemalonate, which ring closed to the bicyclic product **3** on prolonged heating at elevated temperature under reduced pressure. Tišler and coworkers[5] have recently described the preparation of 6-chloro-2-hydroximidazo-[1,2-*b*]pyridazine (**4**) and 7-chloro-3,4-dihydropyrimido-[1,2-*b*]pyridazin-2-one (**5**) by fusion of 3-amino-2-(ethoxycarbonylalkyl)-6-chloropyridazinium bromides.



**1a**, R = H
**b**, R = Cl



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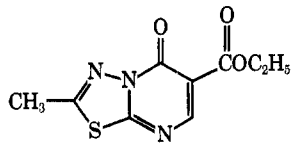

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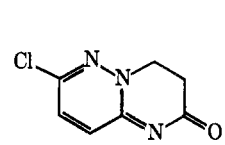

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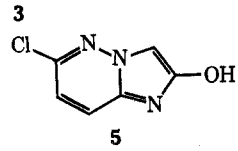

**5**

We wish to report the reaction of chlorinated acrylic and atropic acids (and acid chlorides) with 3-amino-6-chloropyridazine and 2-amino-5-(methylthio)-1,3,4-thiadiazole, which gave derivatives of 2*H*(and 4*H*)-pyrimido[1,2-*b*]pyridazin-2-(and 4)-one, 3*H*-imidazo-[1,2-*b*]pyridazin-2-one, and 7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one.

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