Synthesis of Pyrimido[4,5-*c*]pyridazine (4-Deazafervenulin), Pyrazolo[3,4-*d*]pyrimidine and 6-(Pyrazino-1-yl)pyrimidine Derivatives

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The synthesis of several pyrimido[4,5-*c*]pyridazine (4-deazafervenulin) (**1**), pyrazolo[3,4-*d*]-pyrimidine (**2**) and 6-(pyrazino-1-yl)pyrimidine (**9**) analogs has been accomplished from 6-hydrazinouracil (**3**). This compound could not be used as starting material for the preparation of indolo[3,2-*c*]pyridazino[3,4-*d*]pyrimidine derivatives (**8**) because it yielded the corresponding hydrazones (**7**).

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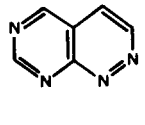
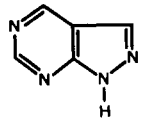
Pyrimido[4,5-c]pyridazines (**1**) are of biological interest not only as isomers of pteridine but also as 4-deaza-analogs of the antibiotic fervenulin (1). Pyrazolo[3,4-*d*]-pyrimidines (**2**) have been synthetized as potential purine antagonists (2). The preparation and investigation of analogs of both fervenulin and purine have produced much revealing information about the biological roles of the ring nitrogen atoms in the metabolic functions of both ring systems, while also several derivatives of potential therapeutical significance were provided (3). We now wish to report the synthesis of some pyrimido[4,5-*c*]-pyridazines and pyrazolopyrimidines of condensed and isolated ring systems. As depicted in Scheme I, reaction of 6-hydrazinopyrimidines with benzil (4), 9-10-phenanthraquinone and acenaphthone, respectively, in acetic acid medium gave polyazaheterocyclic compounds (**4**) in 50-80% yield.

Condensation was always immediately followed by cyclization so that attempts to isolate the condensed products were not successful. Reaction of 3-methyl-6-α-methylhydrazinouracil with α,β-diketones failed to give either cyclized or condensed products, which might be due to steric hindrance under the reaction conditions.

Refluxing 3-methyl-6-α-methylhydrazinouracil with *p*-tolylisothiocyanate in ethanol afforded 1-methyl-3-*p*-tolylaminopyrazolo[3,4-*d*]pyrimidine (**6**) after prolonging the reflux for 3 hours. It is obvious that the first step in this cyclization is the formation of the thiosemicarbazide, which undergoes a cyclization during the prolonged reflux period. In one case we were able to isolate the corresponding thiosemicarbazide (**5**) as an intermediate, the structure of which was confirmed by elemental analysis as well as by spectral data.



1



2

Reaction of 6-hydrazinouracil with ethoxymethyl-enecyanoethylacetate, ethoxymethylenemalononitrile and methyldimethylmercaptomethylenecyanoacetate gave the corresponding 6-(pyrazolo-1-yl)pyrimidines (**9**) in good yield (Scheme II).

Condensation of 6-hydrazinouracil with isatin in equimolar quantities in acetic acid medium did not yield the anticipated indolo[3,2-*c*]pyridazino[3,4-*d*]pyrimidine compounds (**8**). Rather, the corresponding hydrazones (**7**) were formed and isolated.

The structures of all compounds were assigned by spectral data and elemental analysis. The mass fragmentation pattern of a representative pyrimido[4,5-*c*]-pyridazine, *e.g.*, compound **4c-b** is presented in Scheme III.

EXPERIMENTAL

Melting points were determined on a Tottoli apparatus and are uncorrected. The ir spectra were recorded on a Beckmann Acculab no. 4 spectrometer. The nmr spectra were run on a Jeol JNM-PTF 100 spectrometer with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Jeol JMS-01SG apparatus operating at 70 eV ionization energy.

3,4-Diphenyl-6,8-dimethyl-5,7-dioxotetrahydropyrimido[4,5-*c*]-pyridazine (**4a-b**).

A mixture of 1,3-dimethyl-6-hydrazinouracil (0.05 mole) with benzil (0.05 mole) in acetic acid was refluxed for 5 hours. The reaction mixture was evaporated *in vacuo* and the residue was covered with water. The resulting yellow solid which separated was washed with diethyl ether and crystallized from ethanol (50%), m.p. 200-202° dec. (lit. (4) m.p. 208-209°); ms: m/e 344.

Anal. Calcd. for $C_{20}H_{16}N_4O_2$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.92; H, 4.8; N, 16.11.

3,4-Diphenyl-5-oxodihydro-7-aminopyrimido[4,5-*c*]pyridazine (**4a-c**).

A mixture of 2-amino-4-oxodihydro-6-hydrazinopyrimidine (0.05 mole) and benzil (0.05 mole) in acetic acid was refluxed for 3 hours. After cooling, the precipitate was filtered off, washed with diethyl ether and crystallized from dimethylformamide (50%), m.p. >300°; ms: m/e 315.

Anal. Calcd. for $C_{18}H_{13}N_5O{\cdot}H_2O$: C, 66.67; H, 4.32; N, 21.6. Found: C, 66.72; H, 4.12; N, 20.8.

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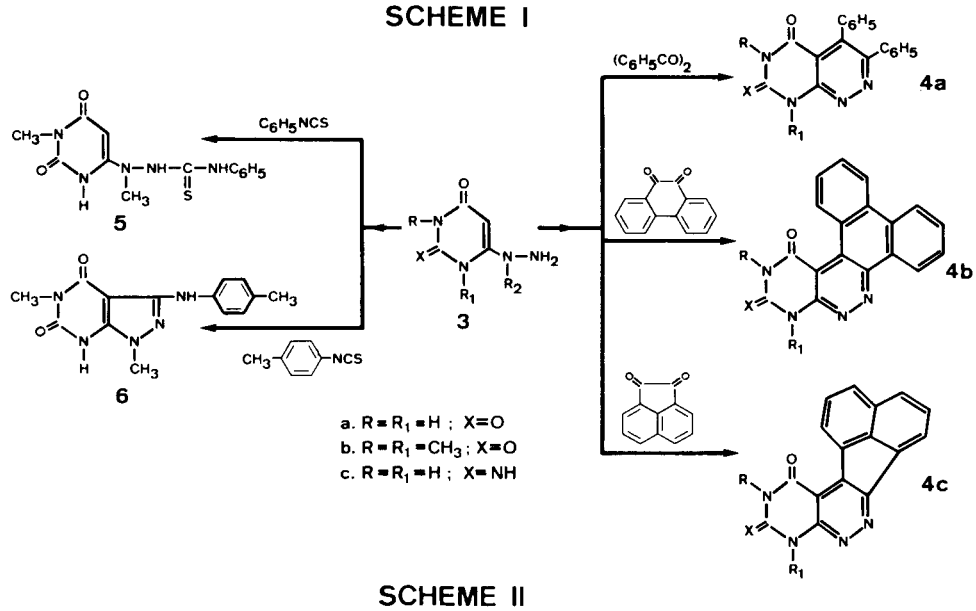
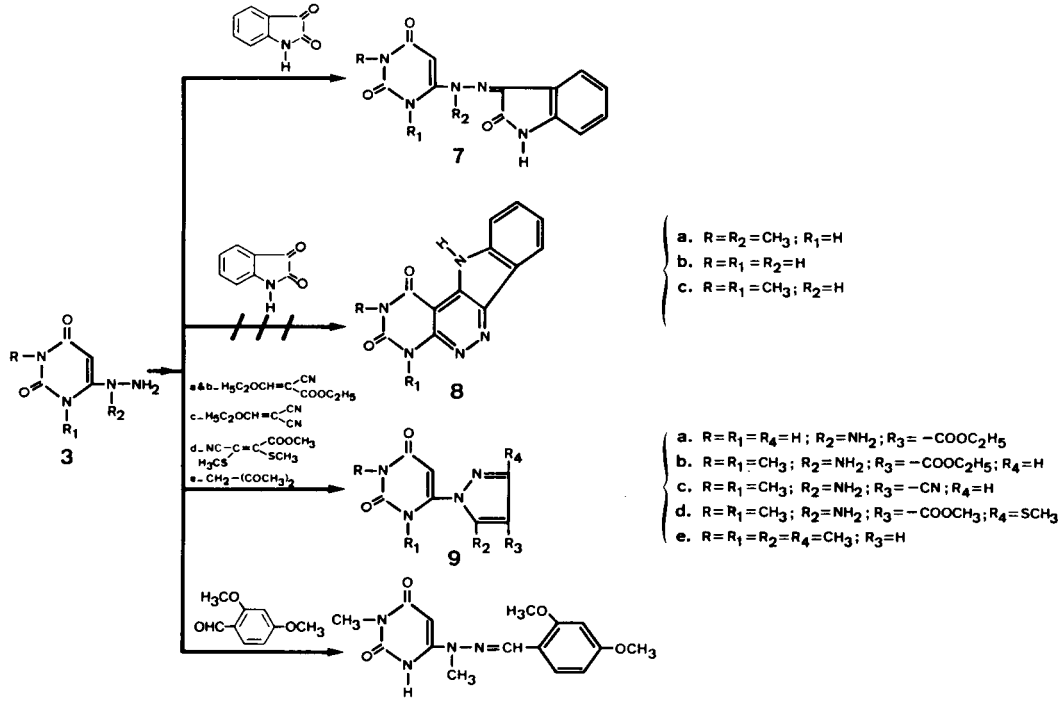
SCHEME I



SCHEME II



3,4-Phenanthreno-5,7-dioxotetrahydropyrimido[4,5-*c*]pyridazine (**4b-a**).

A mixture of 9,10-phenanthraquinone (0.05 mole) and 6-hydrazinouracil (0.05 mole) in glacial acetic acid was refluxed for 3 hours. After cooling, the precipitate was filtered off, washed with cold acetic acid and crystallized from acetic acid (80%) m.p. >300°; ms: m/e 314.

Anal. Calcd. for $C_{18}H_{10}N_4O_2$: C, 68.7; H, 3.1; N, 17.8. Found: C, 68.5; H, 3.5; N, 17.6.

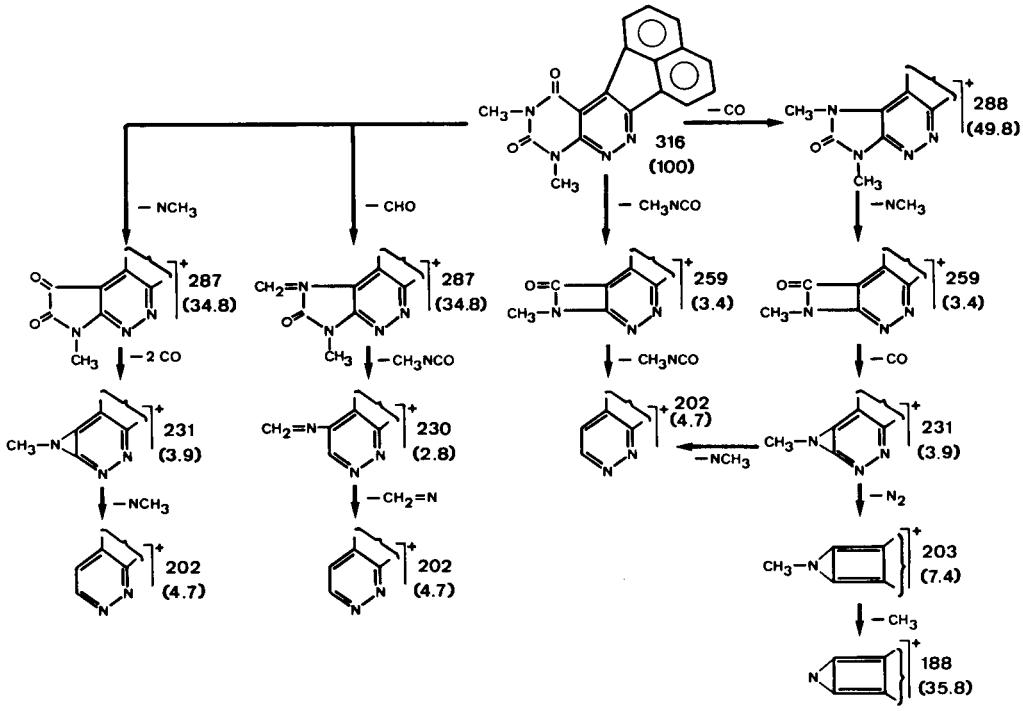
3,4-Phenanthreno-5,7-dioxotetrahydro-6,8-dimethylpyrimido[4,5-*c*]pyridazine (**4b-b**).

A mixture of 1,3-dimethyl-6-hydrazinouracil (0.05 mole) with phenanthraquinone (0.05 mole) in acetic acid was refluxed for 3 hours. The compound was isolated as described in the preceding experiment (70%), m.p. > 300°; ms: m/e 321 (M^+), 314 (M^+-CO), 285 (314-NCH_3), 257 (285-CO), 242 (257-CH_3), 214 (242-N_2); nmr (deuteriotrifluoroacetic acid): δ 3.80 (s, 3H, 8-N-CH_3), 4.02 (s, 3H, 6-N-CH_3), 7.72-8.92 (m, 8H, aromatic H).

Anal. Calcd. for $C_{20}H_{14}N_4O_2$: C, 70.17; H, 4.09; N, 16.37. Found: C, 70.3; H, 4.2; N, 16.5.

3,4-Phenanthreno-5-oxodihydro-7-aminopyrimido[4,5-*c*]pyridazine (**4b-c**).

SCHEME III



This compound was prepared as described in the preceding experiment from 2-amino-4-oxodihydro-6-hydrazinopyrimidine and phenanthraquinone and crystallized from dimethylformamide (60%), m.p. >300°; ms: m/e 313.

Anal. Calcd. for $C_{18}H_{11}N_5O$: C, 69.0; H, 3.5; N, 22.3. Found: C, 69.2; H, 3.6; N, 22.4.

3,4-Acenaphtheno-5,7-dioxotetrahydropyrimido[4,5-*c*]pyridazine (**4c-a**).

This compound was prepared as described earlier from 6-hydrazinouracil and acenaphthone and crystallized from acetic acid (60%), m.p. >300°; ms: m/e 288.

Anal. Calcd. for $C_{16}H_8N_4O_2$: C, 66.6; H, 2.7; N, 19.4. Found: C, 66.8; H, 2.5; N, 19.6.

3,4-Acenaphtheno-5,7-dioxotetrahydro-6,8-dimethylpyrimido[4,5-*c*]pyridazine (**4c-b**).

This compound was synthetized from 1,3-dimethyl-6-hydrazinouracil and 1,2-acenaphthone in the usual way and crystallized from an acetic acid water mixture (69%), m.p. >300°; ms: m/e 316 (M^+), 288 (M^+-CO), 259 (288-NCH_3), 231 (259-CO), 203 (231-N_2), 188 (203-N_2); nmr (deuteriotrifluoroacetic acid): δ 3.80 (s, 3H, 8-N-CH_3), 4.02 (s, 3H, 6-N-CH_3), 8.04-8.92 (m, 6H, aromatic H).

Anal. Calcd. for $C_{18}H_{12}N_4O_2$: C, 68.35; H, 3.8; N, 17.7. Found: C, 68.6; H, 4.0; N, 18.1.

3,4-Acenaphtheno-5-oxodihydro-7-aminopyrimido[4,5-*c*]pyridazine (**4a-c**).

This compound was prepared from 2-amino-4-oxodihydro-6-hydrazinopyrimidine and acenaphthone in the usual way and crystallized from dimethylformamide (50%), m.p. > 300°; ms: m/e 287.

Anal. Calcd. for $C_{16}H_9N_5O$: C, 66.9; H, 3.1; N, 24.3. Found: C, 67.1; H, 3.4; N, 24.5.

1-Methyl-1-(3-methyl-2,4-dioxotetrahydropyrimido-6-yl)-4-phenylthiosemicarbazide (**5**).

A mixture of 3-methyl-6-α-methylhydrazinouracil (0.01 mole) and phenylisothiocyanate (0.01 mole) in ethanol was refluxed for 1.5 hours. After cooling the precipitate was filtered off, washed with ethanol and crystallized from a dimethylformamide-water mixture (28%), m.p. 193-194°; ms: m/e 305; uv (methanol): λ max nm (log ε) 268 (4.25); nmr (DMSO-d_6): δ 3.10 (s, 3H, 1-N-CH_3), 3.14 (s, 3H, 3-N-CH_3, ring), 4.80 (s, 1H, 4-NH), 7.16-7.60 (m, 5H, phenyl), 9.93 (s, 1H, 2-NH), 9.98 (s, 1H, 1-NH, ring).

Anal. Calcd. for $C_{13}H_{15}N_5O_2S$: C, 51.1; H, 4.9; N, 22.9. Found: C, 50.9; H, 4.5; N, 23.1.

1-Methyl-3-*p*-tolylamino-4,6-dioxotetrahydro-5-methylpyrazolo-[3,4-*d*]-pyrimidine (**6**).

This compound was prepared from 3-methyl-6-α-methylhydrazinouracil and *p*-tolylisothiocyanate in ethanol as described earlier. It was crystallized from ethanol (30%), m.p. 223-224°; ms: m/e 285 (M^+), 256 (M^+-NCH_3), 228 (256-CO), 200 (228-CO), 185 (200-NH).

Anal. Calcd. for $C_{14}H_{15}N_2O_2$: C, 58.9; H, 5.2; N, 24.5. Found: C, 58.7; H, 5.3; N, 24.6.

3-Methyl-6-α-methyl(indoline-2-one)hydrazinouracil (**7a**).

This compound was prepared from 3-methyl-6-α-methylhydrazinouracil and isatin and crystallized from a formamide-water mixture (85%), m.p. 241-242°; ms: m/e 299; nmr (deuteriotrifluoroacetic acid): δ 3.64 (s, 3H, 6-N-CH_3), 3.80 (s, 3H, 3-N-CH_3), 6.12 (s, 1H, 5-CH), 7.24-7.74 (m, 4H, aromatic H), 9.70 (s, 1H, 1-NH).

Anal. Calcd. for $C_{14}H_{13}N_5O_3$: C, 56.18; H, 4.34; N, 23.41. Found: C, 56.3; H, 4.5; N, 23.6.

6-(Indoline-2-one)hydrazinouracil (**7b**).

To a suspension of 6-hydrazinouracil (0.01 mole) in ethanol, isatin (0.01 mole) was added and the mixture was refluxed for 3 hours. After cooling, the precipitate was filtered off and crystallized from formamide (70%), m.p. > 300°; ms: m/e 271.

Anal. Calcd. for $C_{12}H_9N_5O_3$: C, 53.1; H, 3.32; N, 25.83. Found: C, 53.3; H, 3.2; N, 25.5.

1,3-Dimethyl-6-(indoline-2-one)hydrazinouracil (**7c**).

This compound was prepared from 1,3-dimethyl-6-hydrazinouracil and isatin as described in the precedent experiment and crystallized from an acetic acid-water mixture (80%), m.p. >300°; ms: m/e 299 (M^+), 271 (M^+-CO), 214 (271-CH_3NCO), 185 (214-NCH_3), 145 (185-HC≡C-NH), 118 (145-HCN); nmr (deuteriotrifluoroacetic acid): δ 3.70 (s, 3H, 1-N-CH_3), 3.84 (s, 3H, 3-N-CH_3), 6.84 (s, 1H, 5-CH), 7.12-7.84 (m, 4H, aromatic H), 9.60 (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{13}N_5O_3$: C, 56.2; H, 4.3; N, 23.4. Found: C, 56.3; H, 4.5; N, 23.1.

6-(3-Amino-4-carbethoxypyrazolo-1-yl)uracil (**9a**).

To a solution of 6-hydrazinouracil (0.01 mole) in ethanol, ethylethoxymethylenecyanoacetate (0.01 mole) was added and the mixture was refluxed for 4 hours in the presence of a few drops of glacial acetic acid. After cooling, the precipitate was filtered off and crystallized from water (50%), m.p. 274-275°; ms: m/e 265; nmr (deuteriotrifluoroacetic acid): δ 1.48 (t, 3H, $COOCH_2CH_3$), 4.48 (q, 2H, $COOCH_2CH_3$), 6.48 (s, 1H, 5-CH), 8.24 (s, 1H, 4-CH).

Anal. Calcd. for $C_{10}H_{11}N_5O_4$: C, 45.28; H, 4.15; N, 26.4. Found: C, 45.4; H, 4.3; N, 26.6.

1,3-Dimethyl-6-(3-amino-4-carbethoxypyrazol-1-yl)uracil (**9b**).

This compound was prepared from 1,3-dimethyl-6-hydrazinouracil and ethylethoxymethylenecyanoacetate as described earlier and crystallized from ethanol (75%), m.p. 170-172°; ms: m/e 293 (M^+), 265 (M^+-CO), 208 (265-CH_3NCO), 193 (208-CH_3), 179 (208-NCH_3), 154 (179-CH≡C); nmr (deuteriotrifluoroacetic acid): δ 1.64 (t, 3H, $COOCH_2CH_3$), 2.58 (s, 3H, 1-N-CH_3), 276, (s, 3H-NH), 4.68 (m, 2H, $COOCH_2CH_3$), 6.80 (s, 1H, 5-CH), 8.60, (s, 1H, 4-CH).

Anal. Calcd. for $C_{12}H_{15}N_5O_4$: C, 49.14; H, 5.12; N, 23.9. Found: C, 49.1; H, 5.13; N, 24.1.

1,3-Dimethyl-6-(3-amino-4-cyanopyrazol-1-yl)uracil (**9c**).

This compound was prepared from 6-hydrazinouracil and ethoxymethylenemalononitrile as described earlier and crystallized from ethanol (60%), m.p. 270-271°; ms: m/e 246 (M^+), 218 (M^+-CO), 189 (218-NCH_3), 161 (189-CO), 134 (161-HCN), 108 (134-CN); ir (potassium bromide): 3400, 3340, 3240, 3200 (amine), 2240 (cyanate).

Anal. Calcd. for $C_{10}H_{10}N_6O_2$: C, 48.78; H, 4.06; N, 34.1. Found: C, 48.9; H, 4.2; N, 34.3.

1,3-Dimethyl-6-(3-methylmercapto-4-carbmethoxy-5-aminopyrazol-1-yl)uracil (**9d**).

This compound was prepared from 1,3-dimethyl-6-hydrazinouracil and methyldimethylmercaptomethylenecyanoacetate as described earlier and crystallized from ethanol (35%), m.p. 215-216°; ms: m/e 325; nmr (deuteriotrifluoroacetic acid): δ 2.70 (s, 3H, SCH_3), 3.48 (s, 3H, 1-NCH_3), 3.60 (s, 3H, 3-NCH_3), 6.70 (s, 1H, 5-CH).

Anal. Calcd. for $C_{12}H_{15}N_5O_4S$: C, 44.3; H, 4.6; N, 21.5. Found: C, 44.4; H, 4.7; N, 21.6.

1,3-Dimethyl-6-(3,5-dimethylpyrazol-1-yl)uracil (**9e**).

This compound was synthetized from 6-hydrazinouracil and acetylacetone in the usual way and crystallized from acetone (48%), m.p. 65-67°; ms: m/e 234 (M^+), 177 (M^+-CH_3NCO), 149 (177-CO), 134 (149-CH_3), 108 (149-CH_3CN).

Anal. Calcd. for $C_{11}H_{14}N_4O_2$: C, 56.4; H, 5.98; N, 23.9. Found: C, 56.5; H, 6.2; N, 24.0.

3-Methyl-6-α-methyl-(2,4-dimethoxybenzal)hydrazinouracil (**10**).

This compound was prepared from 3-methyl-6-α-methylhydrazinouracil and 2,4-dimethoxybenzaldehyde as described earlier, and crystallized from a formamide-water mixture (90%), m.p. 199-200°; ms: m/e 318.

Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.5; H, 5.6; N, 17.6. Found: C, 56.3; H, 5.7; N, 17.8.

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