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SYNTHESIS OF PYRIDAZINE DERIVATIVES—III

FORMATION OF SOME BICYCLIC HETEROCYCLIC SYSTEMS

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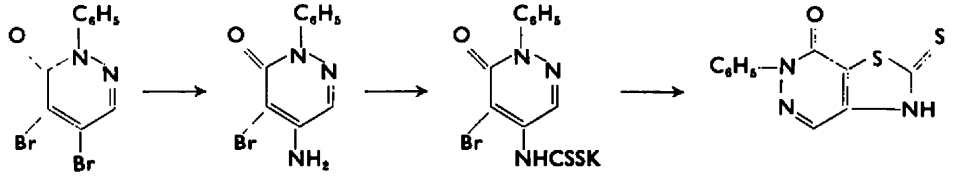
Abstract—2-Thio-6-phenyl-thiazolino(4,5-d)-pyridazin-7-one (IV) and 2,3-dihydro-6-phenyl-*p*-dithiino-(2,3-d)-pyridazin-5(6H)-one (VIII) and some derivatives have been prepared from 1-phenyl-4,5-dibromo-6(1H)-pyridazinone (I). Treatment of I with ammonia yielded the monoamino compound (II) and with ethanolic KHS solution the corresponding dimercapto compound (V) was obtained.

CONTINUING investigations in the pyridazine field[1,2] attention was drawn to the possibility of nucleophilic displacement of the halogens in 1-phenyl-4,5-dibromo-6(1H)-pyridazone (I) and the formation of some bicyclic systems. The incorporation of the 1-phenyl-6(1H)-pyridazone is of particular interest as some compounds with this system possess antipyretic and analgesic activity.[3,4]

The nucleophilic displacement of bromine in I has so far only been performed with sodium ethoxide and some aliphatic amines. There is conclusive evidence that only bromine in the position 4 is replaced with alkoxy or alkylamino groups.[3,5] However, with P_4S_{10} in pyridine both bromines are replaced with mercapto groups.[6]

In an attempt to replace both bromines in I with amino groups, it was found that only one could be replaced giving rise to the 4-amino derivative (II). This can be further transformed into the potassium salt of the corresponding dithiocarbamic acid (III) which on heating in diethylene glycol monomethyl ether at about 160° affords the bicyclic product (IV). This bicyclic system is known as in a similar reaction 2-aminothiazolo-(4,5-d)-pyridazine-7-thiol[7] was obtained.

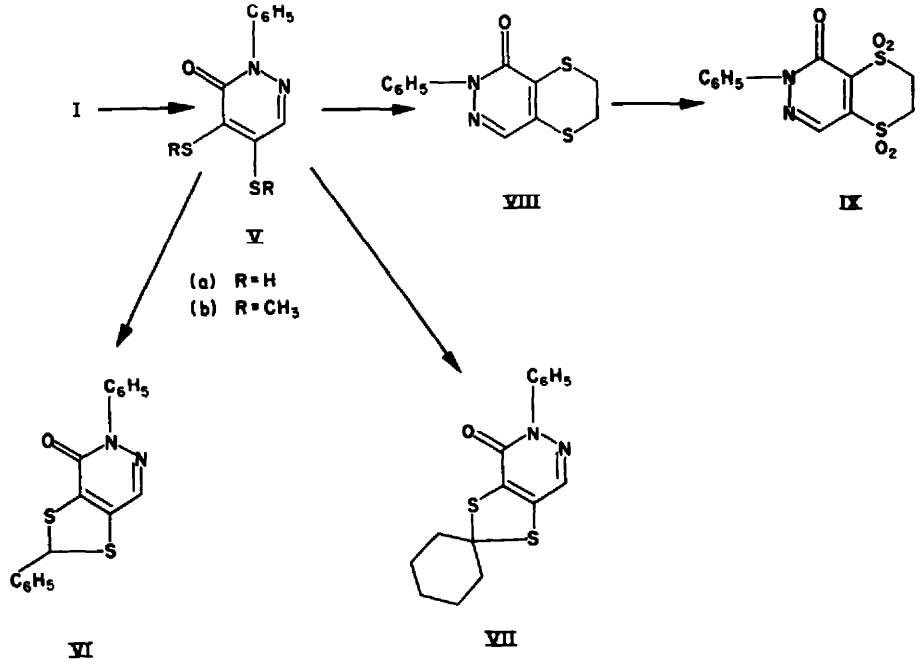


I II III IV

The structure of IV in the thioamide form is consistent with the observed UV and IR spectra. The absence of SH vibrations in the IR spectrum and the differences in the UV spectra of IV and its S-methyl derivative, which is capable of existing only in the fixed iminothiol form, all support the proposed structure.

[1] A. Pollak and M. Tišler, *Tetrahedron Letters* 253 (1964).
[2] B. Stanovnik and M. Tišler, *Croat Chem. Acta* **36**, 81 (1964).
[3] K. Meier, B. H. Ringier and J. Druey, *Helv. Chim. Acta* **37**, 523 (1954).
[4] J. Druey, A. Huni, K. Meier, B. H. Ringier and A. Staehelin, *Helv. Chim. Acta* **37**, 510 (1954).
[5] A. Sonn, *Liebigs Ann.* **518**, 290 (1935).
[6] R. N. Castle and K. Koji, *Tetrahedron Letters*, 393 (1962).
[7] T. Kuraishi and R. N. Castle, *J. Heterocyclic. Chem.* **1**, 42 (1964).

On the other hand, 1-phenyl-4,5-dimercapto-6(1H)-pyridazone (V) was prepared from I by reaction with an alcoholic KHS solution under pressure. This dimercapto compound forms cyclic thioacetals or thioketals. Thus with benzaldehyde the cyclic thioacetal (VI) and with cyclohexanone the corresponding spiro-compound (VII) are obtained. Furthermore, the dimercapto compound reacts with 1,2-dibromoethane giving rise to 2,3-dihydro-6-phenyl-*p*-dithiino-(2,3-d)-pyridazine-5(6H)-one (VIII)[8] in good yield. With a solution of peroxyacetic acid in acetic anhydride–glacial acetic acid both endocyclic sulphur atoms are oxidized and the corresponding tetroxide (IX) is obtained.



EXPERIMENTAL

IR spectra were obtained with a Perkin–Elmer spectrophotometer Model 21 equipped with an NaCl prism. UV spectra were measured with a Beckman Model DU spectrophotometer. M.ps were determined on a Kofler heating microscope.

1-*Phenyl*-4,5-*dibromo*-6(1H)-*pyridazone* was prepared from mucobromic acid and phenylhydrazine hydrochloride, according to Bistrzycki and Simonis.[9] λ_{max}^{EtOH} 269 and 322 mμ; ε 5,490 and 6,290.

1-*Phenyl*-4-*amino*-5-*bromo*-6(1H)-*pyridazone* (II)

A mixture of 6·6 g (0·02 mole) 1-phenyl-4,5-dibromo-6(1H)-pyridazone and 30 ml liquid ammonia were placed in an autoclave and heated for 4 hr at 100°. On cooling the autoclave was vented and to the residue 50 ml water was added. The separated crystals were collected and washed with water to

[8] This heterocyclic ring system was mentioned recently in a paper of W. Wolf, E. Degener and S. Petersen, *Angew. Chem.* 72, 963 (1960).

[9] A. Bistrzycki and H. Simonis, *Ber. Dtsch. Chem. Ges.* 32, 534 (1899).

yield 3·5 (65%) of the crude product. After crystallization from ethyl acetate colourless crystals, m.p. 225–226° were obtained. (Found: C, 45·25; H, 3·17; N, 15·73. $C_{10}H_8BrN_3O$ requires: C, 45·14; H, 3·02; N, 15·79%). λ_{max}^{EtOH} 227 and 310 mμ (ε 25,100 and 10,050). IR Nujol: maxima (cm $^{-1}$) at 3484, 3300 and 3205 (NH_2), 1634 (CO).

Acetyl derivative, colourless needles from ethyl acetate, m.p. 204–205°. (Found: N, 13·70. $C_{12}H_{10}BrN_3O_2$ requires: N, 13·63%). λ_{max}^{EtOH} 226 and 284 mμ (ε 20,100 and 11,600).

2-Thio-6-phenyl-thiazolino-(4,5-d)*-pyridazin-7-one* (IV)

Potassium (0·8 g) was allowed to react in 30 ml diethylene glycol monomethyl ether and thereafter 2·66 g (0·01 mole) of II and 1·2 g (0·015 mole) of CS_2 were added. The reaction mixture was heated under reflux for 3 hr at 160°. After cooling the reaction mixture was diluted with 100 ml water and acidified with HCl (1:1) to pH 1. The brown precipitate was filtered off and washed with water. The crude product (1·3 g) was crystallized from N,N-dimethylformamide with the addition of charcoal. The almost colourless crystals melted at 315–317°. (Found: C, 50·90; H, 2·90; S, 24·49. $C_{11}H_7N_3OS_2$ requires: C, 50 58; H, 2·70; S, 24·50%). λ_{max}^{EtOH} 236 and 302 mμ (ε 14,300 and 25,400). IR Nujol: maxima (cm $^{-1}$) at 3030, 1618, 1575, 1538.

2-Methylmercapto-6-phenyl-thiazolo-(4,5-d)*-pyridazin-7-one*

Compound IV was dissolved in KOHaq (0 56 g in 20 ml water), filtered free from undissolved products and a solution of 1·5 g MeI in 10 ml EtOH added. The mixture was shaken vigorously with external cooling. After few min, crystals separated and shaking was continued for ½ hr. The precipitate was collected and washed with water. The air dried crude product (2·6 g) was crystallized from ethyl acetate and afforded colourless needles with m.p. 133–134°. (Found: C, 52·57; H, 3·60; S, 23·35. $C_{12}H_9N_3OS_2$ requires: C, 52·37; H, 3·30; S, 23·26%). λ_{max}^{EtOH} 268 and 305 mμ (ε 17,100 and 11,700). The iodine–azide reaction[10] was negative.

*1-Phenyl-4,5-dimercapto-*6(1H)*-pyridazone* (V, R = H)

In a freshly prepared ethanolic solution of KHS (2·25 g KOH were dissolved in 50 ml EtOH and H_2S introduced until pH 7) the dibromo compound (I; 3·3 g) was suspended and the mixture heated in an autoclave at 150° for 4 hr. After cooling 100 ml water were added and the mixture acidified with HCl (1:1) to pH 1. The resulting precipitate was filtered off and thoroughly washed with water. It was dissolved in a 10% Na_2CO_3aq, filtered and the filtrate acidified to pH 1 with HCl. The resulting precipitate was collected and thoroughly washed with water, air dried and recrystallized from *n*-hexane–ethyl acetate (1:1). The pale yellow cubic crystals had m.p. 125·5–126·5° (Lit.[9] gives m.p. 110°), yield 1·2 g (45%). (Found: C, 51·04; H, 3·66; N, 12·30; S, 27·05. $C_{10}H_8N_2OS_2$ requires: C, 50·85; H, 3·41; N, 11·89; S, 27·09%). λ_{max}^{EtOH} 268, 306 and 362 mμ (ε 23,950, 7,260 and 8,250). IR Nujol: maxima (cm^{-1}) at 2427 (SH), 1603 (CO).

*1-Phenyl-4,5-dimethylmercapto-*6(1H)*-pyridazone* (V, R = CH_3)

To a solution of V (1·18 g) in 20 ml 0·5 N KOH, a solution of 1·5 g MeI in 10 ml EtOH was added. The mixture was shaken for 30 min, the precipitate filtered off and washed with water. The product was recrystallized from ethyl acetate–*n*-hexane (1:1) giving rise to colourless needles, m.p. 123·5–124·5°, yield; 1·0 g (65%). (Found: C, 54·55; H, 4·76; S, 23·80. $C_{12}H_{12}N_2OS_2$ requires: C, 54·54; H, 4·58; S, 24·21%). λ_{max}^{EtOH} 250 and 318 mμ (ε 12,050 and 10,030).

Formation of cyclic thioacetal and thioketal from (V)

a. *With benzaldehyde*. To a solution of 1·18 g of V in 20 ml abs. EtOH 0·6 g freshly distilled benzaldehyde was added. Into the reaction mixture dry HCl was introduced to saturation and the mixture heated under reflux for 1 hr. The solvent was evaporated *in vacuo* and to the residue 25 ml water added. The resulting precipitate was filtered off, washed with water and recrystallized from ethyl acetate–tetrahydrofurane (1:1). The colourless crystals of VI melted at 194–195°, yield 1·1 g (36%). (Found: C, 62·66; H, 3·79; S, 19·72. $C_{17}H_{12}N_2OS_2$ requires: C, 62·96; H, 3·73; S, 19·73%). λ_{max}^{EtOH} 258, 314 and 372 mμ (ε 21,950, 7,860 and 3,780).

[10] F. Feigl, Spot Tests, Vol. 2, *Organic Applications* p. 164. Elsevier, Amsterdam (1954).

b. *With cyclohexanone*. The same procedure as under (a) was applied and 0·5 g cyclohexanone used as starting material, yield 1·3 g (41%). The product was recrystallized from ethyl acetate–tetrahydrofurane (1:1) affording colourless crystals of VII, m.p. 150·5–151·5°. (Found: C, 60·95; H, 5·07; S, 20·20. $C_{16}H_{10}N_2OS_2$ requires: C, 60·76; H, 5·10; S, 20·24%). λ_{max}^{EtOH} 256, 312 and 361 mμ (ε 26,400, 8,330 and 4,630).

2,3-*Dihydro*-6-*phenyl*-p-*dithiino*-(2,3-d)-*pyridazin*-5(6H)-*one* (VIII)

To an ethanolic solution of EtONa prepared from 0·5 g Na and 50 ml EtOH, 2·35 g of V and 2·2 g 1,2-dibromoethane were added. The reaction mixture was heated under pressure at 100° for 3 hr. After cooling the solvent was evaporated *in vacuo* and the residue diluted with 50 ml water. The precipitate was collected, washed with water and the product crystallized from cyclohexane–benzene with the addition of charcoal. The colourless needles (1·9 g, 73%) had m.p. 121–122°. (Found: C, 55·18; H, 4·10; S, 24·25. $C_{12}H_{10}N_2OS_2$ requires: C, 54·96; 3·84; S, 24·41%). λ_{max}^{EtOH} 256 and 312 mμ (ε 20,900 and 8,050). IR Nujol: maxima (cm $^{-1}$) at 1642 (CO).

2,3-*Dihydro*-6-*phenyl*-p-*dithiino*-(2,3-d)-*pyridazin*-5(6H)-*one*-1,1,4,4-*tetroxide* (IX)

Acetic anhydride (20 ml) to which a drop of conc. H_2SO_4 was added was cooled with ice to 5°. With further cooling and stirring 5 ml of a 30% H_2O_2 was added. To this solution of peroxyacetic acid 1·0 g of VIII was added and the almost clear solution left at room temp. After about 24 hr, crystals began to separate and after 3 days these were filtered off and washed with glacial acetic acid. The yellow crystals were recrystallized from glacial acetic acid, m.p. 294–295°, yield 0·4 g (28%). (Found: C, 44·41; H, 3·24; S, 19·80. $C_{12}H_{10}N_2O_5S_2$ requires: C, 44·18; H, 3·09; S, 19·61%).

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