Pyridazines XLVII. A Novel Heterocyclic System, Pyrido[2,3-*c*]pyridazine (1)

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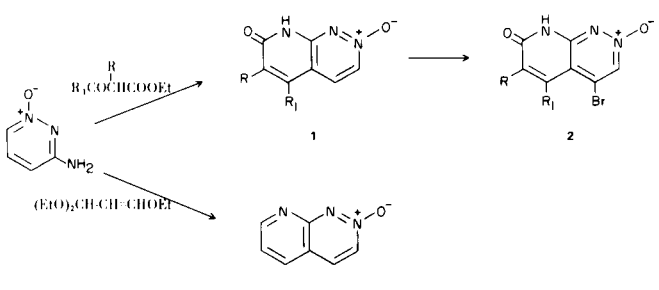
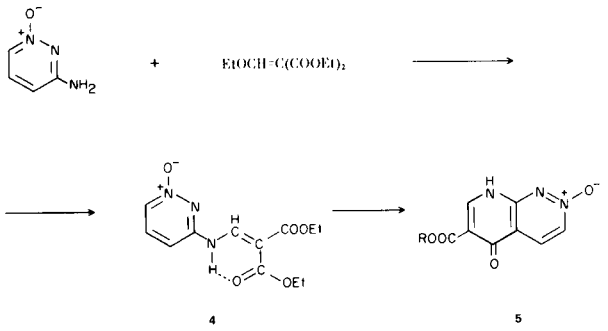
A novel class of heterocyclic compounds, pyrido[2,3-*c*]pyridazines, have been prepared from 3-aminopyridazine 1-oxide and β-keto esters or related compounds.

When aromatic or heteroaromatic amino substituted compounds are cyclized with aliphatic or alicyclic compounds having a carbonyl or ester function a C-C bond is formed in these cyclizations (Conrad-Limpach, Skraup, Döbner-Miller and related reactions). 2-Amino substituted azines follow a similar pattern of reactions, but since here the greatest electron density is located at the ring nitrogen(s), bicyclic compounds with a bridgehead nitrogen may be also formed. This applies also to pyridazines and so far all known cyclizations proceeded towards the formation of bi- and polycyclic systems having one of the pyridazine nitrogens in the bridgehead (2-4). It is further known that a *N*-oxide function can substantially change the electron density at certain carbon atoms in the azine ring and thus enhancement of reactivity for electrophilic or nucleophilic substitution is observed. This prompted us to investigate the behaviour of aminopyridazine *N*-oxides in such cyclizations.

3-Aminopyridazine 1-oxide was considered as the most simple starting compound. Since it is known that direct *N*-oxidation of 3-aminopyridazine or its acetyl derivative gives exclusively or predominantly the 2-oxide (5-7), a new procedure was developed. The known greater reactivity of the chlorine atom at position 3 of 3,6-dichloropyridazine 1-oxide for nucleophilic displacement (8) was taken into account when reacting this compound with ammonia. The 3-amino derivative, accompanied with a small amount of the isomeric *N*-oxide, was formed in reasonable yield and after catalytic dehalogenation 3-aminopyridazine 1-oxide was obtained. The same approach is useful also for the preparation of 3-hydrazinopyridazine 1-oxide.





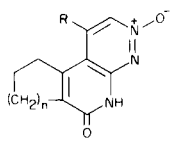
The bicyclic products were formed upon condensing 3-aminopyridazine 1-oxide with several β-dicarbonyl compounds or ethoxymethylene malonate in hot diphenyl ether or preferentially in the presence of polyphosphoric acid. Whilst with 1,3-diketones no definite products could be isolated, with acetoacetic ester a product was formed to which the structure of 5-methylpyrido[2,3-*c*]pyridazin-7(8*H*)one 2-oxide (**1**, R = H, R_1 = Me) was assigned. The reaction could be, however, envisaged as to proceed through an intermediate amide or crotonate giving thus the mentioned bicyclic product or the isomeric 5-oxo compound. The structure of the product as **1** follows from the following considerations. The possibility of the formation of the isomeric pyrimido[1,2-*b*]pyridazines (attack at the ring nitrogen) is excluded on the basis of nmr spectra, ir spectra (absorption due to a -NHCO- group) and stability towards hot 10% sodium hydroxide. The isomeric 5-oxo compound is excluded on hand of nmr spectra which revealed a small coupling constant between

the 5-methyl or methylene group and the hydrogen or methyl group at position 6. Furthermore, if for the synthesis of the bicyclic system diethyl ethoxymethylenemalonate was used, an intermediate (**4**) could be isolated, which on hand of its structure could be transformed only into the corresponding 5-oxo compound (**5**). Moreover, compound **4** could exhibit an enamine-imine tautomerism. The imine structure is excluded on hand of its nmr spectrum which shows a singlet due to a methine proton instead of anticipated two such protons if the compound would exist in the imine form. This is understandable if one considers the stabilization of the enamine by an intramolecular hydrogen bonding of the carbonyl with the amino group.

The parent compound, pyrido[2,3-*c*]pyridazine 2-oxide (**3**) could be prepared in low yield by employing 1,1,3-triethoxypropene-2. Several attempts to deoxygenate this compound or its derivatives with phosphorus trichloride, triphenylphosphine, even under severe reaction conditions, failed. Although a somewhat surprising finding, it should be mentioned that similar observations have been made in the pyrido[1,2-*a*]pyrazinium 2-oxide series (9-11) with the conclusion that large neighbouring hydrocarbon substituents facilitate deoxygenation.

Nmr spectroscopic investigation on H-D exchange revealed that in the case of the 5-methyl compound (**1**, R = H, R_1 = Me) in deuterium oxide and in the presence of sodium deuteroxide (70°, 3 hours) only protons of the methyl group were exchanged ($t_{1/2}$ = 20 minutes) and similar behaviour could be observed for the 5,6-dimethyl analog ($t_{1/2}$ = 45 minutes for the 5-Me group). In concentrated deuteriosulfuric acid a profound change in the pyridazine part of the molecule of the 5-methyl derivative could be observed at 70°. Among attempted electrophilic substitutions bromination afforded a monobromo derivative from which structure it can be concluded that the attack proceeded in the pyridazine part of the molecule at position 4 (**2**). Similarly, the tricyclic systems (**6**, R = H, n = 1,2), obtained from 3-aminopyridazine 1-oxide and ethyl cyclopentanone-2- (or cyclohexanone-2-) carboxylate, were brominated at the same position relative to the *N*-oxide group to give **6** (R = Br, n = 1,2).

On hand of the above observations, one can conclude that pyrido[2,3-*c*]pyridazine 2-oxides represent a stable heteroaromatic system, in fact being oxides of azanaphthyridine.



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EXPERIMENTAL

Melting points were determined on a Kofler melting point apparatus. Ir spectra (in potassium bromide) were recorded on a Perkin-Elmer Model 137 Spectrophotometer, nmr spectra were taken on a JEOL JNM-C-60HL spectrometer (TMS as internal standard) and mass spectra were recorded on a CEC 21-110C instrument using direct sample insertion into the ion source at 170°. Throughout this paper polyphosphoric acid Fluka, containing 83% phosphorus pentoxide was used.

3,6-Dichloropyridazine 1-Oxide.

The known procedures (*N*-oxidation with peroxyacetic, peroxybenzoic or monoperoxyphthalic acid) lead to this compound only in low yield and isolation required chromatographic separation (12-14). The following procedure with the use of peroxymaleic acid gives the desired compound in about 50% yield.

A mixture of hydrogen peroxide (25 g. of 74%) and methylene chloride (500 ml.) (or chloroform) was cooled at 0° and under stirring maleic anhydride (100 g.) was added. After stirring at 0° for 30 minutes, 3,6-dichloropyridazine (30 g.) was added and the mixture stirred for further 30 minutes and thereafter left to stand at 5° for 7 days. The separated maleic acid was filtered off and the filtrate was shaken with an aqueous solution of sodium carbonate (2 times with 200 ml. of a 10% solution) and then with water (100 ml.). The dried extract (sodium sulfate) was filtered and the solvent evaporated *in vacuo*. The crude product was recrystallized from a mixture of benzene and *n*-hexane (2:1) (for 1 g., 4.6 ml. were used). Thus, 17 g. (50%) of the oxide, m.p. 118° (lit. (13) gives m.p. 118-120°) were obtained.

3-Amino-6-chloropyridazine 1-Oxide.

A mixture of 3,6-dichloropyridazine 1-oxide (33 g.) and liquid ammonia (100 ml.) was heated in an autoclave at 80° for 6 hours. The obtained mixture of the isomeric oxides was separated by crystallization from water. In this manner, 3-amino-6-chloropyridazine 1-oxide was obtained in 70% yield (20.5 g.) and had m.p. 225-226°.

Anal. Calcd. for $C_4H_4ClN_3O$: C, 32.99; H, 2.77; N, 28.87. Found: C, 32.89; H, 2.95; N, 28.43.

3-Aminopyridazine 1-Oxide.

The above compound (5.8 g.), palladized charcoal (1.2 g. of 5%) and potassium hydroxide (2.46 g.) in methanol (100 ml.) were shaken in an atmosphere of hydrogen (1 l.) until consumption of hydrogen ceased. The filtrate was evaporated to dryness and the residue was crystallized from ethanol and ethyl acetate (1:1). The pure compound (4.2 g., 95%) had m.p. 136-138° (lit. (15) gives m.p. 139°).

3-Hydrazino-6-chloropyridazine 1-Oxide.

A solution of 3,6-dichloropyridazine 1-oxide (8.5 g.) in ethanol (50 ml.) was treated with hydrazine hydrate (6 g. of 80%) and the mixture was heated under reflux for 1 hour. The separated product was suspended in boiling methanol, water was added dropwise until a solution was obtained and after cooling the product was filtered off and was purified again in this manner (yield 4.8 g., 60%), m.p. 180-181°.

Anal. Calcd. for $C_4H_5ClN_4O$: C, 29.92; H, 3.14; N, 34.40. Found: C, 29.93; H, 3.50; N, 35.06.

3-Hydrazinopyridazine 1-Oxide.

The above hydrazino compound was dehalogenated in a similar manner as described for the amino analog. The product was

crystallized from ethanol and ethyl acetate (1.0 g. from 1.62 g. of the starting compound), m.p. 152-154° (lit. (15) gives m.p. 158-160°).

Diethyl 3-Pyridazinylaminomethylenemalonate 1-Oxide (**4**).

A mixture of 3-aminopyridazine-1-oxide (2.2 g.) and diethyl ethoxymethylenemalonate (4.75 g.) was heated at 115-120° for 3 hours. The cold mixture was then treated with diethyl ether and the residue filtered off. It was recrystallized from ethanol (1.8 g., 32%) and had m.p. 146-148°. Ir, 1698 and 1681 (CO), 1250 cm^{-1} (N-O); nmr (DMSO-d_6), τ = 2.92 (dd, H_4), 2.40 (dd, H_5), 2.13 (dd, H_6), 1.60 (s, CH), -0.2 (broad, NH), 5.80 and 5.86 (q, CH_2), 8.72 (two covered triplets, CH_3); $J_{4,5}$ = 8.0, $J_{5,6}$ = 6.2, $J_{4,6}$ = 1.5 Hz.

Anal. Calcd. for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94. Found: C, 51.43; H, 5.40; N, 14.94.

6-Carbethoxypyrido[2,3-*c*]pyridazin-5(8*H*)one 2-Oxide (**5**, R = Et).

Compound **4** (0.6 g.) was dissolved in diphenyl ether (50 ml.) and the solution was heated to 250° for 15 minutes. The cooled mixture was treated with petrol ether (200 ml.) and the separated product was filtered off. It was crystallized from water (0.35 g.), m.p. 255° dec.; ir 1706 (CO) and 1290 cm^{-1} (N-O); nmr (pentadeuteropyridine), τ = 1.65 (d, H_3), 1.90 (d, H_4), 1.30 (s, H_7), 5.75 (q, CH_2), 8.79 (t, CH_3); $J_{3,4}$ = 6.2 $J_{CH_2CH_3}$ = 7.5 Hz.

Anal. Calcd. for $C_{10}H_9N_3O_4$: C, 51.06; H, 3.82; N, 17.87. Found: C, 51.20; H, 3.87; N, 18.09.

6-Carboxypyrido[2,3-*c*]pyridazin-5(8*H*)one 2-Oxide (**5**, R = H).

The above ester (**5**, R = Et; 1.2 g.) was heated with aqueous potassium hydroxide (10 ml. of 10%) under reflux for 30 minutes, the solution was charcoaled and filtered. Upon cooling and acidification the separated acid was crystallized from water (0.7 g.), m.p. 285°.

Anal. Calcd. for $C_8H_5N_3O_4$: C, 46.37; H, 2.41; N, 20.29. Found: C, 46.27; H, 2.58; N, 20.19.

8,9-Dihydro-7*H*-cyclopenta(5,6)pyrido[2,3-*c*]pyridazin-6(5*H*)one 3-Oxide (**6**, R = H, n = 1).

A mixture of 3-aminopyridazine 1-oxide (1.1 g.), ethyl cyclopentanone-2-carboxylate (1.5 g.) and polyphosphoric acid (18 g.) was heated at 80° for 30 minutes. Upon addition of ice (40 g.) and neutralization with sodium carbonate to *p*H 5-6, the precipitate was filtered off and washed with water and ethyl acetate. The product was recrystallized from ethanol to give 0.75 g. (36%) of the compound with m.p. 252° dec.; nmr (DMSO-d_6), τ = 3.15 (d, H_1), 2.66 (d, H_2), 7.30 and 7.96 (m, $(CH_2)_3$); $J_{1,2}$ = 6.2 Hz.

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.43; N, 20.69. Found: C, 59.16; H, 4.54; N, 20.44.

7,8,9,10-Tetrahydrocyclohexa(5,6)pyrido[2,3-*c*]pyridazin-6(5*H*)-one 3-Oxide (**6**, R = H, n = 2).

It was obtained in a similar way as the above analog from ethyl cyclohexanone-2-carboxylate in 27% yield. M.p. 255-256° dec. (from acetic acid); nmr (DMSO-d_6), τ = 3.16 (d, H_1), 2.70 (d, H_2), 7.65 and 8.30 (m, $(CH_2)_4$); $J_{1,2}$ = 6.2 Hz.

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.07; N, 19.35. Found: C, 60.48; H, 4.90; N, 19.33.

5-Methylpyrido[2,3-*c*]pyridazin-7(8*H*)one 2-Oxide (**1**, R = H, R_1 = Me).

A mixture of 3-aminopyridazine 1-oxide (3.3 g.), acetoacetic ester (3.9 g.) and polyphosphoric acid (45 g.) was heated at 80° for 30 minutes. The cooled mixture was treated with ice (70 g.) and neutralized with sodium carbonate to *p*H 5. The precipitate was filtered off, washed with water and recrystallized from *N,N'*-dimethylformamide (3.4 g., 64%). The compound charred at about 265°; ir, 3247 (NH), 1681 (CO), 1285 cm^{-1} (N-O); nmr (DMSO-d_6), τ = 2.58 (d, H_3), 3.08 (d, H_4), 3.90 (q, H_6), 7.72 (d, CH_3); $J_{3,4}$ = 6.2 $J_{5\text{-Me},\ 6\text{-H}}$ = 0.9 Hz.

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 53.99; H, 3.94; N, 23.55.

5,6-Dimethylpyrido[2,3-*c*]pyridazin-7(8*H*)one 2-Oxide (**1**, R = R_1 = Me).

It was prepared in a similar way from ethyl methylacetoacetate in about 30% yield. M.p. 255° dec.; nmr (DMSO-d_6), τ = 2.63 (d, H_3), 3.10 (d, H_4), 7.70 (d, 5-CH_3), 7.96 (d, 6-CH_3); $J_{3,4}$ = 6.0; $J_{5\text{-Me},6\text{-Me}}$ = 0.9 Hz.

Anal. Calcd. for $C_9H_9N_3O_2$: C, 56.54; H, 4.71; N, 21.98. Found: C, 56.86; H, 4.90; N, 21.87.

5-Carbethoxymethylpyrido[2,3-*c*]pyridazin-7(8*H*)one 2-Oxide (**1**, R = H, R_1 = CH_2COOEt).

The compound was synthesized following the procedure for the above analogs, but employing diethyl acetonedicarboxylate. However, the product was found to be a mixture (1:1) of the expected compound and the 5-methyl analog. Nmr spectrum of the 5-carbethoxymethyl derivative had the following characteristics in DMSO-d_6; τ = 2.52 (d, H_3), 2.95 (d, H_4), 3.72 (t, H_6), 6.36 (d, CH_2COOEt), 5.92 (q, CH_2CH_3), 8.80 (t, CH_3); $J_{5\text{-Me},6\text{-H}}$ = 0.4, $J_{CH_2CH_3}$ = 7.5 Hz.

Pyrido[2,3-*c*]pyridazine 2-Oxide (**3**).

A mixture of 3-aminopyridazine 1-oxide (2.2 g.) and polyphosphoric acid (30 g.) was heated to 110° until a clear solution occurred. The cooled mixture was then treated with 1,1,3-triethoxypropene-2 (3.5 g.) and the mixture was heated and stirred at 90° for 1.5 hours. After addition of ice and neutralization with solid sodium carbonate to *p*H 5, the mixture was extracted with chloroform. The oily residue, obtained after evaporation of the solvent to dryness, was diluted with ethyl acetate (3 ml.) and the separated product was filtered off. The filtrate was evaporated to give 200 mg. of a dark oil which was purified by thin layer chromatography, using silica gel (Merck PSC-Fertigplatten Kieselgel F 254, 2 mm. thick) and a mixture of chloroform and methanol (95:5) for elution. The product with R_f value 0.7 was extracted with methanol and after evaporation the residue was purified again by thin-layer chromatography. The obtained product was then sublimed at 80-100°/0.1 mm. and the pure compound (50 mg.) had m.p. 124°. Mass spectrum: M^+ = 147; nmr (deuteriochloroform), τ = 1.68 (d, H_3), 3.13 (dd, H_4), -0.09 (dd, H_5), 2.89 (dd, H_6), 1.38 (ddd, H_7); $J_{3,4}$ = 5.1, $J_{5,6}$ = 6.9, $J_{6,7}$ = 4.2, $J_{5,7}$ = 1.8, $J_{4,5}$ = 0.75 Hz.

Anal. Calcd. for $C_7H_5N_3O$: C, 57.14; H, 3.40; N, 28.57. Found: C, 56.92; H, 3.52; N, 28.68.

4-Bromo-5-methylpyrido[2,3-*c*]pyridazine-7(8*H*)one 2-Oxide (**2**, R = H, R_1 = Me).

A solution of compound **1** (R = H, R_1 = Me; 1.0 g.) in boiling acetic acid (40 ml.) was treated with potassium acetate (0.65 g.) and bromine (0.9 g.). The separated product was washed with water and crystallized from glacial acetic acid (1 g., 70%), m.p. 245° dec.; nmr (DMSO-d_6), τ = 2.30 (s, H_3), 3.87 (q, H_6), 7.73 (d, CH_3); $J_{5\text{-Me},6\text{H}}$ = 0.9 Hz.

Anal. Calcd. for $C_8H_6BrN_3O_2$: C, 37.50; H, 2.34; N, 16.40.

Found: C, 37.62; H, 2.28; N, 16.53.

In a similar way the following bromo derivatives were synthesized:

(a) 1-Bromo-8,9-dihydro-7*H*-cyclopenta(5,6)pyrido[2,3-*c*]-pyridazin-6(5*H*)one 3-oxide (**6**, R = Br, n = 1), m.p. 260° dec (from glacial acetic acid).

Anal. Calcd. for $C_{10}H_8BrN_3O_2$: C, 42.55; H, 2.83; N, 14.89. Found: C, 42.82; H, 3.02; N, 15.04.

(b) 1-Bromo-7,8,9,10-tetrahydrocyclohexa(5,6)pyrido[2,3-*c*]-pyridazin-6(5*H*)one 3-oxide (**6**, R = Br, n = 2), m.p. 245° dec. (from glacial acetic acid); nmr (DMSO-d_6), τ = 2.25 (s, H_1), 7.35 and 8.25 (m, $(CH_2)_4$).

Anal. Calcd. for $C_{11}H_{10}BrN_3O_2$: C, 44.59; H, 3.38; N, 14.18. Found: C, 44.73; H, 3.62; N, 14.09.

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