Synthesis of Pyridazine Derivatives XXII. *s*-Triazolo[4,3-b]pyridazine 5-Oxides

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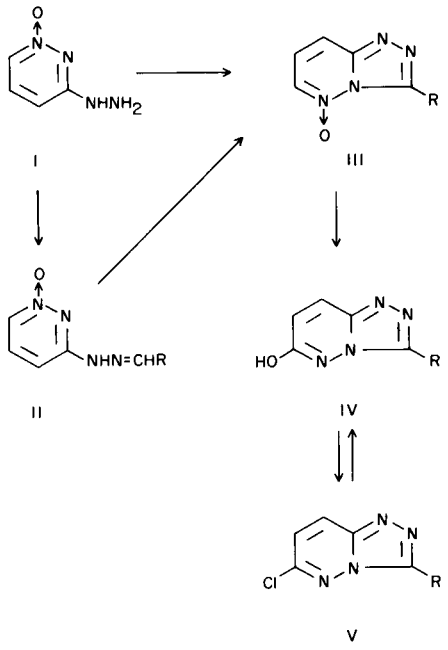
The synthesis of *s*-triazolo[4,3-*b*]pyridazine 5-oxides is reported. To our knowledge, they are the first example of *N*-oxides of heteroaromatic azoloazines with a bridgehead nitrogen. They are easily rearranged, in particular when irradiated with ultraviolet light, into 6-hydroxy-*s*-triazolo[4,3-*b*]pyridazines.

Azoloazines with a bridgehead nitrogen appear to be resistant to *N*-oxidation procedures common to monocyclic azines. Although it has been reported that a *s*-triazolo-[4,3-*a*]pyridine upon treatment with hydrogen peroxide in acetic acid gave an unstable product, formulated as an *N*-oxide, this was not fully characterized (1). There are several examples of peroxidation of indolizines (pyrrolo-[1,2-*a*]pyridines) leading through degradative reactions to α-picolinic acid *N*-oxide (2-5). In a similar experiment, 2-methylindolizine is claimed to afford its *N*-oxide (6), but there was no confirmation of its structure. To our knowledge, it appears that up to now *N*-oxides of heteroaromatic azoloazines with bridgehead nitrogen have not been isolated as such.



Recently, we reported that in a peroxidation attempt of imidazo[1,2-*b*]pyridazines only homolytic methylation of this bicycle could be observed (7). Therefore, it seemed feasible to test another approach to the synthesis of such bicyclic *N*-oxides, starting from the readily accessible pyridazine *N*-oxides. In view of the expected low stability of products, the formation of the *s*-triazolo[4,3-*b*]pyridazine system was chosen, since the cyclization of the five-membered ring can proceed under relatively mild reaction conditions according to methods developed previously (8-10).

s-Triazolo[4,3-*b*]pyridazine 5-oxides were obtained from 3-hydrozinopyridazine 1-oxide (I) which was condensed with aldehydes to yield II and upon oxidative cyclization with lead tetraacetate the desired compounds (III) were obtained in reasonable yields. Another route, which also proved to be applicable, was a direct one-step cyclization of I with cyanogen bromide in the presence of triethylamine to yield the 3-amino derivative (III, R = NH_2). The parent compound, *s*-triazolo[4,3-*b*]pyridazine 5-oxide (III, R = H), was obtained in low yield in a similar reaction from I and diethoxymethyl acetate. With the related dimethylformamide dimethylacetal, however, only the dimethylaminomethylene derivative (II, R = NMe_2) could be isolated even after a prolonged reaction time.

The structure of the *s*-triazolo[4,3-*b*]pyridazine 5-oxides is consistent with their infrared and nmr spectra. Infrared spectra exhibit the N-O stretching frequencies in the region of 1242-1256 cm^{-1} as an absorption of strong intensity. This is comparable with the region characteristic for monocyclic azine *N*-oxides (11-13). The bicyclic *N*-oxides are stable compounds when stored in the dark as solids. In solution and under the influence of sunlight or irradiation with ultraviolet light they are smoothly transformed into the corresponding 6-hydroxy-s-triazolo-

[4,3-*b*]pyridazines (IV). The process can be followed by recording the ultraviolet spectra, since during the rearrangement the wavelength of the absorption maximum is shifted towards longer wavelengths. The identity of the rearranged products was confirmed by an independent synthesis of two examples of IV from the known 6-chloro counterparts (V) which were obtained on the other hand from the irradiated products upon treatment with phosphorus oxychloride in the usual way.

Photorearrangement of several pyridazine *N*-oxides was reported only recently (14). The main reaction products were the corresponding deoxygenated products and hydroxymethyl derivatives. In low yield pyrazoles were obtained and their formation is postulated to proceed through an oxaziridine intermediate. Likewise, experiments on other heteroaromatic *N*-oxides suggest a common intermediate. In a series of irradiation experiments on quinoline 1-oxides and other related *N*-oxides it has been recently postulated that oxaziridines are formed as intermediates and these are subsequently converted into different final products (15-19). Later reports suggested the possibility of valence tautomerization giving rise to oxazepines (20-24). On the other hand, cyclic amides were isolated as the final rearranged products in irradiation experiments on several heteroaromatic *N*-oxides. (25).

In view of the above mentioned findings, it was of interest to determine if such intermediates could be detected during our experiments on rearrangement. Several runs were investigated by nmr and chromatographic techniques for eventual oxaziridine intermediates. Since no such products could be detected, it seems most likely that if the reaction progresses through oxaziridine-type compounds, these may immediately rearrange to the stable 6-hydroxy-*s*-triazolo[4,3-*b*]pyridazines.

EXPERIMENTAL

The NMR spectra of saturated solutions of compounds investigated were recorded in DMSO-d_6 (TMS as an internal standard) on a Varian A-60 NMR spectrometer. UV spectra: Beckman Model DU Spectrophotometer; infrared spectra: Infracord Model 137 Spectrophotometer, as Nujol mulls; melting points: Kofler melting point apparatus, corrected.

3-Hydrazinopyridazine 1-Oxide (I).

This compound was prepared by a modified procedure of Itai and Kamiya (26). 3-Methoxypyridazine 1-oxide (4.0 g.) was dissolved in 2-propanol (10 ml.), 100% hydrazine hydrate added (20 ml.) and the mixture heated under reflux for 1.5 hours. The reaction mixture was evaporated *in vacuo* and the remaining yellow oil solidified overnight to a crystalline solid. The product was filtered, washed with some alcohol and air dried, yield 2.2 g. (55%), m.p. 157-159° (Lit. (26) m.p. 158-160°); IR: 3236 (NH), 1271 (N-O) cm^{-1}.

Arylidene and Alkylidene Derivatives of 3-Hydrazinopyridazine 1-Oxide (II).

One hundredth mole of 3-hydrazinopyridazine 1-oxide was suspended in ethanol (30 ml.), a few drops of glacial acetic acid was added and the mixture heated until a clear solution was obtained. To this was added a solution of 0.011 mole of the corresponding aldehyde in ethanol (5 ml.) and the reaction mixture heated under reflux for 10 minutes. Upon cooling the hydrazine which separated was filtered off (or the solvent was evaporated *in vacuo*) and washed with alcohol. In this way the following compounds were prepared:

(a) 3-Benzylidenehydrazinopyridazine 1-oxide (II, R = C_6H_5) in 90% yield, m.p. 255-256° (ethanol); UV λ max (EtOH), 232, 258 and 318 mμ (ε = 13,900, 18,700 and 32,400); IR, 3205 (NH), 1274 (N-O) cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.16. Found: C, 61.51; H, 4.85; N, 26.33.

(b) 3-(*p*-Methoxybenzylidenehydrazino)pyridazine 1-oxide (II, R = p-$MeOC_6H_4$) in 86% yield, m.p. 246-247° (toluene and *N,N*-dimethylformamide, 2:1); UV λ max (EtOH), 225, 262 and 326 mμ (ε = 14,800, 18,300 and 32,600); IR, 3215 (NH), 1244 (OMe) and 1282 (N-O) cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}N_4O_2$: C, 59.01; H, 4.95; N, 22.94. Found: C, 58.91; H, 5.00; N, 23.06.

(c) 3-Ethylidenehydrazinopyridazine 1-oxide (II, R = Me) in 88% yield, m.p. 156-157° (ethyl acetate); UV λ max (EtOH), 240, 276 and 350 mμ (ε = 16,900, 21,400 and 4,010); IR, 3215 (NH), 1277 (N-O) cm^{-1}.

Anal. Calcd. for $C_6H_8N_4O$: C, 47.36; H, 5.30; N, 36.82. Found: C, 46.97; H, 5.43; N, 36.57.

3-Substituted *s*-Triazolo[4,3-*b*]pyridazine 5-Oxides (III).

A suspension of the above hydrazone (0.005 mole) in glacial acetic acid (10-15 ml.) was treated with lead tetraacetate (2.3 g., 0.005 mole). The reaction mixture was stirred at room temperature. Heat was evolved and the hydrazone went into solution. After standing in the dark at room temperature for 30 minutes, the mixture was poured into water (30 ml.), the solution neutralized with solid sodium bicarbonate, the product which separated was filtered, washed with some water and dried *in vacuo* over potassium hydroxide.

In this manner the following compounds were obtained:

(a) 3-Phenyl-*s*-triazolo[4,3-*b*]pyridazine 5-oxide (III, R = C_6H_5) in 40% yield, m.p. 154-155° (ethylacetate); UV λ max (EtOH) 252, 332 mμ (ε = 16,900 and 4820); IR, 1241 cm^{-1} (N-O); NMR, τ = 1.79 (H_6, doublet), τ = 2.62 (H_7, quartet), τ = 2.0 (H_8, doublet), τ = 2.50 (5H of C_6H_5, multiplet); $J_{6,7}$ = 6.0 cps; $J_{7,8}$ = 9.0 cps; $J_{6,8}$ not observed.

Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.25; H, 3.80; N, 26.40. Found: C, 62.15; H, 4.21; N, 26.38.

(b) 3-(*p*-Methoxyphenyl)-*s*-triazolo[4,3-*b*]pyridazine 5-oxide (III, R = *p*-$MeOC_6H_4$) in 43% yield, m.p. 187-188° (ethyl acetate); λ max (EtOH), 260 mμ (ε = 22,950); IR, 1250 cm^{-1} (N-O).

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.55; H, 4.14; N, 23.15.

(c) 3-Methyl-*s*-triazolo[4,3-*b*]pyridazine 5-oxide (III, R = Me) was obtained in 35% yield in a somewhat modified procedure. Upon neutralization with sodium bicarbonate, the product was extracted with chloroform, the chloroform layer was separated and dried over magnesium sulfate. The solvent was evaporated *in vacuo* and the product crystallized from ethanol and ethyl acetate (1:1), m.p. 199-200°; UV λ max (EtOH), 232 and 331 mμ (ε = 16,100 and 5900); IR, 1242 cm^{-1} (N-O); NMR τ = 1.86 (H_6, doublet), τ = 2.70 (H_7, quartet), τ = 2.12 (H_8, doublet), τ = 7.03 (3H of CH_3, singlet); $J_{6,7}$ = 6.0 cps, $J_{7,8}$ = 9.0 cps, $J_{6,8}$ not observed.

Anal. Calcd. for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.87; H, 4.13; N, 37.15.

3-Amino-*s*-triazolo[4,3-*b*]pyridazine 5-Oxide (III, R = NH_2).

To a stirred solution of I (1.25 g.) in methanol (30 ml.) cyanogen bromide (1.05 g.) was added. Heat was evolved and after a few minutes yellow crystals began to separate. The mixture was allowed to stand for 1 hour and thereafter triethylamine (1 g.) was added. Stirring was continued for 1 hour, and the product was filtered off, washed with methanol and purified by crystallization from ethanol; yield 0.8 g. (52%), m.p. 206-208° dec., UV λ max (EtOH), 220, 250, 294 and 375 mμ (ε = 10,410, 18,550, 2260 and 2520); IR, 3344 (NH), 1242 cm^{-1} (N-O).

Anal. Calcd. for $C_5H_5N_5O$: C, 39.73; H, 3.33; N, 46.34. Found: C, 39.85; H, 3.32; N, 46.34.

s-Triazolo[4,3-*b*]pyridazine 5-Oxide (III, R = H).

A mixture of I (0.2 g.) and diethoxymethyl acetate (0.7 ml.) was heated under reflux for 10 minutes. The crude product separated from the dark solution upon cooling. It was washed with ethanol and crystallized from diethoxymethylacetate giving 53 mg. of the pure compound, m.p. 243-244°; IR, 1256 cm^{-1} (N-O).

Anal. Calcd. for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.17. Found: C, 44.47; H, 3.08; N, 40.94.

3-Dimethylaminomethylenehydrazinopyridazine 1-Oxide (II, R = Me_2N).

A mixture of I (1 g.) and *N,N*-dimethylformamide dimethylacetal (5 ml.) was heated under reflux for 5 minutes and the product which separated was collected and crystallized from ethanol (yield 88%), m.p. 194°, IR, 3205 (NH), 1282 cm^{-1} (N-O).

Anal. Calcd. for $C_7H_{11}N_5O$: C, 46.40; H, 6.12; N, 38.65. Found: C, 46.19; H, 5.95; N, 38.62.

No cyclization product was obtained even if the reaction mixture was heated under reflux for 5 hours.

6-Hydroxy-*s*-triazolo[4,3-*b*]pyridazine (IV, R = H).

Compound III (R = H, 30 mg.) was dissolved in hot benzene (20 ml.) and the solution irradiated with a Hanovia Q 81 lamp for 3 hours. The solvent was concentrated *in vacuo* to about 2 ml., the product which separated was filtered off and crystallized from water (yield 12 mg.). The compound was found to be identical with the product, prepared according to the procedure of Takahayashi (27), m.p. and mixed m.p. 310-312° (Lit. (27) m.p. 291°).

6-Hydroxy-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (IV, R = C_6H_5).

(a) Compound III (R = C_6H_5, 1 g.) was dissolved in dry chloroform (150 ml.) and the solution irradiated (Hanovia Q 81 lamp) at room temperature for 5 hours. The crystals which separated were collected and washed with chloroform. Upon crystallization from ethanol the pure compound (62% yield) had m.p. 297-298°; UV λ max (EtOH), 258 mμ (ε = 20,700).

Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.25; H, 3.80; N, 26.40. Found: C, 62.20; H, 4.05; N, 26.34.

(b) A suspension of 6-chloro-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (8) (3.45 g.) in aqueous potassium hydroxide (15 ml. of 2*N* solution) was heated under reflux. After about 15 minutes the substance dissolved and the reaction mixture was heated for 2 hours. The cooled and filtered solution was acidified with concentrated hydrochloric acid, the precipitate collected and dried *in vacuo* over potassium hydroxide (yield 2.8 g., 90%). For analytical purposes the product was crystallized from ethanol and the colourless crystals melted at 297-298°. On the basis of m.p., mixed m.p., UV and IR spectra the compound is identical with the rearrangement product obtained as described under (a).

6-Hydroxy-3-(*p*-methoxyphenyl)-*s*-triazolo[4,3-*b*]pyridazine (IV, R = *p*-$MeOC_6H_4$).

Photorearrangement of the corresponding *N*-oxide was performed in the same way as described for the 3-phenyl analog. The compound, obtained in 59% yield, was crystallized from ethanol, m.p. 294-296°.

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.68; H, 4.31; N, 23.08.

6-Hydroxy-3-methyl-*s*-triazolo[4,3-*b*]pyridazine (IV, R = Me).

(a) This compound was obtained from an irradiation experiment, as described for the 3-phenyl analog, in 48% yield, m.p. 263-264° (water); UV λ max (EtOH), 270 mμ (ε = 4250); NMR, τ = -0.05 (broad signal for H of OH), τ = 2.88 (H_7, doublet), τ = 1.72 (H_8, doublet), τ = 7.35 (3H of CH_3, singlet); $J_{7,8}$ = 9.0 cps.

Anal. Calcd. for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 48.22; H, 4.25; N, 37.40.

(b) A mixture of 6-chloro-3-methyl-*s*-triazolo[4,3-*b*]pyridazine (28) (V, R = Me; 1.6 g.) and aqueous potassium hydroxide (10 ml. of 2*N* solution) was heated under reflux for 8 hours. The cooled and filtered solution was extracted three times with 15 ml. portions of chloroform, the aqueous solution acidified with hydrochloric acid (1:1) to *p*H 4 and the product which separated was filtered and dried *in vacuo* over potassium hydroxide. Upon crystallization from water there was obtained colourless needles, m.p. 263-264°. Mixed m.p. with the compound prepared as described under (a) was without depression and the UV and IR spectra were identical.

6-Chloro-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (V, R = C_6H_5).

Compound IV (R = C_6H_5; 1.06 g.) obtained above in the photorearrangement experiment, was heated under reflux with phosphorus oxychloride (10 ml.) and pyridine (0.4 g.) for 3 hours. Thereafter, the solvent was evaporated *in vacuo* and the residue poured onto crushed ice (20 g.). The product was purified by crystallization from ethyl acetate and was found to be identical with an authentic specimen (8) m.p. 200-201°.

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