Synthesis of Some [1,2,3]Thiadiazolo[5,4-*d*]pyrimidines and Pyrimido[4,5-*b*][1,4]thiazines[1]

EDWARD C. TAYLOR AND EDWARD E. GARCIA

Department of Chemistry, Princeton University, Princeton, New Jersey

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A number of 7-substituted [1,2,3]thiadiazolo[5,4-*d*]pyrimidines and 4-substituted pyrimido[4,5-*b*][1,4]thiazines have been prepared. Diazotization of 5-amino-4-mercapto-6-methoxypyrimidine gave 7-methoxy[1,2,3]-thiadiazolo[5,4-*d*]pyrimidine, which underwent facile nucleophilic displacement of the 7-methoxy group when treated with amines, and pyrimidine ring cleavage to methyl 5-amino-1,2,3-thiadiazole-4-carboxylate when heated with acid. Catalytic reduction of 4-carboxymethylthio-6-methoxy-5-nitropyrimidine gave 4-methoxy-7*H*-pyrimido[4,5-*b*][1,4]thiazin-6(5*H*)-one. Treatment of 5-amino-4-mercapto-6-methoxypyrimidine with phenacyl chloride in alkali yielded 4-methoxy-6-phenyl-7*H*-pyrimido[4,5-*b*][1,4]thiazine.

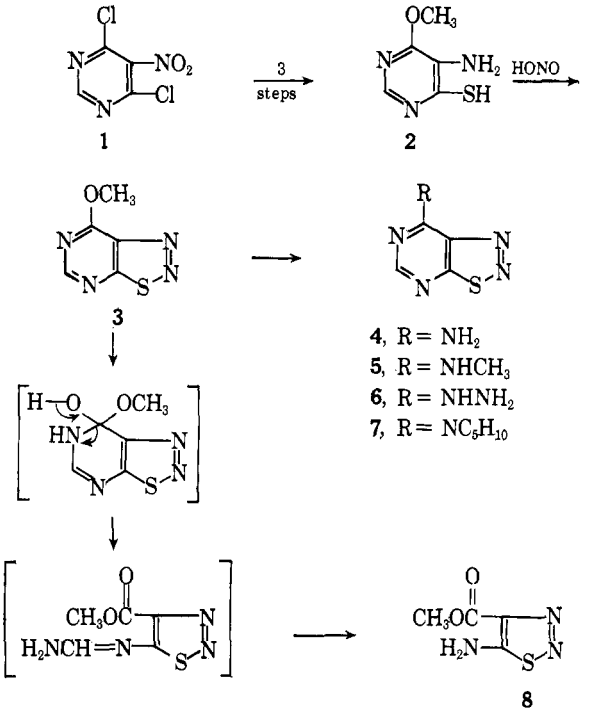
As a part of our continuing program directed towards the synthesis of potential purine and pteridine analogs as antimitotic agents, we wish to describe the preparation of a number of [1,2,3]thiadiazolo[5,4-*d*]pyrimidines and pyrimido[4,5-*b*][1,4]thiazines.

4,6-Dichloro-5-nitropyrimidine (**1**) was converted by a three-step sequence[2] to 5-amino-4-mercapto-6-methoxypyrimidine (**2**), which served as the starting material for many of the syntheses to be described. Thus, diazotization of **2** at 0° in dilute hydrochloric acid gave a pale yellow solid which upon vacuum sublimation yielded a white, crystalline material. Microanalysis and the absence of diazo absorption in the infrared spectrum of the material established its structure as 7-methoxy[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**3**).[3] A series of 7-substituted derivatives was then readily prepared from **3** by nucleophilic displacement of the extremely labile methoxy group.[4] Thus, treatment of **3** with ethanolic ammonia gave 7-amino-[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**4**). Similar treatment of **3** with methylamine, hydrazine, and piperidine gave the corresponding 7-substituted derivatives **5**, **6**, and **7** (Scheme I).

An attempt to effect hydrolysis of the methoxy group in **3** to give the corresponding 7-hydroxy derivative led to an unexpected cleavage reaction. Heating **3** with 2.5 *N* hydrochloric acid for approximately 10 min. followed by cooling resulted in the separation of a white, crystalline solid which exhibited bands at 2.94, 3.06, and 5.89 μ in the infrared, and whose microanalysis indicated the loss of a nitrogen atom but probable retention of the methoxy group. Such a result could only be compatible with hydrolytic cleavage of the pyrimidine ring to give methyl 5-amino-1,2,3-thiadiazole-4-carboxylate (**8**), which probably occurs as shown. There is ample precedent for pyrimidine cleavage reactions at the N-3–C-4 position occurring under similar conditions. For example, Albert[5] showed that acid hydrolysis of 4-methylpteridine (**9**) gave N′-(3-acetyl-2-pyrazinyl)formamidine (**10**); pteridine (**11**) under the same conditions gave 2-aminopyrazine-3-carboxaldehyde (**12**). In a similar type of cleavage reaction, 4-methylmercaptopyrimido-[4,5-*d*]pyrimidine (**13**), when dissolved at room temperature in dilute acetic acid, gave after 24 hr. a 63% yield of 4-formylamino-6-methylmercaptopyrimidine-5-carboxaldehyde (**14**).[6] Likewise, 4-amino- and 4-substituted aminopyrimido[4,5-*d*]pyrimidines (**15**) upon hydrolysis with 0.5 *N* hydrochloric acid were shown to give 4,6-diaminopyrimidine-5-carboxaldehydes (**16**), presumably *via* the hydrolytic pathway shown in Scheme II.[6] Finally, Shealy and Clayton[7] recently have shown that basic reagents under mild conditions cleave the pyrimidine ring of [1,2,5]thiadiazolo[3,4-*d*]-pyrimidin-7(6*H*)-one (**17**) to give derivatives of 4-amino-1,2,5-thiadiazole-3-carboxylic acid (**18**).

Confirmation for the assigned structure **8** for the hydrolysis product of **3** was obtained in the following manner. Treatment of **8** with an excess of formamidine acetate in 2-ethoxyethanol gave [1,2,3]thiadi-

SCHEME I



(1) This work was supported by a research grant (CY-2551) to Princeton University from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) E. C. Taylor, J. W. Barton, and W. W. Paudler, *J. Org. Chem.*, **26**, 4961 (1961).

(3) The only previously described derivatives of this ring system appear to be the 7-amino [M. Ishidate and H. Yuki, *Chem. Pharm. Bull.* (Tokyo), **8**, 131 (1960)], the 5-amino-7-methyl [F. L. Rose, *J. Chem. Soc.*, 3448 (1952)], and the 5-mercapto-7-methyl [R. S. Karlinskaya, N. V. Kromov-Borisov, *Zh. Obshch. Khim.*, **32**, 1847 (1962)] derivatives.

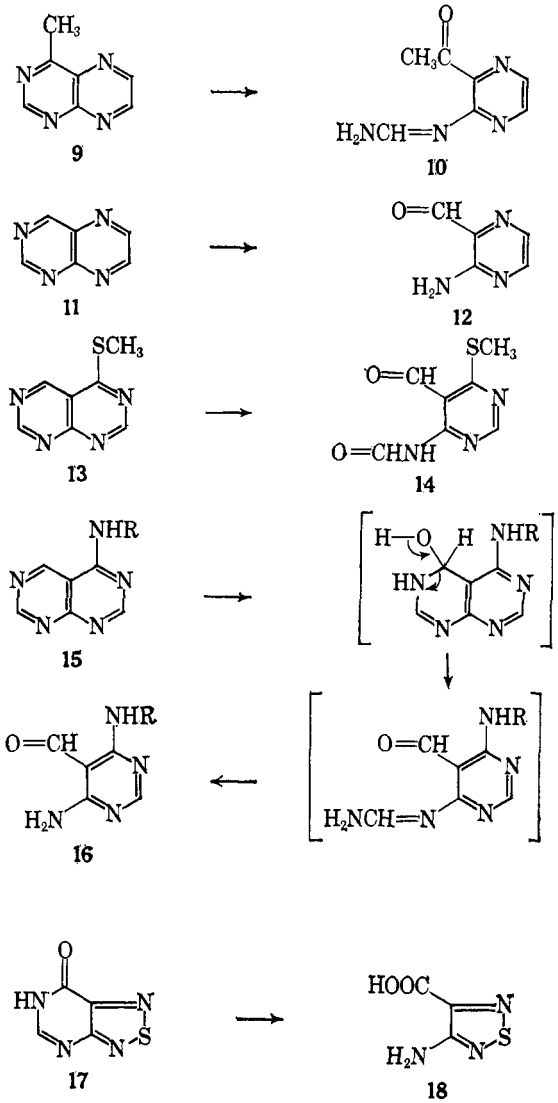
(4) Facile nucleophilic displacement reactions at position 7 in [1,2,5]-thiadiazolo[3,4-*d*]pyrimidine derivatives have been reported by Y. F. Shealy, J. D. Clayton, and J. A. Montgomery, *J. Org. Chem.*, **27**, 2154 (1962).

(5) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 2066 (1956).

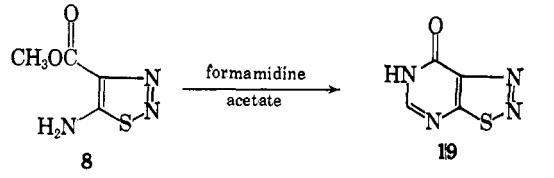
(6) E. C. Taylor and W. A. Ehrhart, unpublished observations.

(7) Y. F. Shealy and J. D. Clayton, *J. Org. Chem.*, **28**, 1491 (1963).

SCHEME II

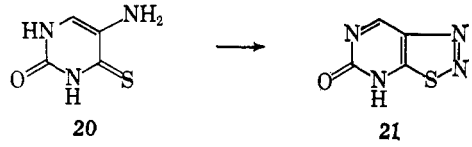


azolo[5,4-*d*]pyrimidin-7(6*H*)-one (**19**), which was identical in physical properties with a sample of the same material prepared by a different route by workers at the Southern Research Institute.[8]



Unexpectedly, all attempts to convert the ester **8** to the corresponding carboxamide were unsuccessful.

A further derivative of the [1,2,3]thiadiazolo[5,4-*d*]-pyrimidine ring system was prepared from 5-amino-uracil by treatment with phosphorus pentasulfide in refluxing pyridine to give 5-amino-4-thiouracil (**20**) followed by diazotization to give **21**.

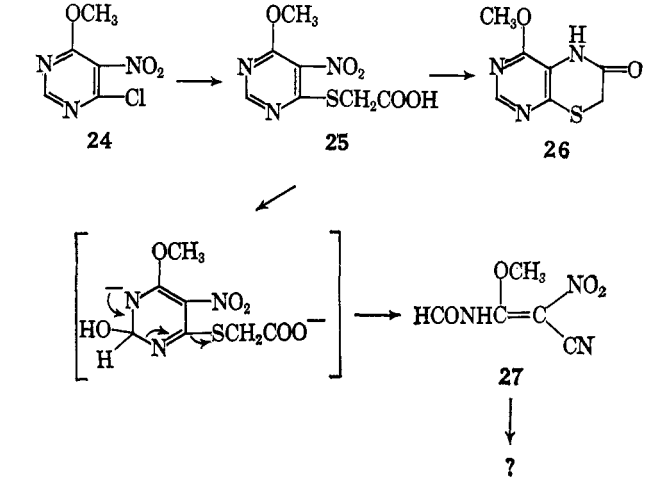


(8) Courtesy of Dr. J. A. Montgomery.

One modification of the pteridine ring system which might give rise to biologically active compounds would be the replacement of one of the nitrogen atoms in the pyrazine ring by sulfur. Recently, Schroeder and Dodson[9] have described the preparation of a number of derivatives of pyrimido[5,4-*b*][1,4]thiazine (**22**);

we wish to describe at this time the synthesis of several derivatives of the isomeric system **23**. Reaction of 4-chloro-6-methoxy-5-nitropyrimidine (**24**), one of the intermediates in the conversion of **1** to **2**, with mercaptoacetic acid at 0° in alkaline solution, followed by acidification, gave 4-carboxymethylthio-6-methoxy-5-nitropyrimidine (**25**) (Scheme III). Catalytic reduction of **25** then gave directly the ring-closed product,

SCHEME III



4-methoxy-7*H*-pyrimido[4,5-*b*][1,4]thiazin-6(5*H*)-one (**26**).[10] In contrast to the behavior of the methoxy derivative **3**, compound **26** proved to be inert towards displacement reactions; only starting material could be obtained upon heating **26**, even under very vigorous conditions, with a variety of amines and hydrazine.

The reaction of **24** with mercaptoacetic acid in alkaline solution proved to be very sensitive to temperature. When the reaction was carried out at room temperature rather than at 0°, none of the desired product **25** was formed; the only product obtained was an impure solid which exhibited strong $-NH_2$ bands and a $-CN$ band in the infrared. It thus seems probable that, under the alkaline condition employed, ring opening of **25** had taken place to give **27**. Analogous ring cleavages of mercapto-substituted pyrimidine heterocycles in alkaline solution previously have been observed[11]; the cleavage of 4-mercapto-pteridine (**28**) to 2-amino-3-cyanopyrazine (**29**) upon

(9) E. F. Schroeder and R. M. Dodson, *J. Am Chem. Soc.*, **84**, 1904 (1962).

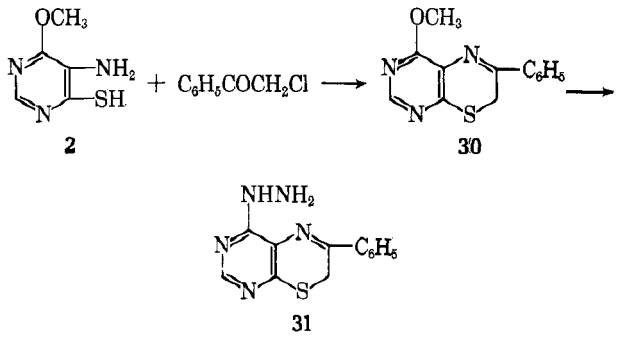
(10) Previously prepared derivatives of this system appear to be the 2-amino-4-methyl [F. L. Rose, *J. Chem. Soc.*, 3448 (1952)] and the 4-amino and 4-carboxymethylthio [M. Ishidate and H. Yuki, *Chem. Pharm. Bull.* (Tokyo), **8**, 131 (1960)] derivatives.

(11) E. C. Taylor, R. J. Knopf, J. A. Cogliano, J. W. Barton, and W. Pfleiderer, *J. Am. Chem. Soc.*, **82**, 6058 (1960).

28 29

treatment with chloroacetic acid and alkali is illustrative.

An alternative route to derivatives of the pyrimido-[4,5-*b*][1,4]thiazine ring system (**23**) involved treatment of 5-amino-6-mercapto-4-methoxypyrimidine (**2**) in alkaline solution with phenacyl chloride. 4-Methoxy-6-phenyl-7*H*-pyrimido[4,5-*b*][1,4]thiazine (**30**) was formed directly in 62% yield. Here again the methoxy group proved surprisingly unreactive towards nucleophilic displacement reactions; for example, only starting material could be recovered from an attempted reaction of **30** with alcoholic ammonia. Treatment of **30** with hydrazine hydrate in refluxing ethanol, however, led to the 4-hydrazino derivative (**31**) in good yield.



2 30 31

Experimental[12]

5-Amino-4-mercapto-6-methoxypyrimidine (**2**).—Compound **2** was prepared according to the procedure of Taylor, *et al.*,[9] using 4,6-dichloro-5-nitropyrimidine purchased from Aldrich Chemical Co.

7-Methoxy [1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**3**).—To 6.0 g. (0.038 mole) of 5-amino-4-mercapto-6-methoxypyrimidine (**2**) dissolved in a mixture of 40 ml. of concentrated hydrochloric acid and 350 ml. of water, and cooled to 0°, was added with stirring a solution of 3.1 g. (excess) of sodium nitrite in 15 ml. of water. During the addition, which was made portionwise over 15 min., a solid formed. After stirring for an additional 2 hr. at 0–5°, filtration and vacuum drying gave 5.0 g. of a pale yellow solid. Vacuum sublimation at 115–125° (0.5 mm.) yielded 4.3 g. (67%) of white crystals, m.p. 151–152°; λ_{max} 234 (sh), 261, 280 mμ ($\epsilon \times 10^3$ 5.4, 6.7, 5.0).

Anal. Calcd. for $C_5H_4N_4OS$: C, 35.72; H, 2.40; N, 33.33. Found: C, 35.68; H, 2.54; N, 33.30.

7-Amino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**4**).—Anhydrous ammonia was bubbled through a solution of 1.6 g. of 7-methoxy-[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**3**) in 120 ml. of hot ethanol for 0.5 hr. During this period the solution was heated on a hot plate. A solid separated almost immediately. Filtration and washing with hot ethanol gave 1.3 g. (86%) of a white solid, m.p. >270° dec. (slow). For analysis a sample was sublimed at 155–165° (0.5–0.7 mm.). This compound is reported[3] to melt with decomposition above 250°; λ_{max} 244, 263 (sh), 272 (sh), 313 mμ ($\epsilon \times 10^3$ 6.2, 3.2, 2.9, 4.9).

Anal. Calcd. for $C_4H_3N_5S$: C, 31.38; H, 1.98; N, 45.75; S, 20.89. Found: C, 31.41; H, 2.29; N, 45.75; S, 20.62.

7-Methylamino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**5**).—Anhydrous methylamine was bubbled for 1.5 hr. through a solution of 1.0 g. of 7-methoxy[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**3**) dissolved in 35 ml. of dioxane. The solution was heated on a steam bath during the initial 0.5 hr. of the reaction. Filtration and concentration of the filtrate yielded 0.9 g. (90%) of a slightly yellow solid, m.p. 217–219° dec. Two sublimations at 125° (0.5 mm.) gave white crystals, m.p. 219° dec.; λ_{max} 247, 267 (sh), 274 (sh), 325 mμ ($\epsilon \times 10^3$ 8.1, 3.7, 3.5, 5.9).

Anal. Calcd. for $C_5H_5N_5S$: C, 35.93; H, 3.02; N, 41.91; S, 19.15. Found: C, 35.94; H, 3.34; N, 42.00; S, 19.27.

7-Hydrazino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**6**).—A hot solution of 0.4 g. (0.0024 mole) of 7-methoxy[1,2,3]thiadiazolo-[5,4-*d*] pyrimidine (**3**) in 25 ml. of ethanol was treated with 0.2 g. (excess) of 85% hydrazine. Instantaneously a feathery, yellow solid precipitated. The mixture was then heated for 5 min. on a hot plate and then allowed to stand at room temperature for 10 min. Filtration gave 0.3 g. (75%) of product, m.p. 204–206° dec. For analysis the solid was recrystallized from a large volume of ethanol and had m.p. 208–209° dec.; λ_{max} 247, 275 (sh), 328 mμ ($\epsilon \times 10^3$ 7.7, 3.8, 6.9).

Anal. Calcd. for $C_4H_4N_6S$: C, 28.57; H, 2.40; N, 49.99. Found: C, 28.54; H, 2.41; N, 49.70.

7-Piperidino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine (**7**).—A solution of 1.0 g. (0.006 mole) of 7-methoxy[1,2,3]thiadiazolo[5,4-*d*]-pyrimidine (**3**) in 40 ml. of boiling ethanol was treated with 0.8 g. (excess) of piperidine and refluxed for 5 hr. Concentration of the resultant yellow-green solution produced a white solid, which after washing with water and drying weighed 1.1 g., m.p. 81–83°. Recrystallization from petroleum ether (60–70°) gave 0.95 g. (73%) of microneedles, m.p. 84–85°.

Anal. Calcd. for $C_9H_{11}N_5S$: C, 48.86; H, 5.01; N, 31.66. Found: C, 48.80; H, 5.14; N, 31.47.

Methyl 5-Amino-1,2,3-thiadiazole-4-carboxylate (**8**).—A suspension of 3.0 g. (0.018 mole) of 7-methoxy[1,2,3]thiadiazolo-[5,4-*d*]pyrimidine (**3**) in 45 ml. of 2.5 *N* hydrochloric acid was heated to boiling, whereupon solution occurred. In several minutes the originally clear solution became cloudy. After a total of 10 min. of boiling, the mixture was quickly filtered; the filtrate was refrigerated for 1 hr. The white solid which separated was filtered, washed with a little cold water, and dried *in vacuo* to give 1.8 g. (62%), m.p. 170–171° dec. For analysis the product was purified by sublimation at 135–140° (0.7 mm.); λ_{max} 267, 285 (sh) mμ ($\epsilon \times 10^3$ 8.5, 6.6); infrared,[13] λ_{max}^{Nujol} 2.94, 3.06, 3.16, 5.89, 6.20, 6.64, 7.25, 7.55, 8.05, 9.00, 10.40, 11.20, 12.08, 12.89 μ (medium and strong absorptions).

Anal. Calcd. for $C_4H_5N_3O_2S$: C, 30.19; H, 3.17; N, 26.41. Found: C, 30.47; H, 3.34; N, 26.64.

Methyl 5-Acetylamino-1,2,3-thiadiazole-4-carboxylate.—A solution of 0.5 g. (0.0031 mole) of methyl 5-amino-1,2,3-thiadiazole-4-carboxylate (**8**), 8 ml. of acetic anhydride, and 20 ml. of benzene was refluxed for 40 hr. The precipitated solid was filtered, washed with water, and sublimed at 140° (1.5 mm.). The first fraction to sublime appeared to be starting material, m.p. 170–171°. The second fraction obtained at 160° (2 mm.) was a white crystalline solid, m.p. 245–246° dec.

Anal. Calcd. for $C_6H_7N_3O_3S$: C, 35.83; H, 3.51. Found: C, 36.14; H, 3.59.

[1,2,3]Thiadiazolo[5,4-*d*]pyrimidin-7(6*H*)-one (**19**).—A solution of 0.65 g. (0.004 mole) of methyl 5-amino-1,2,3-thiadiazole-4-carboxylate (**8**) and 1.0 g. (excess) of formamidine acetate in 10 ml. of 2-ethoxyethanol was refluxed for 40 min. Concentration to dryness at reduced pressure gave a brown solid which was covered with 10 ml. of water and filtered. Recrystallization of the solid so obtained from ethanol (Norit) yielded 0.3 g. (45%) of white crystals, m.p. 230–231° dec.; $\lambda_{max}^{0.1\ N\ HCl}$ 233, 286 mμ ($\epsilon \times 10^3$ 6.9, 5.3); $\lambda_{max}^{0.1\ N\ NaOH}$ 237, 258 (sh), 310 mμ ($\epsilon \times 10^3$ 7.4, 6.3).

Anal. Calcd. for $C_4H_2N_4OS$: C, 31.16; H, 1.31; N, 36.35; S, 20.81. Found: C, 31.52; H, 1.46; N, 36.38; S, 20.70.

5-Amino-4-thiouracil (**20**).—A mixture of 20 g. (0.016 mole) of 5-aminouracil (Eastman, White Label), 60 g. (large excess) of phosphorus pentasulfide (Monsanto), and 700 ml. of reagent grade pyridine were heated, with stirring, at reflux for approximately 2 hr. The resultant green-black suspension was evaporated to dryness under reduced pressure, and the residue was covered with 400 ml. of water and heated to boiling for 1 hr.

(12) Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. All ultraviolets pectra were determined in ethanol unless otherwise specified.

(13) Infrared and ultraviolet spectra of some 5-substituted amino-1,2,3-thiadiazoles have been reported by E. Lieber, N. Calvanico, and C. N. R. Rao, *J. Org. Chem.*, **28**, 257 (1963).

After overnight refrigeration, filtration gave 16.5 g. of a greenish solid. Two recrystallizations from 10% sulfuric acid (Norit) yielded yellow crystals, which melted slowly with decomposition above 185°. Refrigeration of the filtrate gave a small amount of additional solid, total yield 14.8 g. (*ca.* 50%). The product appeared to be a sulfate salt on the basis of microanalysis.

Anal. Calcd. for $C_4H_5N_3OS \cdot 0.5H_2SO_4$: C, 25.00; H, 3.14; N, 21.88, S, 25.00. Found: C, 24.51; H, 3.31; N, 21.91; S, 24.81.

[1,2,3]Thiadiazolo[5,4-*d*]pyrimidin-5(4*H*)-one (21).—To 5.0 g. (*ca.* 0.026 mole) of the sulfuric acid salt of 5-amino-4-thiouracil (**20**) dissolved in 170 ml. of 2.5 *N* hydrochloric acid and cooled to 0° was added, with stirring, 2.3 g. (excess) of sodium nitrite in 15 ml. of water during 15 min. After an additional 1.5 hr. at 0–5°, the solid was filtered, washed with a little cold water, and oven-dried to yield 3.1 g. (77%) of yellow solid, m.p. 239° (effervescence). Two recrystallizations from a large volume of ethanol gave a pale cream-colored solid, m.p. 239° dec.; λ_{max} 236, 287 mμ ($\epsilon \times 10^3$ 3.7, 8.2).

Anal. Calcd. for $C_4H_2N_4OS$: C, 31.16; H, 1.31; N, 36.35; S, 20.81. Found: C, 31.20; H, 1.65; N, 36.30; S, 20.80.

4-Carboxymethylthio-6-methoxy-5-nitropyrimidine (25).—To a suspension of 9.0 g. (0.047 mole) of 4-chloro-6-methoxy-5-nitropyrimidine in 125 ml. of water immersed in ice, there was added 4.3 g. (0.047 mole) of mercaptoacetic acid (Fisher). At 0° and with vigorous stirring a solution of 3.8 g. (0.095 mole) of sodium hydroxide in 30 ml. of water was added over 20 min. During this addition, color changes of yellow to green to brown were observed. After stirring for an additional 4.5 hr. at 0–5°, the now blue solution was filtered to remove 0.75 g. of starting material, and the ice-cooled filtrate was acidified with concentrated hydrochloric acid. After standing for 5 min. at room temperature the precipitated blue-purple solid was filtered and dissolved in a large volume of ethanol. Three treatments with Norit gave a yellow-green solution which was concentrated to a small volume, treated with a little water and refrigerated. Filtration and vacuum drying (80°) yielded 6.4 g. (55%) of yellow-green crystals, m.p. 136–138°, with preliminary shrinking about 120°. One additional recrystallization from ethanol brought the melting point to 138–139°.

Anal. Calcd. for $C_7H_7N_3O_5S$: C, 34.29; H, 2.88; N, 17.14; S, 13.06. Found: C, 34.49; H, 2.77; N, 16.92; S, 12.77.

4-Methoxy-7*H*-pyrimido[4,5-*b*][1,4]thiazine-6(5*H*)-one (26).—A solution of 2.5 g. (0.01 mole) of 4-carboxymethylthio-6-methoxy-5-nitropyrimidine (**25**) in 70 ml. of methanol was treated with 0.5 g. of platinum oxide and hydrogenated in a Parr apparatus (*ca.* 2 atm.). After 2 hr., the catalyst was filtered off and the filtrate was concentrated to dryness to give a red oily solid. Two treatments with 25-ml. portions of ethyl acetate followed by evaporation of solvent gave 1.8 g. of brown solid. Two recrystallizations from ethanol–petroleum ether (b.p. 60–70°) yielded white crystals, 1.4 g. (70%), m.p. 190–191°; λ_{max} 236, 246 (sh), 283 (sh), 295 mμ ($\epsilon \times 10^3$ 15.0, 13.5, 5.0, 5.5).

Anal. Calcd. for $C_7H_7N_3O_2S$: C, 42.64; H, 3.58; N, 21.32; S, 16.14. Found: C, 42.68; H, 3.48; N, 21.39; S, 16.11.

4-Methoxy-6-phenyl-7*H*-pyrimido[4,5-*b*][1,4]thiazine (30).—A solution of 4.9 g. (0.031 mole) of 5-amino-6-mercapto-4-methoxypyrimidine (**2**) in 40 ml. of 10% sodium hydroxide was treated with 4.9 g. (0.031 mole) of phenacyl chloride and stirred for 24 hr. at room temperature. After filtering and washing with a little ether, the resultant tan solid, m.p. 175–180°, weighed 5.8 g. Two recrystallizations from ethanol–benzene gave 5.0 g. (62%) of pale yellow needles, m.p. 177–179° (does not form a clear melt); λ_{max} 233, 268, 295, 344 mμ ($\epsilon \times 10^3$ 13.6, 20.0, 6.4, 8.4).

Anal. Calcd. for $C_{13}H_{11}N_3OS$: C, 60.69; H, 4.31; N, 16.34. Found: C, 60.60; H, 4.63; N, 16.29.

4-Hydrazino-6-phenyl-7*H*-pyrimido[4,5-*b*][1,4]thiazine (31).—A solution of 0.5 g. (0.002 mole) of 4-methoxy-6-phenyl-7*H*-pyrimido[4,5-*b*][1,4]thiazine (**30**) in 10 ml. of ethanol was treated with 2 ml. of 85% hydrazine and refluxed for 5 hr. The solution was filtered hot. Cooling of the filtrate then gave 0.35 g. (70%) of long, yellow needles, m.p. 198–202°. The analytical sample was recrystallized from ethanol to give deep orange needles, m.p. 198–200°; λ_{max} 276, 378 (broad) mμ ($\epsilon \times 10^3$ 21.0, 7.5).

Anal. Calcd. for $C_{12}H_{11}N_5S$: C, 56.02; H, 4.31; N, 27.23; S, 12.44. Found: C, 56.01; H, 4.33; N, 27.01; S, 12.35.

Heterocyclic Studies. XII. The Base-Catalyzed Deuterium Exchange and Rearrangement of 2,3-Dihydro-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one to α-Aminopyridines[1,2]

JAMES A. MOORE AND ESTELLE C. ZOLL

Department of Chemistry, University of Delaware, Newark, Delaware

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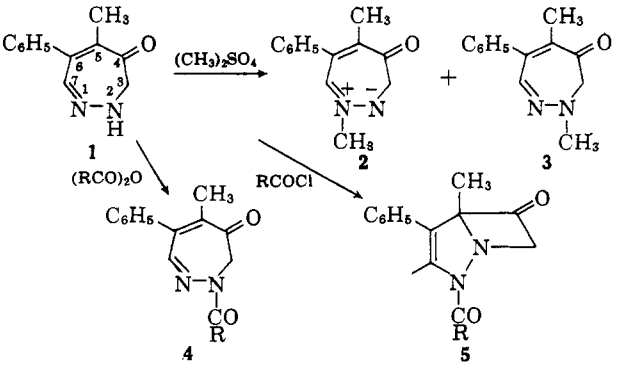
Deuterium exchange of the diazepinone **1** in basic solution was determined by n.m.r. spectra and found to occur at C-3 and more slowly at C-7 to give the 3,3,7-d_3 compound by deuteration of the anions **6** and **7**. Rearrangement of **1** in basic solution gives 2- and 6-amino-3-hydroxy-4-methyl-5-phenylpyridines in approximately equal amounts. The 2-methyldiazepinone **3** gives the 2-methylaminopyridine **11**. A suggested mechanism for the rearrangement is cleavage to the acyclic intermediate **14** and recyclization.

In previous papers we have described the formation of and structural evidence for the diazepinone **1**.[3,4] Electrophilic reagents attack **1** at both nitrogen atoms; with methyl sulfate in alkaline solution, equal amounts of the 1- and 2-methyl derivatives **2** and **3** are produced. Acylation with acid chlorides in pyridine solution occurs at N-1; in this case the substitution is accompanied by bridging to give the bicyclic ketone **5**.[5] With acid anhydrides the 2-acyl derivatives **4** are obtained.

The factors governing the position of attack of **1** with various reagents are not yet fully understood;



1 2 3 4 5

some of these products have been assumed to arise by participation of the anion **6** and others from the neutral molecule.[4] The ketone **1** is soluble in dilute aqueous alkali, and this acidic character has been attributed to

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(2) Paper XI: J. A. Moore and C. L. Habraken, *J. Am. Chem. Soc.*, **86**, 1456 (1964).

(3) J. A. Moore and R. W. Medeiros, *ibid.*, **81**, 6026 (1959).

(4) J. A. Moore and J. Binkert, *ibid.*, **81**, 6029 (1959).

(5) J. A. Moore, F. J. Marascia, R. W. Medeiros, and E. Wyss, *ibid.*, **84**, 3022 (1962).