Pyridazines. XXIV. Syntheses of Some Thiazolopyridazinium Systems

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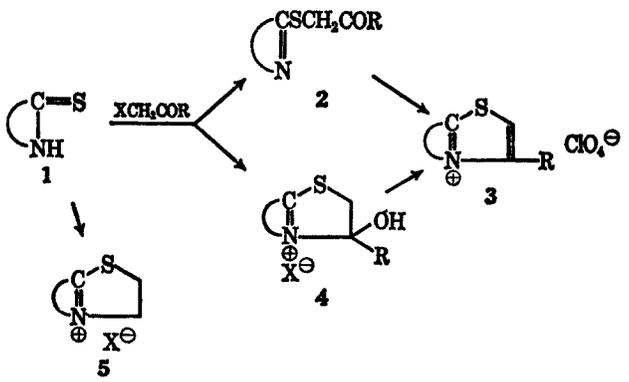
The reaction between α-halo ketones and different pyridazinethiones was investigated. It was found that, depending on reaction conditions, the reaction can lead to keto sulfides **2** or hhdroxythiazolinium salts **4**. The five-membered ring of the latter is easily cleaved and compounds are converted into keto sulfides **2**, whereas in the presence of concentrated sulfuric acid they aromatize to thiazolium salts **3**. These are also obtainable directly from **2**.

In 1964, Bradsher[1] and Russian workers[2] discovered that α-halo ketones or acetals of α-haloaldehydes reacted with heteroaromatic compounds containing a thioamide group as a part of their cycle to form thiazoloazinium salts. Since then several new heteroaromatic systems having a fused thiazolium ring have been synthesized.[1-5]

The formation of azoloazinium salts is considered to be related to aromatic cyclodehydration and therefore an intermediate **4** should be expected to result from the proposed concerted reaction mechanism.[6] However, so far such intermediates could not be isolated, although their existence has been observed recently by nmr examination of keto sulfides of pyrimidinones.[4] However, it should be pointed out that some hydroxythiazolidines have been isolated previously,[7-14] but these compounds are formed upon treatment of α-halocarbonyl compounds with thioureas or cyclic systems where on the adjacent ring nitrogen a mobile hydrogen is located.

When applying the above reaction for the formation of a fused thiazolium ring to several heterocyclic systems which we have investigated recently and which have in common a pyridazine ring, we were able to isolate as intermediates compounds of type **4** of different stability. As starting compounds we have employed pyrido[2,3-*d*]pyridazine-5(6H)- and -8(7H)-thione, *s*-triazolo[4,3-*b*]pyridazine-6(5H)-thione and 6-chloropyridazine-3(2H)-thione. These compounds were transformed into the corresponding keto sulfides **2** when the reaction with α-halo ketones was conducted in the presence of sodium alkoxide (Scheme I). However, in the absence of the base and when the reaction was performed in an organic solvent (ethanol, ethyl acetate or tetrahydrofuran), intermediates of type **4** could be isolated and characterized.

SCHEME I



The most stable **4** are those derived from pyrido-[2,3-*d*]pyridazinethiones. However, all hydroxythiazolinium salts **4** (Chart I), except the 3-methyl derivative of **4b**, are converted into keto sulfides **2** when crystallized from a mixture of ethanol and N,N-dimethylformamide. Similarly, the cyclic product based on the *s*-triazolo[4,3-*b*]pyridazine ring system **4c**, when dissolved in 20% aqueous ethanol, was immediately converted into **2c**. Most unstable are hydroxythiazolinium salts derived from 6-chloropyridazine-3(2H)-thione which upon standing at room temperature in a sealed tube are decomposed in few days. The conversion of **4c** and **4d** into **2c** and **2d** can be followed easily by ir spectroscopy. Thus a sample of **4c** (R = Ph), left for few minutes in air, displayed in the recorded ir spectrum the presence of **2c** (R = Ph), as judged from the appearance of a carbonyl band at 1678 cm^{-1}. The conversion of the more stable **4a** and **4b** into the corresponding **2** is particularly enhanced in the presence of an acid or base or in a solution of a hydroxylic solvent like ethanol.

It seems that the formation of stable **4** is limited to systems containing a =N—N= group, like pyridazine, since we were not able to obtain such intermediates from monoazines, *e.g.*, pyridine-2(1H)-thione. Here, the only reaction product under varying reaction conditions was the keto sulfide of type **2**.

Both **2** and **4** were easily transformed into the corresponding thiazolium heterocycles **3** in the presence of concentrated sulfuric acid at room temperature and

(1) C. K. Bradsher and D. F. Lohr, *Chem. Ind.* (London), 1801 (1964).
(2) F. S. Babichev and V. N. Bubnovskaya, *Ukr. Khim., Zh.*, **30**, 848 (1964).
(3) C. K. Bradsher and W. J. Jones, *J. Org. Chem.*, **32**, 2074 (1967).
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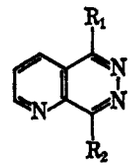
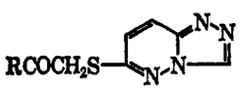
(10) K. M. Murav'eva and M. N. Shchukina, *Dokl. Akad. Nauk SSSR*, **136**, 1274 (1959).
(11) A. Takamizawa, K. Hirai, T. Ishiba, and Y. Matsumoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 731 (1967).
(12) B. M. Regan, F. T. Galysh, and R. N. Morris, *J. Med. Chem.*, **10**, 649 (1967).
(13) A. E. Alper and A. Taurins, *Can. J. Chem.*, **45**, 2903 (1967).
(14) G. Doleschall, G. Hornyak, M. Hornyak-Hamori, K. Lempert, and A. Wolfner, *Acta Chim. Acad. Sci. Hung.*, **53**, 385 (1967).

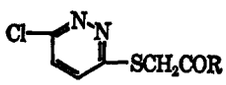
CHART I



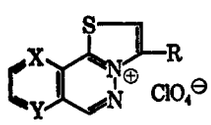
2a, R_1 = $PhCOCH_2S$; R_2 = H
b, R_1 = H; R_2 = $PhCOCH_2S$ or $MeCOCH_2S$



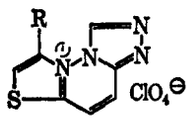
2c



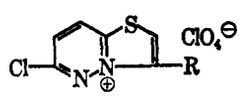
2d



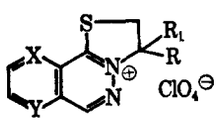
3a, X = CH; Y = N
b, X = N; Y = CH

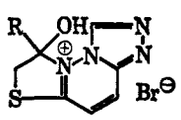


3c



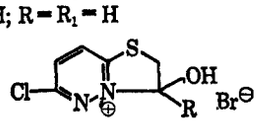
3d





4a, X = CH; Y = N; R = OH; R_1 = Ph
b, X = N; Y = CH; R = OH; R_1 = Ph or Me
5a, X = CH; Y = N; R = R_1 = H
d, X = N; Y = CH; R = R_1 = H

4c



4d

they were isolated and characterized as perchlorate salts. Yields were in both cases almost the same. This procedure proved to be unsuccessful only with 6-phenacylthio-*s*-triazolo[4,3-*b*]pyridazine and in this particular case heating with polyphosphoric acid has to be applied to obtain **3c** (R = Ph). Thiazolium salts **3** are relatively stable when dissolved in 0.1 *N* hydrochloric acid or ethanol, but are quickly transformed in 0.1 *N* sodium hydroxide solution back to keto sulfides **2**.

The nmr spectrum of 8-methylthiazolo[3,2-*b*]-*s*-triazolo[3,4-*f*]pyridazin-9-ium sulfate is in accordance with the proposed structure. Evidence was obtained that this compound, when dissolved in a mixture of trifluoroacetic anhydride and deuteriotrifluoroacetic acid, exchanges protons of the methyl group and H_7 with deuterium whereas other positions in this ring system remain unaffected.

Finally, in connection with the recent interest in the formation of fused dihydrothiazolium rings,[15,16] we have also performed the reaction between compounds of type **1** and 1,2-dibromoethane to form new heterocyclic systems of type **5**.

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(16) C. K. Bradsher and W. J. Jones, *Rec. Trav. Chim. Pays-Bas*, **87**, 274 (1968).

Experimental Section

Melting points were taken on a Kofler micro hot stage and are corrected. Infrared spectra were recorded on a Perkin-Elmer 137 Infracord as mulls in Nujol or hexachlorobutadiene. Nmr spectra were recorded on a Varian A-60 spectrometer.

5-Phenacylthiopyrido[2,3-*d*]pyridazine (**2a**, R_1 = $PhCOCH_2S$, R_2 = H).—Pyrido[2,3-*d*]pyridazine-5(6H)-thione[17] (1.63 g) was dissolved in a methanolic solution of sodium methoxide, prepared from 0.23 g of sodium and 15 ml of methanol. This solution was treated with phenacyl bromide (1.99 g) and heated under reflux for 5 min. The solution was then evaporated *in vacuo* to half of its original volume and poured into ice water (20 ml). The separated product was filtered and washed with iced water. Purification was performed by crystallization from EtOH to give 1.8 g (64%) of crystals with mp 160°; ir (Nujol 1678 cm^{-1} (C=O). *Anal.* Calcd for $C_{15}H_{11}N_3OS$: C, 64.05; H, 3.94; N, 14.94. Found: C, 63.86; H, 4.08; N, 14.77.

In an analogous way the following compounds were prepared.

8-Phenacylthiopyrido[2,3-*d*]pyridazine (**2b**, R_1 = H; R_2 = $PhCOCH_2S$) was prepared from pyrido[2,3-*d*]pyridazine-8(7H)-thione[17] in 58% yield: mp 196° (from ethanol and N,N-dimethylformamide, 4:1; ir (Nujol) 1678 cm^{-1} (C=O). *Anal.* Calcd for $C_{15}H_{11}N_3OS$: C, 64.05; H, 3.94; N, 14.94; S, 11.38. Found: C, 64.19; H, 4.35; N, 14.72; S, 11.46.

8-Acetonylthiopyrido[2,3-*d*]pyridazine (**2b**, R_1 = H; R_2 = $MeCOCH_2S$), prepared by using bromoacetone, was obtained in 57% yield, mp 146–147° (EtOH–H_2O, 2:1). *Anal.* Calcd for $C_{10}H_9N_3OS$: C, 54.79; H, 4.14; N, 19.17; S, 14.60. Found: C, 54.98; H, 4.32; N, 19.31; S, 14.49.

6-Phenacylthio-*s*-triazolo[4,3-*b*]pyridazine (**2c**, R = Ph).—*s*-Triazolo[4,3-*b*]pyridazine-6(5H)-thione[18] (1.52 g) was dissolved in a methanolic solution of sodium methoxide (prepared from 12 ml of MeOH and 0.23 g of Na). To this solution phenacyl bromide (1.99 g) was added and the mixture was allowed to stand at room temperature overnight. The separated crystals were washed with 2 ml of EtOH and crystallized from EtOH: mp 185°; ir (Nujol) 1678 cm^{-1} (C=O). *Anal.* Calcd for $C_{13}H_{10}N_4OS$: C, 57.77; H, 3.73; N, 20.73; S, 11.84. Found: C, 57.75; H, 3.71; N, 20.72; S, 11.84.

The compound formed a hydrobromide salt, mp 215–217° (EtOH). *Anal.* Calcd for $C_{13}H_{11}BrN_4OS$: C, 44.45; H, 3.16; N, 15.95; S, 9.13. Found: C, 44.86; H, 3.45; N, 15.65; S, 9.26.

Following the above procedure the following compound was prepared.

6-Acetonylthio-*s*-triazolo[4,3-*b*]pyridazine (**2c**, R = Me).—The reaction mixture was poured into 10 ml of iced water and the separated crystals were crystallized from EtOH: mp 150°; yield 38%; ir (Nujol) 1718 cm^{-1} (C=O). *Anal.* Calcd for $C_8H_8N_4OS$: C, 46.15; H, 3.87; N, 26.92; S, 15.37. Found: C, 46.32; H, 3.92; N, 26.85; S, 15.29.

6-Chloro-3-phenacylthiopyridazine (**2d**, R = Ph).—To a solution of NaOEt in EtOH, prepared from 0.23 g of Na and 20 ml of absolute EtOH, under vigorous stirring 6-chloropyridazine-3(2H)-thione[19–21] (1.47 g) was added and thereafter a solution of phenacyl bromide (2 g) in EtOH (10 ml). The reaction mixture was left on ice for 1 hr and thereafter poured onto 100 g of crushed ice. The separated product was filtered off and crystallized from EtOH to give 1.7 g (66%) of the pure compound, mp 118–119°. *Anal.* Calcd for $C_{12}H_9ClN_2OS$: C, 54.45; H, 3.43; N, 10.59; S, 12.11. Found: C, 54.61; H, 3.60; N, 10.35; S, 12.65.

6-Chloro-3-acetonylthiopyridazine (**2d**, R = Me).—A solution of 6-chloropyridazine-3(2H)-thione[19–21] (1.47 g) in ethanolic NaOEt (prepared from 0.23 g of Na and 30 ml of EtOH) was prepared. The filtered solution was treated under stirring dropwise with bromoacetone (1.34 g) dissolved in 20 ml of EtOH.

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(18) N. Takahayashi, *J. Pharm. Soc. Jap.*, **76**, 765 (1956).
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(21) N. Takahayashi, *J. Pharm. Soc. Jap.*, **75**, 778 (1955).

The reaction mixture was cooled with ice and the temperature was not allowed to rise above 3°. The mixture was then left at room temperature for 2 hr and the separated product (0.3 g) was filtered off. The filtrate was evaporated to one-fourth of its original volume and another crop of crystals (1.1 g) was obtained. After crystallization from EtOH and H_2O (2:1) the pure compound had mp 100–102°. The over-all yield was 68%; ir (Nujol) 1730 cm^{-1} (C=O). *Anal.* Calcd for $C_7H_7ClN_2OS$: C, 41.48; H, 3.48; N, 13.82; S, 15.81. Found: C, 41.62; H, 3.66; N, 13.90; S, 16.03.

2-Phenacylthiopyridine Hydrobromide.—To a stirred solution of pyridine-2(1H)-thione (1.1 g) in EtOH (10 ml) phenacyl bromide (1.99 g) was added. Immediately a precipitate of the hydrobromide salt was formed and was crystallized from EtOH: yield 2.8 g (90%); mp 194° (lit.[22] mp 184.5–185.5°); ir (Nujol) 1669 cm^{-1} (C=O). *Anal.* Calcd for $C_{13}H_{12}BrNOS$: C, 50.31; H, 3.90; N, 4.51. Found: C, 50.16; H, 4.29; N, 4.39.

The same product was obtained if instead of EtOH ethyl acetate was used as solvent.

8-Phenylthiazolo[3,2-*b*]-*s*-triazolo[3,4-*f*]pyridazin-9-ium Perchlorate (3c, R = Ph).—Compound 2c (R = Ph; 0.5 g) was suspended in polyphosphoric acid (15 ml) and the mixture heated on a water bath for 18 hr. The condenser was equipped with an absorption tube to prevent the access of moisture. The cooled reaction mixture was poured onto crushed ice (about 50 g), filtered and the filtrate treated with 70% $HClO_4$ (about 1 ml). The precipitate was filtered off and washed with H_2O and EtOH. The yield was almost quantitative, mp 200–201°. *Anal.* Calcd for $C_{13}H_9ClN_4O_4S$: C, 44.25; H, 2.57; N, 15.88; S, 9.09. Found: C, 44.48; H, 2.88; N, 15.98; S, 9.08.

8-Methylthiazolo[3,2-*b*]-*s*-triazolo[3,4-*f*]pyridazin-9-ium Perchlorate (3c, R = Me).—Compound 2c (R = Me; 0.5 g) was treated with concentrated H_2SO_4 (5 ml) and the mixture left aside at room temperature for 24 hr. The resultant reddish solution was poured slowly into 100 ml of ice cold ether. After some time an oil separated and the ethereal layer was decanted, the residual oil dissolved in H_2O (10 ml) and the perchlorate salt precipitated with dropwise addition of 70% $HClO_4$. It was crystallized from H_2O (yield 61%): mp 215–217°; nmr of the sulfate [CF_3COOH:$(CF_3CO)_2O$, 1:1] τ 0.55 (s, H_1), 1.67 (d, H_4), 2.13 (d, H_5), 1.63 (s, H_7), 5.39 (s, CH_3), $J_{4,5}$ = 9.5 cps.

Anal. Calcd for $C_8H_7ClN_4O_4S$: C, 33.06; H, 2.43; N, 19.28. Found: C, 33.27; H, 2.71; N, 19.66.

In essentially the same way the following compounds were obtained.

3-Phenylpyrido[3,2-*d*]thiazolo[3,2-*b*]pyridazin-4-ium Perchlorate (3a, X = CH; Y = N; R = Ph).—The crude salt was washed with water and then with hot EtOH: yield 93%; mp 272–273°. *Anal.* Calcd for $C_{15}H_{10}ClN_3O_4S$: C, 49.50; H, 2.77; N, 11.55. Found: C, 49.68; H, 3.59; N, 11.52.

3-Phenylpyrido[2,3-*d*]thiazolo[3,2-*b*]pyridazin-4-ium Perchlorate (3b, X = N; Y = CH; R = Ph).—The crude product was washed with H_2O and EtOH; yield 88%; mp 314–315° dec. *Anal.* Calcd for $C_{15}H_{10}ClN_3O_4S$: C, 49.50; H, 2.77; N, 11.55. Found: C, 49.82; H, 3.17; N, 11.48.

The same compound was also obtained from **4b** (X = N; Y = CH; R = OH; R_1 = Ph) in the following way: compound **4b** (X = N; Y = CH; R = OH; R_1 = Ph; 1.0 g) was dissolved in concentrated H_2SO_4 (7 ml) whereupon HBr gas was evolved. The reaction mixture was left aside at room temperature overnight and poured into 50 ml of ice cold ether. The oil was separated from the ethereal layer and dissolved in 15 ml of H_2O. Under stirring 70% $HClO_4$ was added dropwise and the crude perchlorate salt was washed with H_2O and EtOH: yield 0.81 g (80%); mp 314–315° dec. The mixture melting point with the above specimen was undepressed.

3-Methylpyrido[2,3-*d*]thiazolo[3,2-*b*]pyridazin-4-ium Perchlorate (3b, X = N; Y = CH; R = Me).—The crude product was washed with ice cold water and hot EtOH and then crystallized from EtOH: yield 78%; mp 306–308°. *Anal.* Calcd for $C_{10}H_8ClN_3O_4S$: C, 39.80; H, 2.67; N, 13.93; S, 10.63. Found: C, 39.57; H, 3.17; N, 13.59; S, 10.55.

The compound was found identical with that obtained from **4b** (X = N; Y = CH; R = OH; R_1 = Me) in essentially the same way as outlined in the above case.

6-Chloro-3-phenylthiazolo[3,2-*b*]pyridazin-4-ium Perchlorate (3d, R = Ph).—A reaction mixture consisting of **2d** (R = Ph; 1.7 g) and concentrated H_2SO_4 (10 ml) was left at room temperature for 48 hr, cooled with ice and under stirring slowly poured into 80 ml of ice cold ether. The separated oil was dissolved in 80 ml of H_2O, the solution heated to boil, charcoal was added and the solution filtered. The cold filtrate was treated under stirring dropwise with 5 ml of 70% $HClO_4$. The formed precipitate was filtered off, dried and crystallized from AcOH and H_2O (5:1): yield 1 g (44%); mp 216–220°. *Anal.* Calcd for $C_{12}H_8Cl_2N_2O_4S$: C, 41.52; H, 2.32; N, 8.07; S, 9.24. Found: C, 41.55; H, 2.37; N, 7.73; S, 9.26.

6-Chloro-3-methylthiazolo[3,2-*b*]pyridazin-4-ium Perchlorate (3d, R = Me).—The reaction mixture, consisting of 0.2 g of 3-acetonylthio-6-chloropyridazine (**2d**, R = Me) and 7 ml of concentrated H_2SO_4, was left to stand at room temperature for 48 hr and then treated as described in the case of **3c**, R = Me. The crude perchlorate salt was washed with H_2O and EtOH, mp 223–224°. *Anal.* Calcd for $C_7H_6Cl_2N_2O_4S$: C, 29.49; H, 2.12; N, 9.83; S, 11.25. Found: C, 29.36; H, 2.07; N, 10.10; S, 11.65.

The same compound could be also obtained from **4d**, R = Me.

3-Hydroxy-3-phenyl-2,3-dihydropyrido[2,3-*d*]thiazolo[3,2-*b*]-pyridazin-4-ium Bromide (4b, X = N; Y = CH; R = OH; R_1 = Ph).—Pyrido[2,3-*d*]pyridazine-8(7H)-thione (1.63 g) was dissolved in minimum quantity of hot EtOH, phenacyl bromide (1.99 g) was added and the mixture heated to boiling. It was set aside and upon cooling the separated product was filtered off and washed with EtOH: yield 2.75 g (76%); mp 260–262° (slowly decomposes above 250°); ir 3356 cm^{-1} (OH). *Anal.* Calcd for $C_{15}H_{12}BrN_3OS$: C, 50.01; H, 2.80; N, 11.67; S, 8.91. Found: C, 49.87; H, 3.14; N, 11.90; S, 8.80.

If crystallization of the above bromide were attempted from N,N-dimethylformamide and EtOH (1:4), the salt would be converted into 8-phenacylthiopyrido[2,3-*d*]pyridazine.

Following the above procedure, other hydroxydihydrothiazolium salts were prepared.

3-Hydroxy-3-methyl-2,3-dihydropyrido[2,3-*d*]thiazolo[3,2-*b*]-pyridazin-4-ium Bromide (4b, X = N; Y = CH; R = OH; R_1 = Me).—This compound was obtained in 90% yield: mp 242–245° (from EtOH and N,N-dimethylformamide, 5:1); ir (Nujol) 3155 cm^{-1} (OH). The compound remained unchanged after 100 days when stored at room temperature in a sealed tube. *Anal.* Calcd for $C_{10}H_{10}BrN_3OS$: C, 40.01; H, 3.36; N, 14.00. Found: C, 40.26; H, 3.72; N, 14.06.

3-Hydroxy-3-phenyl-2,3-dihydropyrido[3,2-*d*]thiazolo[3,2-*b*]-pyridazin-4-ium Bromide (4a, X = CH; Y = N; R = OH; R_1 = Ph).—This compound could be obtained in 47% yield, mp 180–182°. *Anal.* Calcd for $C_{15}H_{12}BrN_3OS$: C, 50.01; H, 2.80; N, 11.67. Found: C, 50.14; H, 3.07; N, 11.82.

The compound, on attempted crystallization from N,N-dimethylformamide and EtOH (1:4), is transformed into 5-phenacylthiopyrido[2,3-*d*]pyridazine.

All above compounds of type **4**, when dissolved in 20% EtOH, are converted into the corresponding keto sulfides of type **2**. The reaction is particularly enhanced if some $NaHCO_3$ is added.

8-Hydroxy-8-phenyl-7,8-dihydrothiazolo[3,2-*b*]-*s*-triazolo[3,4-*f*]-pyridazin-9-ium Bromide (4c, R = Ph).—*s*-Triazolo[4,3-*b*]-pyridazine-6(5H)-thione (0.7 g) was dissolved in boiling ethyl acetate (45 ml) and treated with a solution of phenacyl bromide (1 g) in ethyl acetate (10 ml). The reaction mixture was allowed to cool down and left to stand at room temperature overnight. The separated crystals were filtered off, washed with ethyl acetate and dried *in vacuo*: yield 1.1 g; mp 210–212°; ir (Nujol) 3226 cm^{-1} (OH). *Anal.* Calcd for $C_{13}H_{11}BrN_4OS$: C, 44.45; H, 3.16; N, 15.96. Found: C, 44.45; H, 3.46; N, 15.78.

The above compound, when dissolved in 20% EtOH, is immediately converted into 6-phenacylthio-*s*-triazolo[4,3-*b*]pyridazine, mp 185°. The mixture melting point with an authentic specimen was undepressed. Also after 45 days of storing the compound at room temperature in a sealed tube it was transformed into **2c**, R = Ph [ir (hexachlorobutadiene) 1678 cm^{-1} (C=O)].

8-Hydroxy-8-methyl-7,8-dihydrothiazolo[3,2-*b*]-*s*-triazolo[3,4-*f*]-pyridazin-9-ium Bromide (4c, R = Me).—The compound was prepared by following the above procedure and the crude product was dried *in vacuo* at 63°: mp 260–263°; yield 82%; ir (Nujol) 3356 cm^{-1} (OH). *Anal.* Calcd for $C_8H_9BrN_4OS$: C, 33.23; H, 3.14; N, 19.38; S, 11.09. Found: C, 33.64; H, 3.44; N, 19.09; S, 10.90.

3-Hydroxy-3-phenyl-6-chloro-2,3-dihydrothiazolo[3,2-*b*]pyrida-

(22) C. Djerassi and G. R. Pettit, *J. Amer. Chem. Soc.*, **76**, 4470 (1954).

zin-4-ium Bromide (4d, R = Ph).—6-Chloro-3(2H)-pyridazinethione (1.47 g) was dissolved in tetrahydrofuran (50 ml) and under stirring phenacyl bromide (1.99 g) was added. The reaction mixture was left to stand at room temperature for 2 hr, and the separated product was filtered off, washed with some hot tetrahydrofuran and dried *in vacuo*: yield 77%; mp 163–164°; ir (Nujol) 3390 cm^{-1} (OH). *Anal.* Calcd for $C_{12}H_{10}BrClN_2OS$: C, 41.70; H, 2.92; N, 8.11; S, 9.28. Found: C, 41.37; H, 3.10; N, 8.47; S, 9.35.

In an analogous way the **3-methyl analog (4d, R = Me)** was prepared. The reaction mixture was evaporated to half of its original volume, and the residue was cooled on ice, filtered, washed with some tetrahydrofuran and dried *in vacuo*: yield 53%; mp 178–179°; ir (Nujol) 3378 cm^{-1} (OH). The compound is unstable and darkens after exposure on air after 15 min. *Anal.* Calcd for $C_7H_8BrClN_2OS$: C, 29.64; H, 2.84; N, 9.88. Found: C, 30.02; H, 3.30; N, 10.20.

2,3-Dihydropyrido[3,2-*d*]thiazolo[3,2-*b*]pyridazin-4-ium Bromide (5a, X = CH; Y = N; R = R_1 = H).—To a solution of pyrido[2,3-*d*]pyridazine-5(6H)-thione (1.63 g) in N,N-dimethylformamide (10 ml), K_2CO_3 (1.4 g) and 1,2-dibromoethane (1.88 g) were added. The reaction mixture was stirred at room temperature for 5 hr and then left to stand on ice overnight. The precipitated mixture of salts was filtered off and the pyridazinium salt was dissolved in hot anhydrous EtOH (about 15 ml). Upon cooling crystals separated and were filtered off and crystallized from EtOH: yield 0.73 g (27%); mp > 330° (at about 320° slow decomposition started). *Anal.* Calcd for $C_9H_8BrN_3S$: C, 38.08; H, 3.13; N, 16.28; S, 12.42. Found: C, 38.32; H, 3.33; N, 16.49; S, 12.09.

In an analogous way the isomeric **2,3-dihydropyrido[2,3-*d*]thiazolo[3,2-*b*]pyridazin-4-ium bromide (5b, X = N; Y = CH; R = R_1 = H)** was obtained in 23% yield, mp > 330° (from EtOH and N,N-dimethylformamide, 1:2). *Anal.* Calcd for $C_9H_8BrN_3S$: C, 38.08; H, 3.13; N, 16.28; S, 12.42. Found: C, 38.09; H, 3.63; N, 15.94; S, 12.22.

Registry No.—**2a**, 18599-27-4; **2b** (R_1 = H; R_2 = $PhCOCH_2S$), 18599-28-5; **2b** (R_1 = H; R_2 = $MeCOCH_2S$), 18599-29-6; **2c** (R = Ph), 18598-86-2; **2c**·HBr. (R = Ph), 18621-00-6; **2c** (R = Me), 18592-50-2; **2d** (R = Ph), 18592-51-3; **2d** (R = Me), 18592-52-4; 2-phenacylthiopyridine·HBr, 3166-30-1; **3a** (R = Ph), 18592-54-6; **3b** (R = Ph), 18592-55-7; **3b** (R = Me), 18592-56-8; **3c** (R = Ph), 18592-57-9; **3c** (R = Me), 18592-58-0; **3d** (R = Ph), 18621-01-7; **3d** (R = Me), 18592-59-1; **4a** (R = Ph), 18592-60-4; **4b** (R_1 = Ph), 18592-61-5; **4b** (R_1 = Me), 18592-62-6; **4c** (R = Ph), 18592-63-7; **4c** (R = Me), 18592-64-8; **4d** (R = Ph), 18592-65-9; **4d** (R = Me), 18592-66-0; **5a**, 18592-67-1; **5b**, 18592-68-2.

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1,3-Butadiynes in the Synthesis of Heterocyclic Compounds. I. 2,3-Dihydro-1,4-diazepine, Pyrazole, and Isoxazole Derivatives

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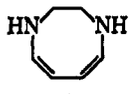
The condensation of 1,3-butadiyne with ethylenediamine has been shown to yield 5(7)-methyl-1H-2,3-dihydro-1,4-diazepine **2** ⇋ **3** rather than the reported 1,2,3,4-tetrahydro-1,4-diazocine (**1**). The reaction of hydrazine with appropriately substituted 1,3-butadiynes afforded pyrazoles **6a–d**, while 1,4-diphenyl-1,3-butadiyne, when treated with hydroxylamine, yielded isoazole **7**. Isomeric isoxazole **9** was also prepared and its structure was proven by nmr and mass spectrometric techniques.

The syntheses of pyrroles, thiophenes and selenophenes by the addition of ammonia, hydrogen sulfide and hydrogen selenide, respectively, to 1,3-butadiynes have recently been the subject of several papers.[1-3] An extension of this reaction utilizing ethylenediamine instead of monoamines has also been described.[4] The condensation product of ethylenediamine with 1,3-butadiyne is reported to afford 1,2,3,4-tetrahydro-1,4-diazocine (**1**).



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In view of our interest in diazocines[5-7] we repeated this reaction and obtained a "compound" which distilled at the reported boiling point [136° (6 mm)]. The nmr spectrum of this material is, however, not in agreement with that expected for 1,2,3,4-tetrahydro-1,4-diazocine (**1**). The nmr spectral data of the compound (*cf.* Experimental Section) show the presence of a methyl group, an olefinic two-proton (AB) system and a four-proton singlet along with an exchangeable one-proton peak. The nmr spectrum of the material obtained by distillation shows, in addition to the absorptions reported in the Experimental Section, a multitude of smaller peaks indicative of impurities. These impurities are no longer present when the reaction mixture is treated under milder conditions than those reported.[4] In fact, the yield of the compound is increased from 55 to 91% and the material crystallizes (mp 72–73°).

The purification process did not alter the molecular formula ($C_6H_{10}N_2$) of the compound. A consideration of the nmr spectrum strongly suggests that the correct structure of this material is the dihydrodiazepine (**2** or **3**). This assignment was readily confirmed by the catalytic reduction of the diazepine material to the known hexahydrodiazepine **4**.[8] The question as to

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