21273-18-7; IV, n = 4, R = Me, 21273-24-5; IV, n = 3, R = Et, 21273-25-6; V, n = 2, 7497-89-4; V, n = 3, 21273-27-8; XI, 21273-28-9; XI (trimethylsilyl ester), 21273-40-5; XII, 21273-29-0; XII (trimethylsilyl ester), 21273-41-6; XIII, 21273-30-3; XIII (trimethylsilyl ester), 21273-42-7; XIV, 21273-31-4; XIV (trimethylsilyl ester), 21273-43-8; XV, 21273-32-5; XV (trimethylsilyl ester), 21273-44-9; XVI, 21273-33-6; XVI (trimethylsilyl ester), 21273-45-0; 5-phenoxypentanoic acid, 7170-40-3; 4-phenoxy-1-bromobutane, 1200-03-9; 7-phenoxyheptanoic acid, 7170-42-5; 11-phenoxyundecanoic acid, 7170-44-7; 1,1-d_2-2-phenoxyethanol, 21273-38-1; 1,1-d_2-2-phenoxyethyl bromide, 21273-39-2.

Pyrimido[5,4-e]-as-triazines. IV. The Preparation and Some Reactions of Pyrimido[5,4-e]-as-triazine-5(6H)-thiones[1]

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Reaction of 5-(benzylthio)- and 5-chloro-1,2-dihydropyrimido[5,4-e]-as-triazine (**8** and **4**), respectively, with NaSH gave 1,2-dihydropyrimido[5,4-e]-as-triazine-5(6H)-thione (**3**). Treatment of **4** with thiourea also gave **3** and a 2-thiospeudourea addition product that was rearranged in HCl to give 9-amino-9H-purine-8(7H)-one-6(1H)-thione (**11**). Oxidation of **3** and some 5-alkylthio derivatives with diethyl azodicarboxylate gave the corresponding heteroaromatic compounds. Replacement of the 5-alkylthio group with various nucleophiles occurred readily to give 5-substituted pyrimido[5,4-e]-as-triazines. Also, the rearrangement of 7-hydrazinothiazolo[5,4-d]pyrimidine to **3** is demonstrated.

In the previous papers of this series, the preparation and some reactions of 5-substituted pyrimido[5,4-e]-as-triazines were reported.[2] The present paper is concerned with the preparation of pyrimido[5,4-e]-as-triazine-5(6H)-thione and some of its 5-alkylthio derivatives. The latter were desired as potential substrates for nucleophilic displacement reactions to give various 5-substituted compounds. In addition, rearrangements involving the 7-hydrazinothiazolo[5,4-d]pyrimidine–pyrimido[5,4-e]-as-triazine-5(6H)-thione ring systems are discussed.

The preparation of **3** by the reaction of **1** with hydrazine to give **2**,[3] and cyclization of the latter with the $(EtO)_3CH$–concentrated HCl reagent[2c] was unsuccessful (see Scheme I). This reaction gave only the HCl salt of **2**. To increase the solubility and reactivity of **2**, the thione group was blocked by alkylation. Although **2** has been reported to undergo rapid oxidation in an alkaline medium,[3] treatment of a NaOH solution of **2** with $C_6H_5CH_2Cl$ gave a good yield of 4-(benzylthio)-pyrimidine **5**. Cyclization of **5** with the $(EtO)_3CH$–concentrated HCl reagent gave the HCl of 5-(benzylthio)-1,2-dihydropyrimido[5,4-e]-as-triazine (**8**), and a smaller amount of the 9-[(ethoxymethylene)amino]-purine **6**. Acid hydrolysis of the latter gave the known 9-aminopurine **7**.[4] The free base of **8** was obtained by neutralization of a solution of the HCl with $NaHCO_3$.

The interaction of **8** with hydrated NaSH in EtOH replaced the benzylthio group to give a 59% yield of **3**.[5] Similarly, the reaction of **4**[2c] with NaSH gave an 85% yield of **3**. The preparation of **3** was also attempted by reaction of **4** with thiourea. This reaction gave a 13% yield of **3**, apparently formed from the 2-thiopseudourea **9**. Also, a second product was obtained in 52% yield that analyzed correctly for the hydrochloride of **9**, but treatment of this material with aqueous NaOH gave none of **3**. This result suggested that **9** had undergone an intramolecular addition reaction to give the hydrochloride of the isomeric tricyclic compound **10** (see Scheme II). Support for structure **10** was provided by its rearrangement in HCl to give **11**, identified by elemental anaylses and comparison of its ultraviolet spectrum with that of purine-8(7H)-one-6(1H)-thione.[6] A similar tricyclic compound, obtained from the reaction of 6-chloropurine with thiourea, also undergoes this type of rearrangement,[7] which, in the present case, involves cleavage of both the thiazole and as-triazine rings, and hydrolysis of the guanidino moiety of **10** to give, presumably, the intermediate pyrimidine **12** which then undergoes cyclization and deformylation to give **11**.

Reaction of **3** with 4 N HCl at room temperature cleaved the as-triazine ring to give the pyrimidine **2**. In contrast, the product resulting from treatment of **3** with CF_3CO_2H was identified by elemental analyses and spectral data as the thiazolo[5,4-d] pyrimidine **13** (see Scheme III). The nmr spectrum of **3** in CF_3CO_2D showed the appearance of two new CH peaks in about 20 min and the disappearance of the two CH peaks of **3** in about 1 hr. Presumably, this rearrangement involves the trifluoroacetylation and ring opening of **3** to give **15**, which then undergoes recyclization to give **13**. The nmr data suggested that the recyclization step might have occurred during the reaction work-up. The assignment of the position of the CF_3CO group in **13** is based on analogy with the products obtained from the acylation and ring opening of the triazine ring of other 1,2-dihydropyrimido[5,4-e-]-as-triazines with carboxylic acids.[2a,c] To study the reverse rearrangement (**14** → **16** → **3**), the preparation of the known 7-hydra-

(1) This investigation was supported by funds from the C. F. Kettering Foundation and the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract PH43-64-51.

(2) (a) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, **34**, 2102 (1969); (b) C. Temple, Jr., and J. A. Montgomery, *ibid.*, **28**, 3038 (1963); (c) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *ibid.*, **28**, 923 (1963).

(3) E. C. Taylor, J. W. Barton, and W. W. Paudler, *ibid.*, **26**, 4961 (1961).

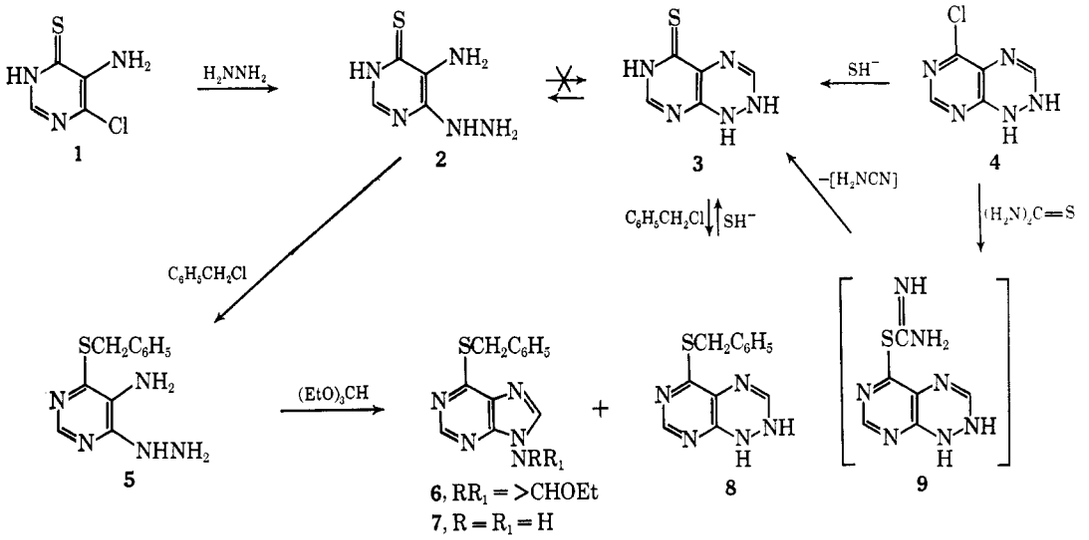
(4) C. Temple, Jr., A. G. Laseter, and J. A. Montgomery, *J. Heterocycl. Chem.*, **5**, 711 (1968).

(5) A similar reaction with a 4-(benzylthio)pteridine has been described by J. J. McCormach and H. G. Mautner, *J. Org. Chem.*, **29**, 3370 (1964).

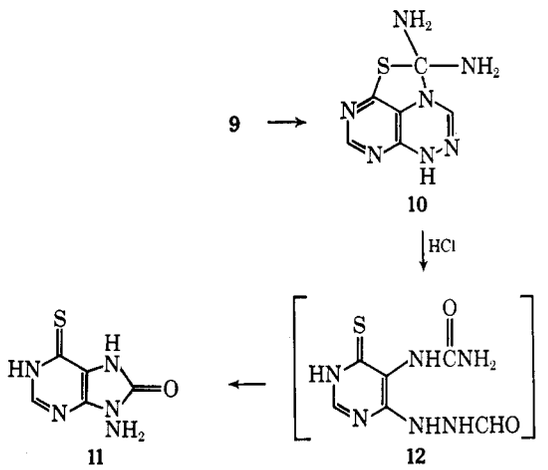
(6) R. K. Robins, *J. Amer. Chem. Soc.*, **80**, 6671 (1958).

(7) C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **31**, 1417 (1966).

SCHEME I



SCHEME II



zinothiazolo[5,4-*d*]pyrimidine (**14**) was undertaken.[8] Treatment of **19**[8] in ethanolic N_2H_4 by the reported procedure gave a mixture from which only the hydrazinopyrimidine **2** was obtained. In reactions carried out in MeOH, the products were identified as **1**, **2**, and 5-hydrazinopyrimido[5,4-*e*]-*as*-triazine.[2a] Compound **1** results from cleavage of the thiazolo ring of **19** and presumably **2** results from cleavage of the thiazolo ring of **14**. The sequence of reactions leading to the formation of the pyrimido[5,4-*e*]-*as*-triazine is unknown, but must involve the replacement of both the chloro and sulfur atoms of **19** with hydrazine moieties and air oxidation of an intermediate dihydro compound. Treatment of **19** with $N_2H_5{}^+OAc^-$ in aqueous dioxane, however, gave a product that was shown by its nmr spectrum to be a 1:2 mixture of **14**–**3**. A sample of **14** was finally obtained by treatment of an Et_2O solution of **19** with N_2H_4. Although the nitrogen analysis on this material for anhydrous **14** was 1% low, the CH analysis was correct and its ultraviolet spectrum was consistent with that previously reported for the hemihydrate of **14**.[8] The nmr spectrum of this material in deuterated DMSO initally showed only two CH peaks, but after 24 hr the two CH peaks of **3** were also detected. Additional studies on this type of rearrangement are being investigated and will be reported at a later date.

The benzylation of **3** gave the 5-benzylthio compound **8** described above. The alkylation of **3** with chloroacetonitrile gave a product that analyzed correctly for **17**, but the absence of a CN band in its ir spectrum indicated that intramolecular cyclization of the latter to a tricyclic compound might have occurred as in the conversion of **9** to **10**. Comparison of the ultraviolet spectrum of this material with that of **10** and **18**, however, provided support for structure **17**. In the methylation of **3** a 50% yield of the dihydro compound **18** and a 6% yield of the heteroaromatic compound **21** were obtained. Presumably, **21** is formed during the reaction by the air oxidation of **18**. Oxidation of **3** with diethyl azodicarboxylate in $CHCl_3$ gave the heteroaromatic compound **20**, identified by elemental analysis and by methylation to give the 5-methylthio compound **21** described above. Apparently this is the first instance in which diethyl azodicarboxylate has been used for the oxidation of a heterocyclic system.[9] Similarly, oxidation of **18** and **8** with this reagent gave **21** and **22**, respectively. As with **8**, reaction of **18** with ethanolic NaSH gave **3**. Treatment of **21** with NaSH, however, gave a mixture of **3** and **24**[2a] rather than **20**, the product expected from simple displacement of the methylthio group. The formation of **3** results from replacement of methylthio group and reduction of the *as*-triazine ring, both by NaSH. Apparently, **24** results from hydrolysis of the methylthio group of **21**. Also, the replacement of the benzylthio group of **22** with nitrogen nucleophiles occurred readily. Reaction of **22** with ethanolic NH_3 at room temperature gave a mixture of **23** (60%), **24** (37%), and benzyl disulfide (77%).[2a] Similarly, reaction of **22** with hydroxylamine, guanidine, and (diphenylmethyl)amine, respectively, gave **25**, **26**, and **27**.

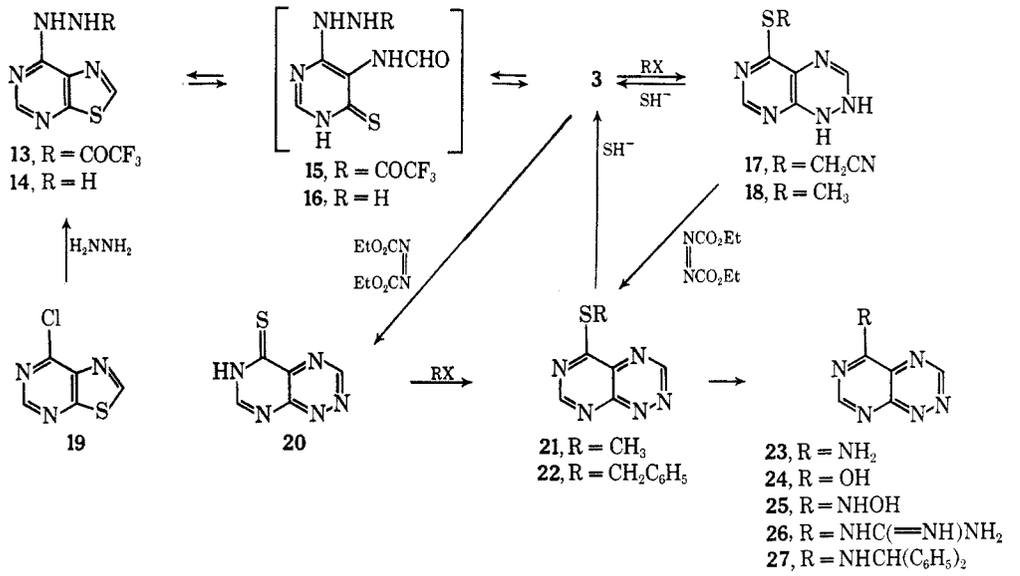
Experimental Section

Melting points were determined on a Kofler–Heizbank apparatus and are corrected. The uv absorption spectra of solutions were determined with a Cary Model 14 spectrophotometer, whereas the ir absorption spectra were determined in pressed

(8) L. Marchad, R. Promel, R. H. Martin, and A. Cardon, *Bull. Soc. Chim. Belges.*, **69**, 177 (1960).

(9) For other types of oxidation with this reagent, see (a) O. Diels, *Ber.*, **56**, 1933 (1923); (b) F. Yoneda, K. Suzuki, and Y. Nitta, *J. Amer. Chem. Soc.*, **88**, 2328 (1966).

SCHEME III



potassium bromide disks with Perkin-Elmer Models 221-G and 521 spectrophotometers. The nmr spectra were obtained on a Varian A-60 spectrometer using tetramethylsilane as an internal reference. Thin layer chromatograms (tlc) were prepared from silica gel H (Brinkmann) and were usually developed with mixtures of $CHCl_3$ and MeOH.

5-Amino-4-hydrazinopyrimidine-6(1H)-thione (2)[3] was prepared from **1** by the reported procedure in 82% yield. This compound also results from **3** by the action of 4 *N* HCl. Nmr (<5% DMSO d_6 w/v) τ 5.20, 3.17 (broad, NH) and 2.18 (CH); nmr (<5% CF_3CO_2D w/v) τ 1.52 and 1.39[10] (CH).

1,2 Dihydropyrimido[5,4-e]*as*-triazine-5(6H)-thione (3).—A mixture of **4** (24 g) and hydrated NaSH (96 g) in EtOH (2400 ml) was refluxed for 1 hr, evaporated to dryness *in vacuo*, and the resulting residue suspended in H_2O (1100 ml). After filtration, the filtrate was neutralized with HOAc; the solid that precipitated was collected by filtration and washed with H_2O (1200 ml). The dried solid was stirred in C_6H_6 (1200 ml) to remove sulfur, then suspended in H_2O (530 ml) and dissolved by the addition of 1 *N* NaOH (128 ml). The solution was filtered and the filtrate was acidified with 1 *N* HCl (150 ml) to deposit **3**, which was dried *in vacuo* over P_2O_5 at 78°: yield 20 g (85%); mp >264°; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$)[11a] 238 (6.83), 256 (7.95) 328 (2.63), and 412 mμ (5.60); ir 3280, 3190, 1650 (NH); 1600, 1580, and 1510 cm^{-1} (C=C, C=N); nmr (<10% DMSO-d_6 w/v) τ 3.75 (d, 1, J = 3 Hz, 3-CH), 3.18 (d, 1,2-NH), 2.45 (1, 7-CH), 1.27 (1, 1-NH), and −2.65 (1, 6-NH); nmr (<5% CF_3CO_2D w/v)[12] τ 2.70 and 1.98 (1, 1, CH).

Anal. Calcd for $C_5H_5N_5S$: C, 35.92; H, 3.02; N, 41.89. Found: C, 35.72; H, 3.20; N, 41.82.

B.—Similarly a mixture of **8** (1.0 g) and hydrated NaSH (2.5 g) was treated as described above to give **3**; yield 0.38 g (59%). Likewise, **18** (0.50 g) gave **3**; yield 0.27 g (58%). Reaction of **21** (0.34 g) with NaSH (2 g) also gave crude **3**; yield 0.12 g (38%). The solid obtained from this reaction filtrate was identified as **24** by tlc.

5-Amino-4-(benzylthio)-6-hydrazinopyrimidine (5).—To a suspension of **2** (35 g) in H_2O (350 ml) was added with stirring $C_6H_5CH_2Cl$ (26 ml) and 1 *N* NaOH (228 ml). After the mixture stirred at room temperature for 95 hr, the solid (55 g) was collected by filtration and recrystallized from C_6H_6 to give **5** in two crops: yield 43 g (78%); mp 131° with presoftening from 127°; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$)[11b] 277 (5.5) and 328 mμ (8.9); ir 3420, 3340, 3280, 3230, 1640 (NH); 1575, 1535, and 1490 cm^{-1} (C=C, C=N).

Anal. Calcd for $C_{11}H_{13}N_5S$: C, 53.42; H, 5 30; N, 28 29; S, 12.96. Found: C, 53.47; H, 5.38; N, 28.38; S, 12.90.

5-(Benzylthio)-1,2-dihydropyrimido[5,4-e]-*as*-triazine (8). A.—Concentrated HCl (6.8 ml) was added slowly to a suspension of **5** (20 g) in $(EtO)_3CH$ (400 ml). The resulting orange mixture was stirred with a strong and efficient stirrer for 4 hr at room temperature. The crude HCl (19 g) was collected by filtration, washed with ether, and suspended in H_2O (900 ml). After the addition of $NaHCO_3$ (5.8 g), the solid was collected by filtration and crystallized from C_6H_6: yield 14 g (67%); mp 160°; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$)[11c] 356 mμ (5.76); ir 3280 (NH), 1660, 1585, and 1530 cm^{-1} (C=C, C=N); nmr (10% DMSO-d_6 w/v) τ 5.70 (2, CH_2), 3.84 (d, 1, J = 3 Hz, 3-CH), 2.68 (6, C_6H_5, 2-NH), 2.33 (1, 7-CH), and 1.37 (1, 1-NH).

Anal. Calcd for $C_{12}H_{11}N_5S$: C, 56.01; H, 4.31; N, 27.25; S, 12.46. Found: C, 56.22; H, 4.46; N, 27.11; S, 12.2.

The combined $(EtO)_3CH$ filtrate and Et_2O wash from above was evaporated to dryness to give **6**: yield 3.9 g (15%); mp 125° with presoftening.

Anal. Calcd for $C_{15}H_{16}N_5OS$: C, 57.30; H, 5.13. Found: C, 57.28; H, 4.91.

A suspension of **6** in 1% HCl (100 ml) was stirred at room temperature for 20 hr. The solid was collected by filtration and recrystallized from THF–petroleum ether (bp 85–105°) to give **7**: yield 2.1 g (10%); mp 166–167° (lit.[4] mp 167–168°).

Anal. Calcd for $C_{12}H_{11}N_5S$: C, 56.01; H, 4.31; S, 12.46. Found: C, 56.27; H, 4.52; S, 12.2.

B.—A mixture of **3** (1.0 g), $C_6H_5CH_2Cl$ (0.7 ml), and K_2CO_3 (0.85 g) in DMF (10 ml) was stirred at room temperature for 20 hr, evaporated to dryness *in vacuo*, and the residue washed with H_2O to give crude **8**; yield 1.2 g (78%). The alkylation of **3** (1.0 g) with $C_6H_5CH_2Cl$ (0.7 ml) was also effected in aqueous NaOH to give crude **8**; yield 0.89 g (58%).

Reaction of 4 with Thiourea.—A suspension of **4** (2.0 g) in PrOH (40 ml) containing thiourea (1.0 g) was refluxed for 1.5 hr. The solid was collected by filtration and extracted with hot MeOH (250 ml). The residue was identified as **3** (75% pure) by its uv, ir, and nmr spectra; yield 0.25 g (13%). The extract was evaporated to dryness, and the resulting residue was dried *in vacuo* over P_2O_5 at 100° to give **10**; yield 1.5 g (52%). This sample melted with decomposition from 190°; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$) 230 (12.0) and 308 mμ (9.68); ir 1670 (NH), 1590, 1550, and 1530 cm^{-1} (C=C, C=N).

Anal. Calcd for $C_6H_7N_7S \cdot HCl$: C, 29.33; H, 3.28; N, 39.91; Found: C, 29.08; H, 3.49; N, 39.66.

9-Amino-9H-purine-8(7H)-one-6(1H)-thione Hydrochloride (11).—A solution of **10** (0.2 g) in 1 *N* HCl (10 ml) was refluxed for 2 hr. The solid that deposited was collected by filtration and dried *in vacuo* over P_2O_5 at 78°; yield 0.05 g (28%); mp >264°; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$)[11a] 239 (11.7) and 332 mμ (14.2); ir 3300–2600 (NH), 1720 (CO), 1615 (NH_2), and

(10) This peak increased with time and was assigned to the product resulting from the interaction of **2** with the solvent.

(11) Each solution contains 10% dissolving solvent and 90% appropriate aqueous solvent: (a) 8% methanolic DMSO; (b) H_2O; (c) MeOH; (d) dissolved in 0.1 *N* NaOH and neutralized with 0.1 *N* HCl.

(12) After 1 hr, this spectrum exhibited peaks only at τ 0.96 and 0.46 (CH), which, on comparison with the peaks exhibited by **13**, suggested the ring opening of **3** to give **15**.

1570 and 1525 cm^{-1} (C=C, C=N); nmr (<2.5 DMSO-d_6-D_2O w/v) τ 1.81 (CH).

Anal. Calcd for $C_5H_5N_5OS\cdot HCl$: C, 27.34; H, 2.75; N, 31.88. Found: C, 27.11; H, 2.87; N, 32.05.

7-[2-(Trifluoroacetyl)hydrazino]thiazolo[5,4-*d*]pyrimidine (13).—A solution of **3** (0.64 g) in CF_3CO_2H (25 ml) was stirred at room temperature for 18 hr and evaporated to dryness. The residue was washed with Et_2O and dried *in vacuo* over P_2O_5 at 78°; yield 0.85 g (84%); mp 209° with decomposition and sublimation; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$)[11a] 266 (10.3), uv (MeOH), 262 mμ (10.2); ir 1715 (CO), 1620 (NH), 1560, 1550, and 1530 cm^{-1} (C=C, C=N); nmr (< 5% DMSO-d_6 w/v) τ 1.42, 0.60 (1, 1, CH); nmr (5% CF_3CO_2D w/v) τ 0.95 and 0.55 (1, 1, CH).

Anal. Calcd for $C_7H_4F_3N_5OS$: C, 31.94; H, 1.53; N, 26.61. Found: C, 31.72; H, 1.74; N, 26.78.

Reaction of 19 with Hydrazine. A.—Hydrazine (95+%) (0.17 ml) was added with stirring to a solution of **19**[8] (0.88 g) in Et_2O (200 ml). After 2 hr, the solid was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5 at 78° to give **14**:[8] yield 0.16 g (19%); mp, rapid decomposition above 200° with sublimation; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$)[11c] 222 (15.3) and 263 mμ (9.75); nmr (<2.5% DMSO-d_6 w/v) τ 1.55 and 0.77 (1, 1, CH) and broad NH;[13] nmr (2.5% CF_3CO_2D w/v) τ 1.07 and 0.57 (1, 1, CH).[14]

B.—A solution of **19** (1.0 g) in dioxane was added with stirring to a mixture of hydrazine (95+%, 1.0 ml), glacial HOAc (1.8 ml), and H_2O (25 ml). After 2 hr, the solid (0.36 g) that deposited was collected by filtration and identified as about a 1:2 mixture of **14**–**3**; nmr (<5% DMSO-d_6 w/v) τ 1.57 and 0.78 (1, 1, CH) (**14**); 3.77 and 2.50 (2, 2, CH) (**3**).

C.—Compound **19** (1.0 g) was added with stirring to a mixture of hydrazine (95+%, 1.0 ml) and MeOH (10 ml). After 18 hr, the solid (0.37 g) that deposited was collected by filtration and identified as **2**[3] by its uv spectrum and tlc [BuOH (5)/HOAc (2)/H_2O (3)]. Acidification of the filtrate with HOAc deposited a solid (0.39 g) that was identified as **1**[3] by its uv spectrum and tlc.

When the same reactants as described above were maintained near 0° for 18 hr, the solid (0.52 g) that deposited was identified as 5-hydrazinopyrimido[5,4-*e*]-*as*-triazine[2a] by its uv and nmr spectra.

[(1,2-Dihydropyrimido[5,4-*e*]-*as*-triazin-5-yl)thio]acetonitrile (17).—To a suspension of **3** (1.0 g) in H_2O (20 ml) was added 1 *N* NaOH (6 ml) and $ClCH_2CN$ (0.4 ml). After 2 hr, the solid was collected by filtration and extracted with hot C_6H_6 (700 ml). This extract deposited the product in two crops: yield 0.38 g (31%); mp about 228° with decomposition; uv (pH 7) λ_{max} ($\epsilon \times 10^{-3}$)[11c] 258 (13.2), 356 (3.54); ir 1650 (NH), 1625, 1590, 1555, and 1495 cm^{-1} (C=C, C=N); nmr (<10% DMSO-d_6 w/v) τ 6.27 (2, CH_2), 2.64, 2.16 (1, 1, CH), 1.43 (broad), and 0.43 (1, 1, NH).

Anal. Calcd for $C_7H_6N_6S$: C, 40.76; H, 2.93; N, 40.75. Found: C, 41.11; H, 3.13; N, 40.63.

1,2-Dihydro-5-(methylthio)pyrimido[5,4-*e*]-*as*-triazine (18).—To a mixture of **3** (10 g) and MeI (3.8 ml) in H_2O (100 ml) was added with stirring 1 *N* NaOH (60 ml). After 1 hr, the solid was collected by filtration and dried *in vacuo* over P_2O_5. This residue was boiled in C_6H_6 (2800 ml), and the unreacted **3** (1.5 g) was removed by filtration. The filtrate was allowed to cool to deposit **18**, which was dried *in vacuo* over P_2O_5: yield 4.6 g (50% based on reacted **7**); mp 208–209° with presoftening from 202°; uv (pH 7) λ_{max} ($\epsilon \times 10^{-3}$)[11c] 239 (10.4) and 381 (5.21); ir 1650, 1590, 1560, and 1510 cm^{-1} (C=C, C=N); nmr (10% DMSO-d_6 w/v) τ 7.63 (CH_3), 3.83 (d, 1, J = 3 Hz, 3-CH), 2.39 (1, 7-CH), 2.72 (d, 1, 2-NH), and 1.50 (1, 1-NH).

Anal. Calcd for $C_6H_7N_5S$: C, 39.73; H, 3.89; N, 38.67; S, 17.68. Found: C, 39.92; H, 3.90; N, 38.79; S, 17.47.

The C_6H_6 filtrate was evaporated to dryness, and the residue was recrystallized from petroleum ether (bp 85–105°) to give **21**: yield 0.53 g (6%); mp 137°.

Pyrimido[5,4-*e*]-*as*-triazine-5(6H)-thione (20).—A mixture of **3** (1.0 g), diethyl azodicarboxylate (1.1 ml), and $CHCl_3$ (100 ml) in a flask completely covered with aluminum foil was stirred at room temperature for 18 hr. The solid was collected by filtration and washed with EtOAc; yield 0.70 g. The nmr spectrum in DMSO-d_6 indicated that this material was a 3:1 mixture of **20** and **3**. The mixture (0.65 g) was treated again with diethyl azodicarboxylate (0.55 ml) in $CHCl_3$ (50 ml) to give pure **20**: yield 0.52 g (53%); mp <260°; uv (pH 7) λ_{max} ($\epsilon \times 10^{-3}$)[11d] 259 (11.7) and 450 mμ (4.96); ir 1585, 1540, 1505, and 1495 cm^{-1} (C=C, C=N); nmr (<5% DMSO-d_6 w/v) τ 1.56, −0.02 (1, 1, CH), and −3 (broad, NH).

Anal. Calcd for $C_5H_3N_5S$: C, 36.35; H, 1.83; N, 42.39; S, 19.41. Found: C, 36.60; H, 2.04; N, 42.68; S, 19.10.

5-(Methylthio)pyrimido[5,4-*e*]-*as*-triazine (21).—A. A mixture of **18** (3.7 g), diethyl azodicarboxylate (3.7 ml), and $CHCl_3$ (185 ml) was stirred at room temperature for 4 hr in a flask completely covered with aluminum foil. The resulting solution was evaporated to dryness *in vacuo*, and the residue was recrystallized from MeOH: yield 2.6 g (71%); mp 137–139°; uv (pH 7) λ_{max} ($\epsilon \times 10^{-3}$)[11c] 238 (11.3), 262 (5.33), and 888 mμ (7.27); ir 3060, 3010 2920, 2845 (CH), 1545, 1525, and 1500 cm^{-1} (C=C, C=N); nmr (10% DMSO-d_6 w/v) τ 7.30 (3, CH_3), 0.73, and −0.20 (1, 1, CH).

Anal. Calcd for $C_6H_5N_5S$: C, 40.20; H, 2.79; N, 39.10; S, 17.87. Found: C, 40.38; H, 3.00; N, 38.99; S, 17.92.

B.—To a suspension of **20** (0.30 g) in H_2O (10 ml) was added MeI (0.12 ml) and 1 *N* NaOH (1.9 ml). After 2 hr, the product was collected by filtration and washed with H_2O: yield 0.18 g (55%); mp 137°.

5-(Benzylthio)pyrimido[5,4-*e*]-*as*-triazine (22) was prepared in 63% yield from **8** and diethyl azodicarboxylate: mp 113°; uv (pH 7) λ_{max} ($\epsilon \times 10^{-3}$)[11c] 240 (13.5) and 391 mμ (8.30, unstable); ir 1550, 1530, 1500 and 1490 cm^{-1} (C=C, C=N); nmr (10% DMSO-d_6 w/v) τ 5.32 (2, CH_2); 2.57 (5, C_6H_5); 0.62, and −0.30 (1, 1, CH).

Anal. Calcd for $C_{12}H_9N_5S$: C, 56.45; H, 3.55; N, 27.44. Found: C, 56.63; H, 3.73; N, 27.25.

Amination of 22.—A solution of **22** (200 mg) in 10% ethanolic NH_3 (10 ml) was stirred at room temperature for 18 hr to deposit **23**,[2a] identified by its tlc; yield 70 mg (60%). The residue obtained from evaporation of the filtrate to dryness was washed with Et_2O to give **24**,[2a] identified by its uv and ir spectra; yield 43 mg (37%). Evaporation of the Et_2O wash gave benzyldisulfide; yield 75 mg (77%); mp 70° (lit. mp 71–72°).

5-(Hydroxyamino)pyrimido[5,4-*e*]-*as*-triazine (25).—A suspension of 22 (1.0 g) in methanolic hydroxylamine (25 ml), prepared from the HCl salt (1.5 g) and NaOMe (1.1 g), was stirred for 4 hr at room temperature. The solid was collected by filtration, washed with MeOH, and dried *in vacuo* over P_2O_5 at 78°: yield 0.62 g (96%); mp >264°; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$)[11a] 381 mμ (6.67); ir 3240, 3050, (NH, OH), 1630 (NH), 1595, and 1510 (C=C, C=N); nmr (<5% DMSO-d_6 w/v) τ 2.26, 0.55 (1, 1, CH), and −1.68 (1, NH).

Anal. Calcd for $C_5H_4N_6O$: C, 36.59; H, 2.46; N, 51.21. Found: C, 36.69; H, 2.60; N, 51.49.

Pyrimido[5,4-*e*]-*as*-triazin-5-ylguanidine (26).—A solution of **22** (0.50 g) in methanolic guanidine (25 ml), prepared from the HCl salt (1.0 g) and NaOMe (0.45 g), was stirred for 1 hr at room temperature to deposit **26**; yield 0.34 g (91%). Recrystallization from H_2O gave the analytical sample: mp >264°; uv (pH 7) λ_{max} ($\epsilon \times 10^{-3}$)[11b] 246 (14.4), 400 (7.53); ir 3445, 3300–3050 (NH), 1640 (NH), 1550, 1535, and 1495 cm^{-1} (C=C, C=N); nmr (<6% DMSO-d_6 w/v) τ 2.03 (NH), 1.35, and 0.03 (1, 1, CH).

Anal. Calcd for $C_6H_6N_8$: C, 37.90; H, 3.18; N, 58.92. Found: C, 37.73; H, 3.10; N, 58.96.

5-[(Diphenylmethyl)amino]pyrimido[5,4-*e*]-*as*-triazine (27).—A solution of **22** (5.0 g) and (diphenylmethyl)amine (17 ml) in MeOH (125 ml) was refluxed for 6 hr and evaporated to a small volume *in vacuo*. This residue was stirred in petroleum ether (700 ml) (bp 80–105°) for 2 hr, and the crude product that formed was collected by filtration: yield 6.0 g (98%); mp 141° dec with presoftening. Recrystallization from petroleum ether (bp 85–105°) and drying the resulting solid *in vacuo* over P_2O_5 at 78° gave the analytical sample: mp 155° with presoftening from 150°; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$)[11c] 253 (sh) and 369 mμ (10.5); ir 3360 (NH), 3055, 3025 (CH), 1575, 1565, and 1520 cm^{-1} (C=C, C=N); nmr (8% DMSO-d_6-D_2O w/v) τ 3.10 [1, $CH(C_6H_5)_2$], 2.63 (10, C_6H_5), 1.20, and −0.13 (1, 1, CH).

Anal. Calcd for $C_{18}H_{14}N_6$: C, 68.78; H, 4.49; N, 26.74. Found: C, 68.64; H, 4.68; N, 26.53.

Registry No.—**3**, 21308-86-1; **5**, 21308-87-2; **6**,

(13) After 24 hr, this spectrum also showed CH peaks at τ 3.75 and 2.49 (**3**).

(14) After 1 hr, this spectrum also showed CH peaks at τ 0.96 and 0.58 (**13**).

21308-88-3; **8**, 21308-89-4; **10**, 21308-90-7; **11**, 21308-91-8; **13**, 21308-92-9; **14**, 21308-93-0; **17**, 21308-94-1; **18**, 21308-95-2; **20**, 21308-96-3; **21**, 21308-97-4; **22**, 21308-98-5; **25**, 21308-99-6; **26**, 21309-00-2; **27**, 21309-01-3.

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Alternate Precursors in Biogenetic-type Syntheses. V.[1] 3-(Indol-3-ylmethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline as a Precursor. The Synthesis and Stereochemistry of 2-Methylcyclohex[*d*]indolo[2,3-*f*]morphan-15-one

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A biogenetic-type synthesis employing 3-(indol-3-ylmethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**2**) as an alternate precursor in place of the corresponding 1-(indol-3-ylmethyl) analog is described. Birch reduction of **2** followed by acid-catalyzed hydrolysis and cyclization leads to the formation of a mixture of epimeric 2-methylcyclohex[*d*]indolo[2,3-*f*]morphan-15-ones (**7a** and **7b**), which differ only in the configuration at C-4. Chemical and spectroscopic evidence indicates the higher melting ketone (major product) to have the geometry of a *trans*-decahydroisoquinoline (**7a**), the other being a *cis*-decahydroisoquinoline (**7b**).

Earlier publications in this series have described the use of 1-(indol-3-ylmethyl)isoquinoline derivatives as alternative precursors[2] for the biogenetic-type synthesis[3] of missing alkaloid systems[1] related to naturally occurring alkaloids. Thus, the indole isosteres of dihydrothebainone[4] and argemonine (N-methylpavine)[1] as well as an indoline analog in the aporphine series[5] have been prepared.

Our observation[1] of the relatively mild conditions required for the rearrangement of 2-alkyl-1-(indol-3-ylmethyl)-1,2-dihydroisoquinolines to 2-alkyl-3-(indol-3-ylmethyl)-3,4-dihydroisoquinolinium salts suggests that compounds derived from the latter may be considered as examples of another type of biologically feasible alternate precursor. Insertion of a 3-(indol-3-ylmethyl)isoquinoline derivative such as **2** at some stage of a biogenetic-type synthesis would be expected to give rise to new types of alkaloidal systems. The present investigation concerns the use of **2** as a precursor in a synthetic scheme, analogous to that employed[4] in the preparation of the indole isostere of dihydrothebainone. The resulting products, the epimeric ketones **7a** and **7b**, are representative of the previously unreported cyclohex[*d*]indolo[2,3-*f*]morphan ring system.[6,7]

Precursor **2** was prepared by reduction of **1** as described previously.[1] While **2** itself could be used as a starting material for the synthetic sequence (Chart I), it was found most convenient to subject **1** directly to the conditions of Birch reduction. The resulting hexahydroisoquinoline **3** was refluxed with aqueous methanolic hydrochloric acid to give the epimeric unsaturated ketones **5**. These were not isolated, since they cyclized, under the reaction conditions, to give a mixture of the epimeric cyclic ketones **7a** and **7b**.[8] The major product, isolated in 48% yield, had a higher melting point (260–262°), a lower solubility in chloroform and methanol, and a slower migration rate on thin layer chromatography than the minor product (mp 227.5–228.5°), which was isolated in 12% yield.[9] Both compounds gave a negative Ehrlich test and ultraviolet spectra which were typical of 2,3-dialkylindoles.

The configuration of the higher melting ketone was established as that of **7a** by examination of the NH frequencies of the alcohols **9a** and **10a** produced, respectively, by lithium aluminum hydride reduction and reaction with phenyllithium. Dreiding models indicate that, in the chair conformation of **9a** and **10a** with the axial hydroxyl, there should be strong intramolecular bonding between the oxygen and the indole

(1) Paper IV in this series: H. Zinnes, F. R. Zuleski, and J. Shavel, Jr., *J. Org. Chem.*, **33**, 3605 (1968).

(2) G. C. Morrison, R. O. Waite, F. Serafin, and J. Shavel, Jr., *ibid.*, **32**, 2551 (1967).

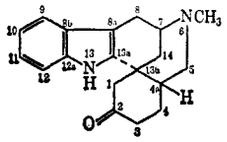
(3) E. E. van Tamelen, "Progress in the Chemistry of Organic Natural Products," Vol. 19, L. Zeckmeister, Ed., Springer-Verlag, Vienna, Austria, 1961, p 242.

(4) G. C. Morrison, R. O. Waite, and J. Shavel, Jr., *J. Org. Chem.*, **32**, 2555 (1967).

(5) G. C. Morrison, R. O. Waite, and J. Shavel, Jr., *ibid.*, **33**, 1663 (1968).

(6) The numbering system (see Chart I) was chosen to conform as closely as possible with that used for the cyclohex[*j*]indolo[2,3-*f*]morphan series.[2] Compounds **7a** and **7b** differ only in the ring junction at C-4. In **7a**, the hydrogen at C-4 is *trans* with respect to the indole group at C-5, so that the geometry of the ring system resembles that of a *trans*-decahydroisoquinoline (see structure **9a**). The geometry of **7b** resembles that of a *cis*-decahydroisoquinoline (see structure **9b**), the hydrogen at C-4 being *cis* to the indole at C-5. Thus, **7a** is referred to as the *trans* epimer and **7b** as the *cis* epimer. In naming compounds of the **a** series, the prefix "*trans*-[5(indolo),4H]" is used, whereas "*cis*-[5(indolo),4H]" is used for the **b** series. The geometry of the *trans* epimer (**a** series) most closely resembles that of the compounds known as *cis*-morphinans (including morphine) since the latter also contain a *trans*-decahydrosioquinoline moiety. This apparent discrepancy arises from the fact that in the morphinans, ring E is fused with both ring C and ring D; the conventional stereochemical designation of the series was apparently chosen with reference to the CE ring fusion. In **7**, the only fusion of ring E is with ring D.

(7) The systematic name for **7a** is *trans*-[13b(indolo),4aH]1,2,3,4,4a,5,6,-7,8,13-decahydro-6-methyl-7,13b-methano-13bH-indolo[3,2-*e*][2]benzazocin-2-one, with the numbering as follows.



It differs from its *cis* epimer in the configuration at C-4a.

(8) Thin layer chromatograms suggested approximately a 70:30 mixture.

(9) Another 18% was isolated as a crystalline mixture of the two ketones.