The Synthesis and Properties of Pyridazino[4,3-*e*]-*as*-triazines and Pyridazino[4,5-*e*]-*as*-triazines, Two Novel Condensed Pyridazine Ring Systems.

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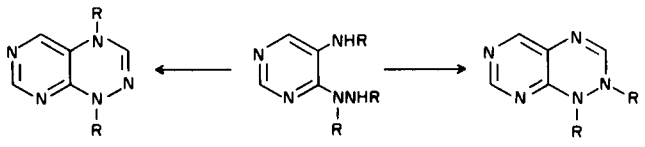
The compounds prepared in the novel pyridazino[4,3-*e*]-*as*-triazine ring system are: 8-chloro-4-methyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine (**21**), 8-chloro-2,4-dimethyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine (**23**), 8-chloro-2-ethyl-4-methyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine (**24**), 4-methyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine-8-thione (**25**), 4-methyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine (**26**), 2,4-dimethyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine (**27**), and 2-ethyl-4-methyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine (**28**). In the novel pyridazino[4,5-*e*]-*as*-triazine ring system the following compounds were prepared: 1,2-dihydropyridazino[4,5-*e*]-*as*-triazine (**31**), 3-methyl-1,2-dihydropyridazino[4,5-*e*]-*as*-triazine (**32**), 3-ethyl-1,2-dihydropyridazino[4,5-*e*]-*as*-triazine (**33**), and 1-methyl-1,2-dihydropyridazino[4,5-*e*]-*as*-triazine (**35**). The preparation of a number of previously unreported intermediates and compounds for structure proof are also described.

There have been several reports (3-10) of the successful synthesis of pyrimidotriazines by cyclizations between adjacent amino and hydrazino groups on a pyrimidine ring. Generally, substitution on the amino or hydrazino group does not effect triazine formation. Unsubstituted amino compounds gave (**1**, R = H) compounds of structure **3** while substitution on the amino group gave compounds of structures **2**.

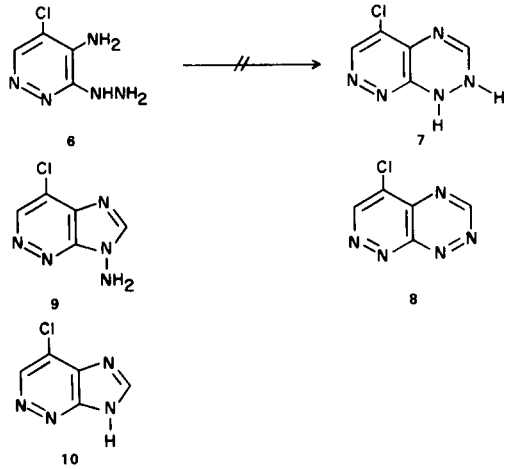


2 **1** **3**

This approach was utilized for the preparation of several substituted and unsubstituted dihydro derivatives of the previously unknown pyridazino[4,3-*e*]-*as*-triazine (**4**) and pyridazino[4,5-*e*]-*as*-triazine (**5**) ring systems. The first attempt to prepare an example of **4** involved the cyclization reaction of 4-amino-5-chloro-3-hydrazinopyridazine (**6**). A solution of **6** in triethylorthoformate was stirred at room temperature while adding concentrated hydrochloric acid to give a compound in 77% yield that gave a correct analysis for **7**. Alternatively, a solution of **6** in triethylorthoformate was refluxed giving the same compound in 30% yield. Several attempts were made to oxidize this compound with potassium ferricyanide to give the corresponding aromatic system **8** but only starting material was recovered. The failure to obtain **8** and

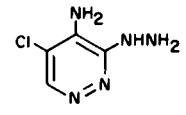
4 **5**

evidence in the ir spectrum for a primary amino group suggested the possibility of a product other than **7** but isomeric with it. One such possibility is 3-amino-7-chloromidazo[4,5-*c*]pyridazine (**9**). If **9** was the product,



6 **7** **9** **8** **10**

then cleavage (11) of the amino group with Raney nickel and hydrogen would give the previously prepared 7-chloroimidazo[4,5-*c*]pyridazine (**10**). This reaction was carried out, but only starting material was recovered. The remaining possibility was that the reaction of **6** with triethylorthoformate gave 8-amino-7-chloro-*s*-triazolo[4,3-*b*]pyridazine (**11**). The ir, uv, and melting point were consistent with that reported for 8-amino-7-chloro-*s*-



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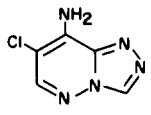

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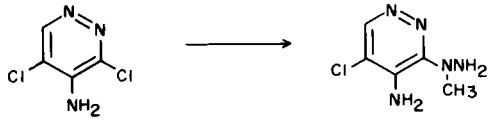
triazolo[4,3-*b*]pyridazine (**11**) by Kuraishi and Castle (12).

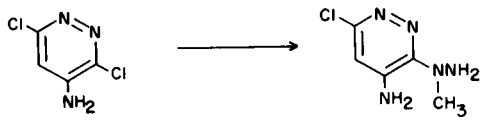
In order to block cyclization to the nitrogen atom of the pyridazine ring, it was necessary to prepare a hydrazinopyridazine substituted on the hydrazino-nitrogen attached to the ring. In this manner, cyclization to the triazolo compound would require destruction of the aromaticity of the pyridazine ring without the compensating extended conjugation into the triazole ring. This approach was successful in preventing triazolopyridazine formation.

4-Amino-5-chloro-3-(1′-methyl)hydrazinopyridazine (**13**) was prepared by heating a solution of 4-amino-3,5-dichloropyridazine (**12**) (11,13) in 95% methylhydrazine to give **13** in 51% yield. The verification of structure involved the elimination of several possibilities. It was necessary to determine whether the chlorine atom at position 3 or 5 was displaced and which nitrogen atom of the methyl-



12 13

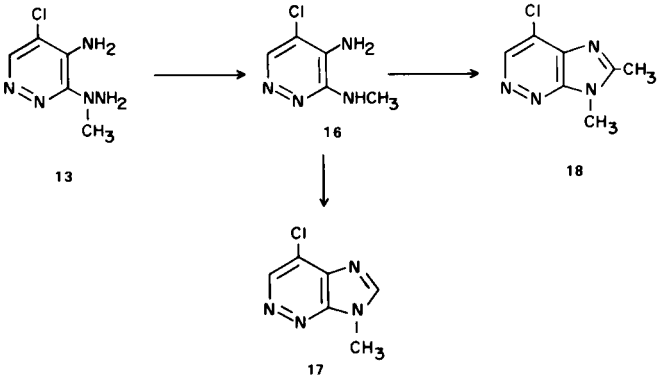
hydrazine molecule became attached to the ring. Earlier work by Kuraishi and Castle (11) showed that the reaction of **12** with hydrazine led to substitution at position 3 to give **6**. On the basis of this report, it could be predicted that methylhydrazine would displace the chlorine atom at position 3 of **12**. Murakami and Castle (14) reported that the reaction of 4-amino-3,6-dichloropyridazine (**14**) with methylhydrazine gave 4-amino-6-chloro-3-(1′-methyl)hydrazinopyridazine (**15**). This suggests that displacement of the chlorine atom at position 3 of **12** with methylhydrazine gives the product **13** where the nitrogen



14 15

atom bearing the methyl group is attached to the ring. Therefore, there was supporting evidence in the literature (11,13) to support the structure **13** as proposed. Confirmation of structure **13** involved several reactions which are discussed below.

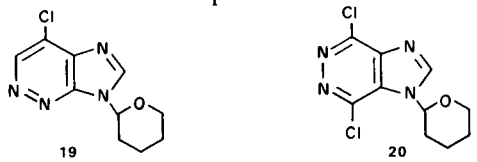
That the nitrogen atom bearing the methyl group was attached to the ring was readily confirmed by cleaving the hydrazino group with Raney nickel and hydrogen. A mixture of **13** and freshly prepared Raney nickel was hydrogenated at atmospheric pressure and room temperature until hydrogen uptake ceased. A 68% yield of 4-amino-5-chloro-3-methylaminopyridazine (**16**) was obtained. Confirmation of the structure of **16** involved preparation of the corresponding imidazopyridazine by cyclization. If structure **16** is correct, then an imidazo[4,5-*c*]pyridazine would be obtained upon cyclization, however, if the methylamino group was at position 5 of **16**, then an imidazo[4,5-*d*]pyridazine would be obtained. Two examples of the cyclized product were obtained by



13 16 18

17

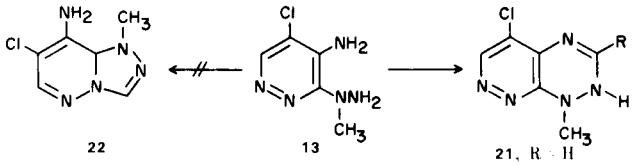
allowing **16** to react with triethylorthoformate or triethylorthoacetate. A solution of **16** in triethylorthoformate was allowed reflux to give 7-chloro-3-methylimidazo[4,5-*c*]pyridazine (**17**) in 58% yield. In a similar manner, a solution of **16** in triethylorthoacetate was refluxed to give 7-chloro-2,3-dimethylimidazo[4,5-*c*]-pyridazine (**18**) in 44% yield. The uv spectra of the cyclized products were consistent with an imidazo[4,5-*c*]-pyridazine and not with imidazo[4,5-*d*]pyridazine. The uv spectra of the products were compared with the spectra of the previously reported (15) 7-chloro-3-(tetrahydro-2′-pyranyl)imidazo[4,5-*c*]pyridazine (**19**) and 5,7-dichloro-3-(tetrahydro-2′-pyranyl)imidazo[4,5-*d*]pyridazine (**20**). The significant difference between the uv spectra of **19** and **20** is that **19** has an absorption at 289 nm while **20** has no absorption in this area. Both of the



19 20

cyclized products, **17** and **18**, have absorption in the 287-290 nm region which confirms that **17** and **18** belong to the imidazo[4,5-*c*]pyridazine series.

A solution of **13** in triethylorthoformate was stirred while concentrated hydrochloric acid was added. The bright red hydrochloride salt that formed was neutralized to give 8-chloro-4-methyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine (**21**) in 60% yield.

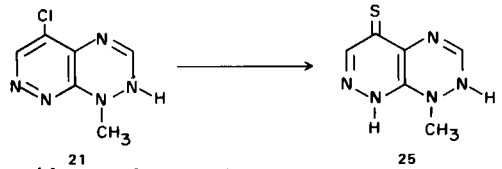


22 13

21, R = H
23, R = CH_3
24, R = C_2H_5

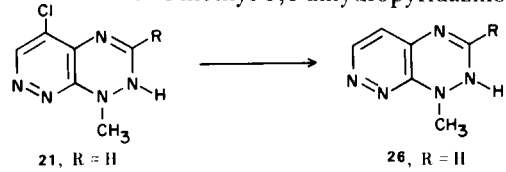
The other possible cyclization product would be the triazolopyridazine (**22**). The triazolopyridazine was eliminated by analytical data since it has a different molecular formula than the pyridazinotriazine. In a similar manner, two more examples of the pyridazino-[4,3-*e*]-*as*-triazine were prepared by cyclization with triethylorthoacetate or triethylorthopropionate. A solution of **13** in triethylorthoacetate was stirred while adding concentrated hydrochloric acid to give the hydrochloride of 8-chloro-2,4-dimethyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine (**23**) in 48% yield. Likewise, treatment of **13** with triethylorthopropionate gave the hydrochloride of 8-chloro-2-ethyl-4-methyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine (**24**) in 84% yield.

It was possible to replace the chlorine atom of **21** with a sulfur atom. A mixture of **21** and sodium hydrosulfide hydrate was heated in a glass pressure bottle at elevated temperatures to give 4-methyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine-8-thione (**25**) in 59% yield.



21 25

The chloro substituted pyridazinotriazines could be catalytically dechlorinated with hydrogen to give the corresponding hydrochlorides. A solution of **21** in absolute ethanol was hydrogenated at room temperature and pressure in the presence of 5% palladium on carbon to give the hydrochloride of 4-methyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine (**26**) in 69% yield. In a similar manner, the hydrochloride salts of **23** and **24** gave the hydrochloride salts of **27** and **28** in 5% and 35% yields, respectively.



21, R = H
23, R = CH_3
24, R = C_2H_5

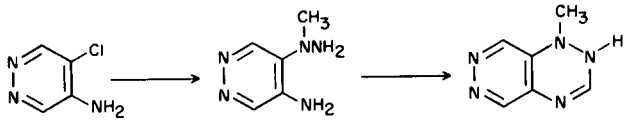
26, R = H
27, R = CH_3
28, R = C_2H_5

Four derivatives of the other new pyridazinotriazine ring were prepared by cyclization reactions with 4-amino-5-hydrazinopyridazine (**29**) (16) and 4-amino-5-(1′-methyl)hydrazinopyridazine (**30**). A solution of **29** in triethylorthoformate was stirred while concentrated hydrochloric acid was added to give the hydrochloride of 1,2-dihydropyridazino[4,5-*e*]-*as*-triazine (**31**) in 76% yield. In a similar manner, treatment of **29** with triethylorthoacetate or triethylorthopropionate gave the hydrochloride salts of **32** and **33** in 51% and 27% yields, respectively.

29

31, R = H
32, R = CH_3
33, R = C_2H_5

Preparation of 4-amino-5-(1′-methyl)hydrazinopyridazine (**30**) was achieved by allowing a mixture of 4-amino-5-chloropyridazine (**34**) (11) and methylhydrazine to react in a glass pressure bottle at elevated temperatures. The methylhydrazinopyridazine could not be obtained as a solid, so it was used without purification in the cyclization reaction. A mixture of crude **30** and triethylorthoformate was stirred in the presence of hydrochloric acid to give the hydrochloride of 1-methyl-1,2-dihydropyridazino[4,5-*e*]-*as*-triazine (**35**) in 7% yield.



34 30 35

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were recorded with Perkin-Elmer 137 and 237 instruments using pressed potassium bromide pellets. The nmr spectra were recorded on a Varian A-60 in the solvent indicated. The uv spectra were recorded on a Cary-14 and Perkin-Elmer 337 spectrophotometer in the solvent indicated.

4-Amino-5-chloro-3-hydrazinopyridazine (**6**).

This compound was prepared by the method of Kuraishi and Castle (11).

8-Amino-7-chloro-*s*-triazolo[4,3-*b*]pyridazine (**11**).

Method I.

A solution of 0.5 g. (0.00313 mole) of 4-amino-5-chloro-3-hydrazinopyridazine (**6**) in 10 ml. of triethylorthoformate was refluxed for 2 hours with stirring (11). The solid product was filtered and washed several times with ether to yield 0.16 g., 30%, m.p. 311-313°. The analytical sample was recrystallized from methanol after treatment with Norite to yield white needles, m.p.

312-313°; pmr (DMSO-d_6): δ = 9.44 (C_6-*H*), 8.28 (CH_3-*H*), 7.76 (NH_2); uv λ max (95% ethanol): 232 (ε, 8,930), 260 (ε, 5,860), 268 (ε, 5,720), 306 (ε, 10,110), 316 nm sh (ε, 7,900); ir cm^{-1}: [3340 (s), 3150 (s) (NH_2)], 1667 (s), 1578 (s), 1505 (s), 1461 (s), 1401 (m), 1356 (s), 1322 (s), 1268 (m), 1178 (s), 1193 (s), 1021 (s), 927 (s), 915 (s), 813 (s), 756 (m), 748 (m), 679 (w), 665 (w), 615 (s), 591 (s), 576 (s), 556 (s), 519 (s).

Anal. Calcd. for $C_5H_4ClN_5$: C, 35.4; H, 2.4; N, 41.3. Found: C, 35.5; H, 2.3; N, 41.3.

Method II.

A solution of 5 g. (0.0313 mole) of 4-amino-5-chloro-3-hydrazinopyridazine (**6**) in 55 ml. of triethylorthoformate was stirred while 2.5 ml. of concentrated hydrochloric acid was added (17). The mixture was stirred for 1 hour at room temperature, filtered and washed with acetone. The white powder was suspended in 100 ml. of water and neutralized with sodium bicarbonate. This was filtered and dried to yield 4.1 g., 77%, m.p. 310°. The ir spectrum was identical to the ir spectrum of the compound prepared by Method I.

4-Amino-5-chloro-3-(1′-methyl)hydrazinopyridazine (**13**).

A solution of 10.0 g. (0.061 mole) of 4-amino-3,5-dichloropyridazine (**12**) in 40 ml. of 95% methylhydrazine was heated on a steam bath for 2.5 hours (14). An equivalent amount of water was added and the solution was cooled and filtered to yield 5.38 g. of light yellow crystals, 51%. The analytical sample was recrystallized from water, m.p. 137-139°; pmr (DMSO-d_6): δ = 8.44 (C_6-*H*), 7.04 (NH_2), 4.90 (NH_2), 3.20 (N-CH_3); uv λ max (95% ethanol) 226 (ε, 16,390), 275 (ε, 7,290), 305 nm sh (ε, 5,300); ir cm^{-1}: [3328 (s), 3172 (m) (NH_2)], 2990 (w), 1604 (s), 1550 (w), 1528 (m), 1466 (m), 1442 (m), 1384 (m), 1331 (w), 1260 (w), 1208 (m), 1111 (s), 1063 (s), 1036 (m), 918 (s), 888 (m), 796 (w).

Anal. Calcd. for $C_5H_8ClN_5$: C, 34.6; H, 4.6; N, 40.4. Found: C, 34.6; H, 4.6; N, 40.4.

4-Amino-5-chloro-3-methylaminopyridazine (**16**).

A mixture of 5.1 g. (0.0295 mole) of 4-amino-5-chloro-3-(1′-methyl)hydrazinopyridazine (**13**) and 1 g. of freshly prepared Raney nickel in 250 ml. of absolute ethanol was hydrogenated at atmospheric pressure and at room temperature (14). The reaction was carried out until hydrogen ceased to be absorbed. The catalyst was filtered and the ethanol was removed *in vacuo*. The crude solid was dissolved in boiling water, treated with Norite and cooled to yield 2.7 g. of light yellow crystals. Concentration of the filtrate yielded an additional 0.5 g. bringing the overall yield to 68%. The analytical sample was recrystallized twice from water, m.p. 203-204°; pmr (DMSO-d_6): δ = 8.24 (C_6-*H*), 6.10 (NH_2,*NH*), 2.98 (N-CH_3, d, J = 5 Hz); uv λ max (95% ethanol): 222 (ε, 19,990), 267 (ε, 6,880), 298 nm (ε, 5,940); ir cm^{-1}: [3450 (s), 3322 (s), 3233 (s), 3196 (s) (NH_2)], 3014 (w), 1642 (s), 1589 (s), 1552 (m), 1507 (w), 1478 (m), 1412 (w), 1392 (m), 1304 (w), 1103 (m), 1084 (w), 1048 (w), 867 (w), 839 (w), 691 (w).

Anal. Calcd. for $C_5H_7ClN_4$: C, 37.9; H, 4.4; N, 35.3. Found: C, 38.3; H, 4.7; N, 34.9.

7-Chloro-3-methylimidazo[4,5-*c*]pyridazine (**17**).

A solution of 0.5 g. (0.00315 mole) of 4-amino-5-chloro-3-methylaminopyridazine (**16**) in 15 ml. of triethylorthoformate was refluxed for 2.5 hours (11). The mixture was cooled, filtered, and washed with acetone to yield a grey powder. This was dissolved in 25 ml. of boiling water and treated with Norite. The water was evaporated *in vacuo* and the residue was recrystallized from ligroin-ethanol. The residue was refluxed with 125 ml. of 90-120°, b.p. ligroin while sufficient ethanol was added to just dissolve the material. This was filtered to remove a small amount of brown material and cooled in an ice bath to yield 0.11 g. of white powder, analytical sample, m.p. 190-191° dec. Concentration of the filtrate yielded an additional 0.2 g. of product bringing the overall yield to 58%; pmr (DMSO-d_6): δ = 9.30 (C_6-*H*), 8.93 (C_2-*H*), 4.06 (N-CH_3); uv λ max (95% ethanol): 212 (ε, 11,490), 261 (ε, 6,660), 290 nm (ε, 5,580); ir cm^{-1}: 3409 (m), 3077 (m), 3036 (m), 1818 (w), 1609 (w), 1599 (s), 1545 (w), 1504 (s), 1471 (m), 1416 (m), 1385 (s), 1348 (s), 1284 (s), 1258 (w), 1243 (s), 1189 (s), 1155 (s), 1075 (s), 941 (s), 880 (m), 728 (m), 648 (w), 635 (m).

Anal. Calcd. for $C_6H_5ClN_4$: C, 42.7; H, 3.0; N, 33.2. Found: C, 43.0; H, 3.2; N, 33.0.

7-Chloro-2,3-dimethylimidazo[4,5-*c*]pyridazine (**18**).

A solution of 0.2 g. (0.00126 mole) of 4-amino-5-chloro-3-methylaminopyridazine (**16**) in 10 ml. of triethylorthoacetate was refluxed for 1.5 hours (11). Initially, a clear solution was present which became progessively darker as time elapsed. After 1.5 hours of refluxing, the mixture had turned black and the reaction was discontinued at this time to avoid further decomposition. This was cooled for 48 hours at 0° and filtered to yield a mixture of black and tan material. The tan material dissolved when heated with 50 ml. of ether while the black solid remained. This was filtered to yield a light yellow solution which was evaporated *in vacuo* to give a white residue. Recrystallization from ligroin yielded 0.1 g. of white powder, 44%, m.p. 149-151°; pmr (DMSO-d_6): δ = 9.20 (C_6-*H*), 3.96 (N-CH_3), 2.73 (C_2-CH_3); uv λ max (95% ethanol): 214 (ε, 13,320), 264 (ε, 8,770), 287 nm sh (ε, 6,030); ir cm^{-1}: 3411 (m), 3046 (w), 1605 (m), 1514 (s), 1497 (s), 1472 (m), 1433 (m), 1407 (m), 1375 (m), 1360 (s), 1281 (m), 1244 (m), 1237 (m), 1208 (w), 1162 (m), 1150 (m), 1068 (m), 1044 (w), 1014 (m), 955 (m), 912 (w), 898 (m), 805 (w), 698 (m), 662 (w).

Anal. Calcd. for $C_7H_7ClN_4$: C, 46.0; H, 3.9; N, 30.7. Found: C, 45.9; H, 3.8; N, 30.5.

8-Chloro-4-methyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine (**21**).

A solution of 1 g. (0.00577 mole) of 4-amino-5-chloro-3-(1′-methyl)hydrazinopyridazine (**13**) in 11 ml. of triethylorthoformate was stirred while 0.5 ml. of concentrated hydrochloric acid was added dropwise (17). The mixture was stirred at room temperature for 16 hours. A fine red powder was filtered and washed with acetone to yield 1.1 g., m.p. 245°. A solution of 0.3 g. of red powder in 10 ml. of water was neutralized with sodium bicarbonate to yield 0.19 g. of bright yellow powder. The analytical sample was prepared by two recrystallizations from a methanol-water mixture, m.p. 231-232°. The adjusted yield for the free base was 60% based upon **13**; pmr (DMSO-d_6): δ = 9.06 (C_7-*H*), 8.00 (C_2-*H*), 6.40 (N-*H*), 2.90 (N-CH_3); uv λ max (95% ethanol): 231 (ε, 20,380), 341-345 nm (ε, 4,770); ir cm^{-1}: 3425 (m), [3133 (s), 2900 (s) (NH)], 1656 (s), 1600 (s), 1531 (s), 1472 (s), 1389 (s), 1345 (m), 1296 (w), 1244 (w), 1216 (w), 1144 (m), 1100 (w), 1133 (m), 869 (m), 856 (w), 824 (w), 555 (m), 507 (w), 483 (w).

Anal. Calcd. for $C_6H_6ClN_5$: C, 39.3; H, 3.3; N, 38.2. Found: C, 39.3; H, 3.4; N, 37.8.

The pmr spectra for the hydrochloride salt of **21** in deuterium oxide (δ) is: 8.06 (C_7-*H*), 6.58 (C_2-*H*), 2.90 (N-CH_3).

8-Chloro-2,4-dimethyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine (**23**).

A solution of 0.2 g. (0.00115 mole) of **13** in 3 ml. of triethylorthoacetate was stirred while adding dropwise 0.1 ml. of concentrated hydrochloric acid (17). The mixture was stirred for 23 hours at room temperature. The red powder was filtered and washed with acetone to yield 0.13 g. of product in 48% yield, m.p. 255°; pmr (deuterium oxide): δ = 8.10 (C_7-*H*), 2.96 (N-CH_3), 1.84 (C_2-CH_3); uv λ max (95% ethanol): 232 (ε, 20,240), 343-347 nm (ε, 4,945); ir cm^{-1}: [3150 (m), 2935 (m), 2541 (s) (NH)], 2000 (w), 1889 (w), 1797 (w), 1663 (m), 1611 (s), 1520 (s), 1482 (s), 1414 (s), 1401 (s), 1382 (m), 1298 (m), 1258 (w), 1215 (m), 1150 (m), 1069 (w), 1038 (w), 996 (w), 971 (w), 902 (m), 870 (w), 827 (m), 752 (w), 718 (m).

Anal. Calcd. for $C_7H_8ClN_5$·HCl: C, 35.9; H, 3.9; N, 29.9. Found: C, 35.9; H, 4.1; N, 29.7.

A solution of 1 g. of the hydrochloride in 50 ml. of water was neutralized with sodium bicarbonate to give a clear yellow solution. This was extracted with two 30 ml. portions of chloroform. The chloroform layer was dried over magnesium sulfate and evaporated *in vacuo* to give 0.43 g. of yellow solid. After standing at room temperature for 10 minutes, a yellow precipitate separated from the aqueous layer. This was filtered to yield 0.22 g. of bright yellow solid. The analytical sample was prepared by recrystallizing from water. The melting point, m.p. 183-185°, was dependent on the heating rate. Drying *in vacuo* at 95° caused decomposition of one sample. The analytical sample was dried *in vacuo* at room temperature; pmr (DMSO-d_6): δ = 8.92 (C_7-*H*), 8.00 (N-*H*), 2.94 (N-CH_3), 1.72 (C_2-CH_3); uv λ max (95% ethanol): 232 (ε, 17,300), 345 nm (ε, 4,320); ir cm^{-1} (in Nujol): [3320 (s) (NH)], 2920 (s), 2840 (s), 2710 (w), 1670 (m), 1600 (s), 1540 (m), 1495 (s), 1460 (s), 1390 (s), 1325 (w), 1305 (m), 1250 (w), 1235 (w), 1215 (w), 1135 (s), 1055 (w), 1030 (w), 1015 (w), 970 (w), 880 (w), 870 (w), 830 (m), 715 (w).

Anal. Calcd. for $C_7H_8ClN_5$·0.5·H_2O: C, 40.7; H, 4.4; N, 33.9. Found: C, 40.5; H, 4.7; N, 33.7.

8-Chloro-2-ethyl-4-methyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine (**24**).

A solution of 0.5 g. (0.00288 mole) of **13** in 5 ml. of triethylorthopropionate was stirred while adding dropwise 0.5 ml. of concentrated hydrochloric acid (17). The mixture was stirred at room temperature for 1.5 hours. It was filtered and washed with acetone to yield 0.6 g. of product in 84% yield, m.p. 232-233°; pmr (deuterium oxide): δ = 8.12 (C_7-*H*), 2.96 (N-CH_3), 2.14 (C_2-C_2H_5, q, J = 7 Hz), 1.11 (C_2-CH_2-CH_3, t, J = 7 Hz); uv λ max (95% ethanol); 232 (ε, 20,230), 342-347 nm (ε, 5,170); ir cm^{-1}: 3399 (w), 3150 (m), 3093 (w), 2922 (m), 2538 (m), 1993 (w), 1885 (w), 1793 (w), 1663 (w), 1612 (s), 1549 (w), 1522 (s), 1482 (s), 1414 (m), 1399 (m), 1296 (w), 1254 (m), 1227 (w), 1179 (w), 1136 (m), 903 (w), 829 (w), 714 (w).

Anal. Calcd. for $C_8H_{10}ClN_5$·HCl: C, 38.7; H, 4.5; N, 28.2. Found: C, 38.9; H, 4.6; N, 28.0.

A solution of 1.2 g. of the hydrochloride of **24** in 50 ml. of water was neutralized with sodium bicarbonate. A bright yellow material immediately separated from the solution. This was filtered to yield 1.12 g. of crude material. The analytical sample was recrystallized from water, m.p. 185-187° (heating rate dependent); pmr (DMSO-d_6): δ = 8.78 (C_7-*H*), 7.96 (N-*H*), 2,90 (N-CH_3), 2.04 (C_2-CH_2CH_3, q, J = 7 Hz), 1.00 (C_2-CH_2CH_3, t, J = 7 Hz); uv λ max (95% ethanol): 234 (ε, 19,050), 346 nm (ε, 4,710); ir cm^{-1} (in Nujol): 3150 (w), [3100 (m), 3040 (m) (NH)], 2920 (s), 2850 (s), 2680 (w), 1660 (m), 1595 (s), 1535 (m), 1490 (s), 1465 (s), 1415 (m), 1385 (s), 1320 (w), 1295 (m), 1235 (w), 1210 (w), 1190 (w), 1135 (m), 1115 (m), 1075 (w), 1030 (m), 945 (w), 875 (w), 835 (m), 775 (w), 715 (w), 690 (w).

Anal. Calcd. for $C_8H_{10}ClN_5$: C, 45.4; H, 4.7; N, 33.1. Found: C, 45.6; H, 4.9; N, 33.2.

4-Methyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine-8-thione (**25**).

A solution of 0.5 g. (0.00272 mole) of **21** and 0.5 g. (0.00674 mole) of sodium hydrosulfide hydrate in 10 ml. of 50% ethanol was stirred and heated in a glass pressure bottle for 6 hours at 148° (15). The mixture was allowed to stand at room temperature for 15 hours and evaporated to dryness *in vacuo*. The residue was dissolved in 10 ml. of water and made acidic with acetic acid. The red-brown solid was filtered and washed with water to yield 0.29 g. in 59% yield. The analytical sample was prepared by recrystallizing from methanol, m.p. 259-260°; pmr (DMSO-d_6): δ = 8.02 (C_7-*H*), 6.54 (N_3-*H*), 3.66 (N_5-*H*), 2.80 (N-CH_3); uv λ max (95% ethanol) (*p*H = 11.0): 220 (ε, 9,790), 255 (ε, 10,700), 296-300 (ε, 6,780), 345-348 nm (ε, 5,040); ir cm^{-1}: [3409 (m), 3233 (m), 3066 (m), 2766 (m) (NH)], 1637 (w), 1577 (w), 1526 (s), 1482 (s), 1450 (s), 1407 (s), 1275 (m), 1230 (w), 1194 (m), 1077 (m), 1045 (w), 951 (w), 879 (w), 816 (w).

Anal. Calcd. for $C_6H_7N_5S$: C, 39.8; H, 3.9; N, 38.7. Found: C, 39.7; H, 4.0; N, 38.7.

General Procedure for the Preparation of Compounds **26**, **27**, and **28**.

The hydrochloride salts of **23** and **24** and the free base **21** dissolved in absolute ethanol were hydrogenated at room temperature at atmospheric pressure in the presence of 5% palladium on carbon (11) (0.1 g. of catalyst and 25 ml. of absolute ethanol was used for each millimole of the chloro compound). The reaction was discontinued when hydrogen uptake ceased. The solutions were filtered and concentrated to one half the original volumes. Cooling for 15 hours yielded the products as brightly colored needles.

4-Methyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine Hydrochloride (**26**).

This compound was obtained as bright orange needles in 69% yield, m.p. 249-251°; nmr (deuterium oxide): δ = 7.84 (C_7-*H*, d, J = 6 Hz), 6.48 (C_2-*H*), 5.92 (C_8-*H*, d, J = 6 Hz), 2.84 (N-CH_3); uv λ max (95% ethanol): 228 (ε, 16,040), 340-343 nm (ε, 4,820); ir cm^{-1}: 3411 (w), 3171 (m), 3088 (m), [3038 (s), 2977 (s), 2760 (s) (NH)], 1916 (w), 1836 (w), 1760 (w), 1645 (m), 1622 (s), 1558 (s), 1490 (s), 1431 (m), 1408 (s), 1327 (w), 1299 (m), 1288 (w), 1214 (m), 1125 (w), 1096 (m), 1047 (w), 963 (w), 938 (m), 918 (w), 877 (m), 850 (m), 811 (s), 711 (w).

Anal. Calcd. for $C_6H_7N_5$·HCl: C, 38.8; H, 4.3; N, 37.7. Found: C, 39.0; H, 4.6; N, 38.0.

2,4-Dimethyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine Hydrochloride (**27**).

This compound was obtained as bright red-orange needles, 5%, m.p. 295°; nmr (deuterium oxide): δ = 7.86 (C_7-*H*, d, J = 6 Hz), 5.88 (C_8-*H*, d, J = 6 Hz), 2.84 (N-CH_3), 1.68 (C_2-CH_3); uv λ max (95% ethanol): 227 (ε, 15,730), 340-344 nm (ε, 4,820); ir cm^{-1}: 3413 (m), 3184 (m), 3122 (m), [2995 (s), 2882 (s), 2718 (s) (NH)], 1988 (w), 1882 (w), 1784 (w), 1722 (w), 1659 (m), 1626 (s), 1563 (s), 1533 (s), 1482 (s), 1404 (s), 1382 (m), 1352 (m), 1318 (w), 1290 (w), 1238 (m), 1134 (w), 1093 (m), 971 (w), 936 (w), 899 (w), 871 (w), 839 (s), 766 (m), 650 (w).

Anal. Calcd. for $C_7H_9N_5$·HCl: C, 42.1; H, 5.1; N, 35.1. Found: C, 42.1; H, 5.3; N, 34.8.

2-Ethyl-4-methyl-3,4-dihydropyridazino[4,3-*e*]-*as*-triazine Hydrochloride (**28**).

This compound was obtained as bright yellow-orange needles, 35% yield, m.p. 285-286°; nmr (deuterium oxide): δ = 7.90 (C_7-H_3, d, J = 6 Hz), 5.96 (C_8-H, d, J = 6 Hz), 2.90 (N-CH_3), 2.02 (C_2-CH_2CH_3, q, J = 7 Hz), 1.06 (C_2-CH_2-CH_3, t, J = 7 Hz); uv λ max (95% ethanol): 228 (ε, 16,750), 342-345 nm (ε, 5,260); ir cm^{-1}: 3405 (w), [3050 (m), 2983 (s), 2858 (s) (NH)], 1945 (w), 1855 (w), 1660 (m), 1619 (s), 1547 (s), 1525 (s), 1493 (s), 1402 (m), 1352 (w), 1282 (w), 1222 (m), 1184 (m), 1125 (w), 1088 (w), 1038 (w), 1022 (w), 947 (w), 878 (w), 825 (m), 752 (w).

Anal. Calcd. for $C_8H_{11}N_5$·HCl: C, 45.0; H, 5.6; N, 32.8. Found: C, 45.0; H, 5.8; N, 32.7.

4-Amino-5-hydrazinopyridazine (**29**).

This compound was prepared by the method of Guither, Clark, and Castle (16).

1,2-Dihydropyridazino[4,5-*e*]-*as*-triazine Hydrochloride (**31**).

A solution of 0.25 g. (0.0199 mole) of 4-amino-5-hydrazinopyridazine (**29**) in 5 ml. of triethylorthoformate was stirred magnetically while 1 ml. of concentrated hydrochloric acid was added dropwise over a 3 minute period (17). The clear reaction mixture became dark purple during the addition of the acid. The mixture was allowed to stir at room temperature for 24 hours. The solution was cooled in an ice bath and the dark purple powder was filtered and washed with acetone to yield 0.26 g. in 76% yield, m.p. 192-194°; pmr (deuterium oxide): δ = 7.22-7.30 (C_5-H and C_8-H), 6.14 (C_3-H); uv λ max (95% ethanol): 231 (ε, 17,420), 313-323 nm (ε, 4,470); ir cm^{-1}: [2900 broad (s) (NH)], 1685 (m), 1647 (s), 1563 (s), 1527 (s), 1493 (s), 1400 (m), 1364 (m), 1326 (m), 1279 (s), 1247 (m), 1088 (w), 1031 (m), 855 (s).

Anal. Calcd. for $C_5H_6N_5Cl$: C, 35.0; H, 3.5; N, 40.8. Found: C, 34.9; H, 4.1; N, 40.6.

3-Methyl-1,2-dihydropyridazino[4,5-*e*]-*as*-triazine Hydrochloride (**32**).

A solution of 0.25 g. (0.020 mole) of **29** in 5 ml. of triethylorthoacetate was stirred magnetically while 1 ml. of concentrated hydrochloric acid was added dropwise over a 5 minute period. The dark purple solution was stirred for 24 hours at room temperature. The mixture was cooled, filtered, and washed with acetone to yield 0.22 g. of a dark purple powder, m.p. 220-225°; pmr (deuterium oxide): δ = 7.16-7.34 (C_5-H and C_8-H), 1.54 (C_3-CH_3); uv λ max (95% ethanol): 234 (ε, 18,100), 335-339 nm (ε, 3,880); ir cm^{-1}: [3180 (s), 3060 (s), 3100 (s) (NH)], 2970 (s), 2890 (s), 2805 (s), 1660 (m), 1600 (m), 1560 (s), 1530 (s), 1485 (m), 1430 (m), 1390 (m), 1370 (m), 1300 (m), 1290 (m), 1260 (m), 1220 (w), 1195 (w), 1030 (m), 970 (w), 950 (w), 890 (w), 825 (m), 700 (m).

Anal. Calcd. for $C_6H_8ClN_5 \cdot 0.5 \cdot H_2O$: C, 37.0; H, 4.7. Found: C, 37.2; H, 5.3. Recrystallization from ethanol or obtaining a new sample did not give better analyses.

3-Ethyl-1,2-dihydropyridazino[4,5-*e*]-*as*-triazine Hydrochloride (**33**).

A solution of 0.21 g. (0.00168 mole) of **29** in 5 ml. of triethylorthopropionate was stirred while 0.25 ml. of concentrated hydrochloric acid was added dropwise over a one minute period (17). The purple reaction mixture was allowed to stir at room temperature for 2 hours. This was diluted with 10 ml. of acetone, filtered, and washed with acetone to give 0.09 g. of a dark purple powder in 27% yield, m.p. 218-221°; pmr (deuterium oxide): δ = 7.20-7.34 (C_5-H and C_8-H), 1.84 (C_3-CH_2CH_3, q, J = 7 Hz), 0.96 (C_3-CH_2CH_3, t, J = 7 Hz); uv λ max (95% ethanol): 232 (ε, 14,640), 335-339 nm (ε, 2,640); ir cm^{-1}: 3416 (w), [3150 (s), 3082 (s) (NH)], 2905 (s), 1663 (s), 1611 (m), 1574 (s), 1526 (s), 1499 (s), 1425 (m), 1377 (w), 1350 (w), 1281 (m), 1216 (w), 1171 (w), 1030 (w), 896 (w), 838 (w), 793 (w).

Anal. Calcd. for $C_7H_9N_5$·HCl: C, 42.1; H, 5.1; N, 35.1. Found: C, 42.2; H, 5.1; N, 34.9.

4-Amino-5-chloropyridazine (**34**).

This compound was prepared by the method of Kuraishi and Castle (11).

4-Amino-5-(1′-methyl)hydrazinopyridazine (**30**).

A mixture of 1 g. (0.00772 mole) of 4-amino-5-chloropyridazine (**34**) and 5 ml. of 95% methylhydrazine was heated in a glass pressure bottle at 140° for 18 hours. Thin layer chromatography with silica gel and methanol showed the absence of starting material (starting material R_f = 0.66, product R_f = 0.50). The mixture was diluted with 5 ml. of water and cooled but no precipitate formed. The solution was evaporated *in vacuo* to give a light green oil that did not crystallize after cooling. The oil was dissolved in 10 ml. of methanol. One-half of this solution was evaporated *in vacuo* and used for the next reaction.

1-Methyl-1,2-dihydropyridazino[4,5-*e*]-*as*-triazine Hydrochloride (**35**).

A solution of 0.5 g. (0.0036 mole) of crude **30** and 5 ml. of triethylorthoformate was stirred while 0.25 ml. of concentrated hydrochloric acid was added dropwise (17). This was stirred at room temperature for 18 hours to yield a dark purple precipitate. The purple powder was dissolved in 10 ml. of water and neutralized with sodium bicarbonate. A precipitate did not form after the neutralization so the aqueous solution was extracted with three 20 ml. portions of chloroform. Hydrogen chloride gas was bubbled into the chloroform solution to give the product, 0.05 g. of purple powder, m.p. 300° in 7% yield; pmr (deuterium oxide): δ = 7.10-7.26 (C_5-H and C_8-H), 6.13 (C_3-H), 2.64 (N-CH_3); uv λ max (95% ethanol): 236 (ε, 20,950), 329-331 nm (ε, 3,480); ir cm^{-1}: [3031 (s), 2900 (s), 2709 (s) (NH)], 1666 (m), 1602 (m), 1571 (s), 1538 (m), 1510 (s), 1460 (w), 1393 (m), 1350 (m), 1311 (s), 1265 (w), 1241 (w), 1124 (m), 1099 (w), 1039 (w), 855 (w), 737 (w).

Anal. Calcd. for $C_6H_7N_5$·HCl·0.25·H_2O: C, 37.9; H, 4.5. Found: C, 38.1; H, 4.2.

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