Pyridazines. IV. The Synthesis and some Reactions of Acetylpyridazines. (1)

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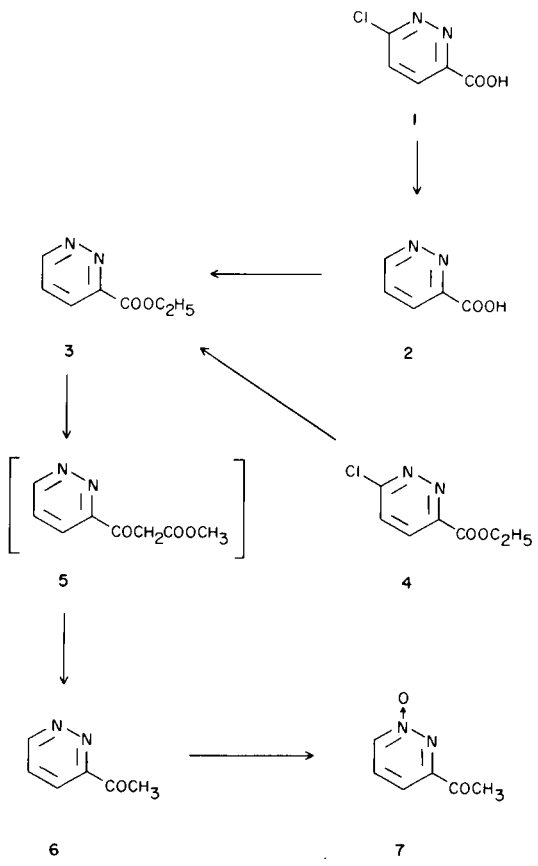
Two 3-acetylpyridazines have been prepared. *N*-Oxidation of 3-acetylpyridazine (**6**) gave only 3-acetylpyridazine 1-oxide (**7**). During the *N*-oxidation of 3-acetyl-6-methoxypyridazine (**10**), three primary products, namely, 3-acetyl-6-methoxypyridazine 1-oxide (**12**), 3-acetyl-6-methoxypyridazine 2-oxide (**13**), 3-acetylpyridazin-6-one (**14**) and an artifact, 3-methoxypyridazine 1-oxide (**15**) were obtained. Furthermore, it has been shown that 3-methoxypyridazine 1-oxide (**15**) can be obtained in quantitative yield by treatment of 3-acetyl-6-methoxypyridazine 2-oxide (**13**) with dilute sodium hydroxide solution at room temperature. This represents a novel deacylation reaction. Nitration of 3-acetylpyridazine 1-oxide, (**7**) gave 3,4-bis(3′-pyridazinoyl)furoxan 1′,1′-dioxide (**19**) rather than a simple nitration product. 3-Acetylpyridazine (**6**) and 3-acetyl-6-methoxypyridazine (**10**) also gave furoxans (**22** and **23**) upon nitration.

The purpose of this investigation was the synthesis of 3-acetylpyridazines for nitration studies. For the synthesis of 3-acetylpyridazine (**6**), 6-chloropyridazine-3-carboxylic acid (**1**) (3) served as the starting material. Compound **1** was catalytically dechlorinated with palladium-charcoal in the presence of aqueous ammonia. The product, pyridazine-3-carboxylic acid, (**2**) (4) was esterified to yield ethyl pyridazine-3-carboxylate (**3**) (4). Compound **3** was more readily prepared by the novel catalytic dechlorination of ethyl 6-chloropyridazine-3-carboxylate (**4**) (5-6) with palladium-charcoal in the presence of triethylamine. Claisen condensation of ethyl pyridazine-3-carboxylate (**3**) with methyl acetate gave the intermediate methyl 3-pyridazinoylacetate (**5**) which was not isolated but hydrolyzed and decarboxylated in acid solution into 3-acetylpyridazine (**6**) in 41% yield. This was superior to the method of Robba (7) who had prepared **6** in 27% yield by the Grignard reaction on 3-cyanopyridazine. After this work was completed Sokolov and Giller (8) published our procedure but with a yield of only 28%. The reaction of 3-acetylpyridazine (**6**) with 30% hydrogen peroxide in acetic acid solution gave 3-acetylpyridazine 1-oxide (**7**) in 77% yield. The alternate *N*-oxide was not present in the reaction mixture (tlc). These transformations are shown in Flow Sheet I.

Flow Sheet I



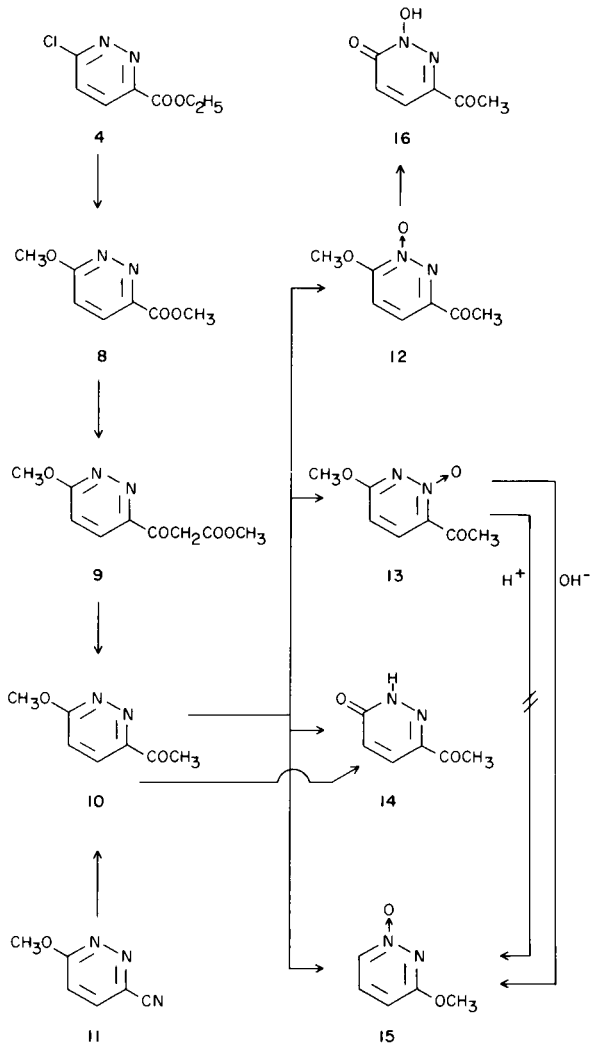
The structure assignment was based upon the NMR spectrum. 3-Acetylpyridazine showed four peaks, a singlet at 2.90 δ and three quartets at 9.39, 8.19 and 7.70 δ. They were assigned to H_6, H_4, and H_5, respectively,

considering the electron attracting effect of the acetyl group. Ring proton signals of 3-acetylpyridazine 1-oxide (**7**), on the other hand appeared at 8.35 and 7.80 δ. The 7.80 peak integrated for two protons showing peak overlapping. Kawazoe and Natsume (9) have revealed in their studies on the NMR spectra of pyridazine derivatives and their *N*-oxides that the introduction of an *N*-oxide function into a pyridazine ring causes an appreciable upfield shift for the 4- and 6-protons and a downfield shift for a proton located at the 5-position compared with those of the parent base. This fact also has been observed in extensive studies of NMR spectra of pyridazine derivatives including their *N*-oxides by Kano, *et al.*, (10). Based upon the previous work cited, the ring proton signals are best interpreted by formulating the structure of **7** as the 1-oxide. Thus, the H_6 signal at 9.39 δ of the parent base shifted upfield to 8.35 δ in the *N*-oxide. The signal at 8.19 δ corresponding to H_4 likewise was shifted upfield causing overlapping of the proton signals of H_4 and H_5 at 7.80 δ

For the synthesis of 6-methoxy-3-acetylpyridazine (**10**), ethyl 6-chloropyridazine-3-carboxylate (**4**) was the starting material. Compound **4** was converted into methyl 6-methoxypyridazine-3-carboxylate (**8**) with sodium methoxide in methanol. Compound **8** was treated with methyl acetate *via* the Claisen condensation and methyl 6-methoxy-3-pyridazinoylacetate (**9**) was isolated. Compound **9** was smoothly hydrolyzed and decarboxylated by boiling in hot water to yield 3-acetyl-6-methoxypyridazine (**10**) in 92% yield from **9**. Compound **10** was also prepared from 3-cyano-6-methoxypyridazine (**11**) (11) by the Grignard reaction using methylmagnesium iodide. A yield of 31% was obtained.

The *N*-oxidation of 3-acetyl-6-methoxypyridazine was complicated in that three products were obtained during the reaction and a fourth product arose upon treatment of the reaction mixture with dilute sodium hydroxide solution during the separation procedure. 3-Acetyl-6-methoxypyridazine (**10**) was treated with 30% hydrogen peroxide in acetic acid solution and 3-acetyl-6-methoxypyridazine 1-oxide (**12**) (20% yield), 3-acetyl-6-methoxypyridazine 2-oxide (**13**) (12% yield) and 3-acetylpyridazin-6-one (**14**) (0.6% yield) were obtained as a direct result of the oxidation procedure. During the isolation and separation of the components, 3-methoxypyridazine 1-oxide (**15**), a known compound (12-13) was obtained in a *novel alkali-catalyzed deacylation reaction.* Proof that **15** arose from 3-acetyl-6-methoxypyridazine 1-oxide (**13**) was obtained when pure **13** was treated with dilute sodium hydroxide solution at room temperature. This novel deacylation process proceeds in quantative yield at room temperature. Furthermore, treatment of **13** with dilute hydrochloric acid did not produce **15**. The novel deacylation of **13** into the known **15** proves the structure of **13**, therefore, the alternate *N*-oxide must be 3-acetyl-6-methoxypyridazine 1-oxide (**12**). Treatment of 3-acetyl-6-methoxypyridazine 1-oxide (**12**) with dilute sodium hydroxide solution at room temperature followed by acidification gave 3-acetyl-1-hydroxypyridazin-6-one (**16**). The proof of structure of **14** was accomplished by acid-catalyzed demethylation of 3-acetyl-6-methoxypyridazine. The product 3-acetylpyridazin-6-one was identical with **14** from the *N*-oxidation reaction in all respects. These reactions are shown in Flow Sheet II.

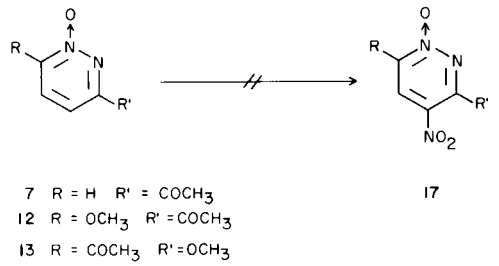
Flow Sheet II



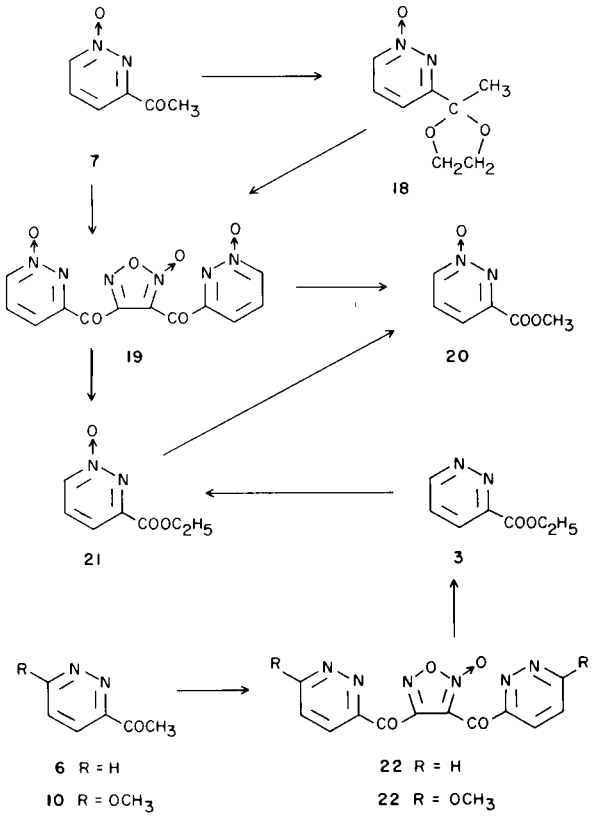
The nitration of 3-acetylpyridazine 1-oxide (**7**), 3-acetyl-6-methoxypyridazine 1-oxide (**12**) and 3-acetyl-6-methoxypyridazine 2-oxide (**13**) under a variety of nitrating conditions did not give a simple nitro compound (**17**). This failure is shown below in Flow Sheet III.

During the attempted nitration of 3-acetylpyridazine 1-oxide (**7**) with 90% nitric acid in concentrated sulfuric

Flow Sheet III



Flow Sheet IV



acid solution at 50°, 3,4-bis(3'-pyridazinoyl)furoxan 1',1'-dioxide (**19**) was obtained. The ethylene ketal (**18**) readily obtained from **7** also gave **19** upon nitration. Recrystallization of **19** from methanol gave methyl pyridazine-3-carboxylate 1-oxide (**20**) which gave a clue to the structure of **19**. Boiling **19** with ethanol without a catalyst gave ethyl pyridazine-3-carboxylate 1-oxide (**21**). Compound **21** was converted into the methyl ester (**20**) by transesterification with sodium methoxide in methanol. Furthermore, ethyl pyridazine-3-carboxylate (**3**) (4) gave **21** upon oxidation with 30% hydrogen peroxide in acetic acid solution. This constitutes a proof of structure of **21**. Other furoxans (**22** and **23**) were prepared by the nitration of 3-acetylpyridazine (**6**) and 3-acetyl-6-methoxypyridazine (**10**). Compound **22** was easily converted into the known ethyl pyridazine-3-carboxylate (**3**) (4) by refluxing in ethanol. These transformations are shown in Flow Sheet IV.

Further evidence for the structures of **19**, **22**, and **23** was obtained from the following data: (a) good elemental analyses were obtained and a molecular weight determination (osmometer) of **22** gave a value of 295 (calcd. 298); (b) the action of nitric acid or nitrogen oxides on aryl methyl ketones are known to give furoxans (14-15); (c) the high melting points and explosive properties support the furoxan structure; and (d) the infrared spectra of **19**, **22**, and **23** further support the furoxan structure.

EXPERIMENTAL (16)

Pyridazine-3-carboxylic Acid (**2**).

Catalytic dechlorination of 6-chloropyridazine-3-carboxylic acid has been described by Leanza, *et al.*, (4) who employed Raney Nickel catalyst under a pressure of 40 p.s.i.

In the following experiment, reduction was carried out with palladium on charcoal at atmospheric pressure.

A mixture containing 5 g. (0.032 mole) of 6-chloropyridazine-3-carboxylic acid, 0.5 g. of 5% palladium on charcoal, 10 ml. of 28% ammonium hydroxide and 50 ml. of water was shaken with hydrogen at atmospheric pressure. The reaction was stopped when the theoretical amount of hydrogen was absorbed. The catalyst was removed by filtration and washed with water, then the combined filtrate and washings were concentrated to a small volume. The concentrated solution was cooled and acidified with concentrated hydrochloric acid. The product was filtered and dried, yielding 3.1 g. (79%) m.p. 195° dec. (Lit. (4) 200-201°).

Ethyl Pyridazine-3-carboxylate (**3**).

A mixture containing 65 g. (0.35 mole) of ethyl 6-chloropyridazine-3-carboxylate (6), 1.5 g. of 5% palladium on charcoal, 39 g. (0.39 mole) of triethylamine and 500 ml. of ethanol was shaken with hydrogen at atmospheric pressure. The reduction stopped when one equivalent of hydrogen was absorbed. The mixture was filtered, the filtrate was evaporated under reduced pressure, water was added to the residue and the resulting solution was extracted with chloroform. Evaporation of the chloroform left colorless crystals which were recrystallized from isopropyl ether affording 42.3 g. (80%) of ethyl pyridazine-3-carboxylate as colorless rhombs, m.p. 66-67°, undepressed on admixture with the sample prepared by esterification (4) of pyridazine-3-carboxylic acid (**2**).

3-Acetylpyridazine (**6**).

To a boiled suspension containing sodium methoxide (prepared from 1.15 g. (0.05 g.-atom, 1.5 equivalents) of sodium and methanol) and 50 ml. of anhydrous benzene was added dropwise a solution containing 5 g. (0.033 mole) of ethyl pyridazine-3-carboxylate (**3**), 4.9 g. (0.066 mole) of methyl acetate and 20 ml. of anhydrous benzene. The resulting solution was refluxed for 10 hours. After cooling, the yellow solid was filtered, dried and dissolved in 100 ml. of water. The solution was acidified by the addition of 10 ml. of concentrated hydrochloric acid, boiled for 2 hours, cooled and made alkaline with sodium bicarbonate. Extraction with ether and removal of the ether by distillation gave

2.3 g. (57%) of crude 3-acetylpyridazine (**6**) which formed colorless leaflets on recrystallization from petroleum ether (b.p. 60-90°), m.p. 89-90° (Lit. (7) 87-88°), yield, 1.65 g. (41%); infrared cm^{-1}, 3080(w), 3060(w), 1700(s), 1660(w), 1570(m), 1550(w), 1440(m), 1420(m), 1380(s), 1360(s), 1297(s), 1193(m), 1149(m), 1118(m), 1078(m), 1045(w), 1000(m), 957(m), 823(s), 760(w), 752(m), 628(w), 603(s); NMR spectrum (deuteriochloroform), 9.39 δ (ring C_6-H, quartet), 8.19 δ (ring C_4-H, quartet) 7.70 δ (ring C_5-H, quartet), 2.90 δ ($COCH_3$, singlet).

Anal. Calcd. for $C_6H_6N_2O$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.43; H, 5.11; N, 23.15.

The hydrazone was prepared by refluxing the ketone with 97% hydrazine in ethanolic solution, colorless plates, m.p. 76-77.5° after recrystallization from isopropyl ether, yield 90%.

Anal. Calcd. for $C_6H_8N_4$: C, 52.93; H, 5.92; N, 41.15. Found: C, 52.83; H, 5.76; N, 41.17.

3-Acetylpyridazine 1-Oxide (**7**).

A solution containing 7.2 g. (0.059 mole) of 3-acetylpyridazine (**6**) and 16.8 g. (0.148 mole, 2.5 equivalent) of 30% hydrogen peroxide and 80 ml. of acetic acid was heated at 60° for 7 hours and concentrated to a small volume *in vacuo*. The residue was diluted with water, concentrated again *in vacuo*, cooled and made alkaline by the addition of sodium bicarbonate. Extraction with chloroform, removal of the solvent from the extract and recrystallization of the residue from benzene yielded 6.3 g. (77%) of 3-acetylpyridazine 1-oxide (**7**) as colorless scales, m.p. 138-139°. The second recrystallization raised the m.p. to 139-140°; U. V. λ max (95% ethanol), 271 (ε, 10,400), 278 (ε, 9,750), 337 mμ (ε, 1,800); infrared cm^{-1}, 3100(m), 2900(w), 1705(s), 1580(m), 1525(w), 1420(s), 1410(s), 1365(m), 1335(s), 1273(s), 1162(m), 1116(m), 1070(w), 1000(m), 964(m), 928(w), 913(w), 813(m), 715(m), 618(m), 572(m), 540(w), 513(w), 418(w); NMR spectrum (deuteriochloroform), 8.35 δ (ring C_6-H, quartet), 7.80 δ (ring C_4-H, quartet), 2.68 δ ($COCH_3$, singlet).

Anal. Calcd. for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.29. Found: C, 52.25; H, 4.50; N, 20.20.

Methyl 6-Methoxypyridazine-3-carboxylate (**8**).

To a stirred mixture containing 70 g. (0.375 mole) of ethyl 6-chloropyridazine-3-carboxylate (**4**) (6) and 100 ml. of methanol was added a sodium methoxide solution prepared by dissolving 10.2 g. (0.444 g. -atom, 1.15 equivalents) of sodium in 200 ml. of methanol at a rate to maintain gentle refluxing. After the addition was completed, the mixture was refluxed for one hour. The reaction mixture was concentrated and the residue was poured onto ice-cold aqueous ammonium chloride solution. The crystalline solid which separated was filtered, washed and dried, yield, 45.5 g. (73%), m.p. 126-128°. Recrystallization from isopropyl ether formed colorless scales, m.p. 127-127.5°; infrared cm^{-1}, 3155(w), 3075(m), 3070(m), 3015(w), 2990(w), 2955(m), 1725(s), 1680(w), 1595(s), 1475(s), 1445(s), 1420(s), 1375(s), 1350(w), 1295(s), 1203(m), 1190(w), 1178(w), 1147(s), 1092(w), 1012(s), 961(m), 873(m), 843(m), 798(m), 728(m), 664(m), 625(m), 550(w), 510(w).

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.74; H, 4.72; N, 16.46.

Methyl 6-Methoxy-3-pyridazinoylacetate (**9**).

To a stirred suspension containing 2.7 g. (0.05 mole, 1.5 equivalents) of sodium methoxide and 50 ml. of anhydrous benzene were added 5.5 g. (0.033 mole) of methyl 6-methoxypyridazine-3-carboxylate (**8**) and then a solution of 4.9 g. (0.066 mole, 2 equivalents) of methyl acetate in 20 ml. of anhydrous benzene. The resulting mixture was stirred under reflux for 12 hours. After cooling, a yellow precipitate was filtered, suspended in ice water and the mixture was acidified with acetic acid. The insoluble material was filtered and was washed with aqueous sodium bicarbonate solution. After drying, the product weighed 4 g. (58%) and melted at 82-84°. This can be used for the next step without further purification. Colorless scales were formed, m.p. 90.5-91.5°; U. V. λ max (95% ethanol), 210 (ε, 13,700), 253 mμ (ε, 10,700); infrared cm^{-1}, 2995(w), 2955(w), 1745(s), 1700(s), 1625(w), 1590(s), 1470(s), 1435(m), 1410(m), 1385(m), 1365(s), 1325(m), 1305(s), 1220(m), 1209(m), 1141(w), 1102(m), 1046(w), 1005(m), 938(w), 853(m), 652(w), 622(w), 596(w), 530(w), 494(w), 465(w).

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.80; N, 13.33. Found: C, 51.50; H, 4.78; N, 13.32.

3-Acetyl-6-methoxypyridazine (**10**).

Method A.

A mixture containing 3.3 g. (0.0157 mole) of methyl 6-methoxy-3-pyridazinoylacetate (**9**) and 120 ml. of water was refluxed for 24 hours. The reaction mixture was cooled, made alkaline by the addition of dilute aqueous sodium hydroxide solution and extracted with ether. Evaporation of the ether and recrystallization of the residue from petroleum ether (b.p. 60-90°) gave 2.2 g. (92%) of pale yellow leaflets, m.p. 97-98°, undepressed on admixture with a sample of methyl 3-acetyl-6-methoxypyridazine (**10**) prepared from 6-methoxy-3-cyanopyridazine (**11**).

Method B.

To a stirred ethereal solution containing methylmagnesium iodide (prepared from 8.84 g. (0.364 g. -atom) of magnesium, 23.3 ml. (0.374 mole) of methyl iodide and 180 ml. of anhydrous ether) was added dropwise a solution containing 17 g. (0.125 mole) of 6-methoxy-3-cyanopyridazine (**11**), 340 ml. of anhydrous ether and 100 ml. of anhydrous benzene at a rate to maintain gentle refluxing. After the addition was completed, the mixture was refluxed for an additional 30 minutes. The reaction mixture was cooled and poured on a mixture of 250 ml. of ice water and 41 g. of ammonium chloride. The aqueous layer was separated, acidified with concentrated hydrochloric acid below 5°, stirred for 2 hours with external ice cooling, made alkaline with dilute aqueous sodium hydroxide solution and extracted with ether. The combined organic layer was dried over sodium sulfate and evaporated. The residue was dissolved in hot petroleum ether (b.p. 60-90°). The solution was treated with silica gel for decolorization, filtered and the filtrate was concentrated. A crystalline solid which separated upon cooling was filtered, yielding 6 g. (31%), m.p. 96-97°. An analytical sample was prepared by recrystallization from petroleum ether (b.p. 60-90°) as pale yellow leaflets, m.p. 96.5-97.5°; infrared cm^{-1}, 3070(w), 3000(w), 2955(w), 1700(s), 1590(s), 1475(s), 1415(m), 1375(s), 1350(m), 1315(s), 1279(s), 1190(w), 1171(w), 1122(s), 1072(w), 1029(w), 1005(s), 958(w), 853(m), 827(w), 597(m), 532(w), 496(w), 474(w); NMR spectrum (deuteriochloroform), 8.04 δ (ring C_4-H, doublet), 7.06 δ (ring C_5-H, doublet), 4.24 δ (OCH_3, singlet), 2.82 δ ($COCH_3$, singlet).

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.12; H, 5.51; N, 18.44.

Oxidation of 3-Acetyl-6-methoxypyridazine (**10**) with Hydrogen Peroxide.

3-Acetyl-6-methoxypyridazine 1-Oxide (**12**).

A solution containing 0.066 mole of 3-acetyl-6-methoxy-

pyridazine (**10**), 165 ml. of acetic acid and 18.5 g. (0.18 mole) of 30% hydrogen peroxide was heated at 60-65° for 3 hours. An additional 18.5 g. (0.18 mole) of 30% hydrogen peroxide was added and again heated at the same temperature for 24 hours. The mixture was concentrated to one-third volume under reduced pressure, the concentrated solution was diluted with water and again was concentrated. The residue was made alkaline by the addition of aqueous sodium bicarbonate solution and the resulting solution was extracted with chloroform. The chloroform solution was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was washed with ether and filtered. The insoluble material, weighing 2.2 g. (20%), m.p. 191-193°, dec., was recrystallized from ethyl acetate, giving 3-acetyl-6-methoxypyridazine 1-oxide (**12**) as colorless scales, m.p. 195-196°; U. V. λ max (95% ethanol), 228 (ε, 18,800), 290 (ε, 7,000), 345 mμ (ε, 5,600); infrared cm^{-1}, 3120(w), 3090(w), 3075(w), 3010(w), 2990(w), 2945(w), 1695(s), 1630(w), 1595(s), 1560(s), 1473(m), 1420(m), 1375(s), 1350(s), 1330(s), 1290(s), 1240(s), 1218(w), 1195(w), 1143(s), 1129(s), 1122(m), 1105(w), 1098(s), 1014(w), 994(m), 948(m), 840(m), 784(m), 680(w), 655(w), 638(w), 598(m), 540(w), 524(w), 480(w), 435(w); NMR spectrum (deuterium oxide), 8.00 δ (ring C_5-H, doublet), 7.73 δ (ring C_4-H, doublet), 4.20 δ (OCH_3, singlet), 2.64 δ ($COCH_3$, singlet).

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.78; H, 4.84; N, 16.40.

3-Acetyl-6-methoxypyridazine 2-Oxide (**13**).

The ethereal filtrate (from above) was washed with water and the aqueous layer was washed with benzene. The ether and benzene solution was combined and, after drying over anhydrous sodium sulfate, the solvent was removed by evaporation. Recrystallization from isopropyl ether afforded colorless leaflets of 3-acetyl-6-methoxypyridazine-2-oxide (**13**), m.p. 123-124°, yield, 1.25 g.; U. V. λ max (95% ethanol), 234 (ε, 13,300), 302 mμ (ε, 8,900); infrared cm^{-1}, 3150(w), 3090(w), 3075(w), 3025(w), 3000(w), 2970(w), 2927(w), 1675(s), 1580(s), 1560(s), 1515(w), 1475(m), 1450(w), 1415(s), 1385(s), 1380(w), 1370(s), 1335(s), 1285(w), 1260(s), 1255(s), 1192(w), 1155(w), 1122(m), 1050(m), 1023(w), 1000(w), 990(w), 982(m), 964(m), 832(m), 746(m), 740(w), 682(w), 589(w), 545(w), 450(w); NMR spectrum (deuteriochloroform), 8.01 δ (ring 5-H, doublet), 6.64 δ (ring C_4-H, doublet), 4.03 δ (OCH_3, singlet).

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.10; H, 4.86; N, 16.42.

The mother liquor of the 2-xoide was evaporated to dryness, and the residue was dissolved in dilute aqueous sodium hydroxide solution. Extraction with ether, removal of the ether and recrystallization of the residue from isopropyl ether gave a further crop of the 2-oxide, weighing 0.05 g., m.p. 120-122°; total yield 12%.

3-Acetylpyridazin-6-one (**14**).

The aqueous layer was saturated with ammonium chloride, and extracted with chloroform. After the evaporation of the chloroform the residue was dissolved in benzene and the benzene solution was poured on a silica gel column which was eluted with benzene-ethyl acetate mixture (1:1) and ethyl acetate. The initial fraction gave 0.05 g. (0.6%) of colorless needles, m.p. 172-174°, after recrystallization from isopropyl ether. No depression of the melting point was observed when mixed with an authentic sample of 3-acetylpyridazin-6-one prepared by hydrolysis of 3-acetyl-6-methoxypyridazine. The following fraction, after recrystallization from ether-isopropyl ether, gave 0.2 g. (2%) of colorless prisms, m.p. 78-80°, undepressed when mixed with an authentic sample of 3-methoxypyridazine 1-oxide (**15**) (12-13).

3-Acetylpyridazin-6-one (**14**) from 3-Acetyl-6-methoxypyridazine (**10**).

A mixture containing 0.3 g. (0.002 mole) of 3-acetyl-6-methoxypyridazine (**10**) and 6 ml. of 1 *N* hydrochloric acid was refluxed for one hour and cooled, whereupon 3-acetylpyridazin-6-one (**14**) separated out as colorless needles, m.p. 173-174°, yield quantitative. Recrystallization from isopropyl ether formed colorless needles, m.p. 173-174°; U. V. λ max (95% ethanol), 212 (ε, 16,900), 261 (ε, 9,900), shoulder 287 mμ (ε, 3,400); infrared cm^{-1}, 3230(w), 3160(m), 3070(m), 3020(m), 2965(m), 2865(m), 1835(w), 1700(s), 1680(s), 1615(s), 1595(s), 1560(w), 1475(w), 1400(s), 1375(s), 1320(w), 1278(s), 1219(s), 1139(w), 1115(s), 1016(w), 1003(m), 955(m), 919(m), 851(s), 829(m), 756(w), 705(w), 626(w), 602(w), 582(s), 513(m), 453(m).

Anal. Calcd. for $C_6H_6N_2O_2$: C, 52.18; H, 4.38; N, 20.28. Found: C, 52.21; H, 4.51; N, 20.10.

Hydrolytic Cleavage of 3-Acetyl-6-methoxypyridazine 2-Oxide (**13**).

A. Sodium Hydroxide Solution.

To 5 ml. of 1 *N* sodium hydroxide solution was added 0.2 g. (0.0012 mole) of 3-acetyl-6-methoxypyridazine 2-oxide at room temperature and the solution was allowed to stand for one hour. Extraction with chloroform, drying the extract over anhydrous sodium sulfate and evaporation of the chloroform gave 0.15 g. (quantitative yield) of 3-methoxypyridazine 1-oxide (**15**), m.p. and mixed m.p., 77-78°. The infrared spectrum of this compound was identical with that of an authentic sample of 3-methoxypyridazine 1-oxide (12-13).

B. Hydrochloric Acid Solution.

A mixture containing 0.1 g. (0.6 mmole) of 3-acetyl-6-methoxypyridazine 2-oxide (**13**) and 5 ml. of 1 *N* hydrochloric acid was allowed to stand at room temperature for 24 hours. Neutralization of the mixture with sodium bicarbonate, extraction with chloroform, and distillation of the solvent afforded almost a quantitative yield of the starting material (0.09 g., m.p. 123-124°).

3-Acetyl-1-hydroxypyridazin-6-one (**16**).

A solution containing 0.3 g. (0.0018 mole) of 3-acetyl-6-methoxypyridazine 1-oxide in 7.5 ml. of aqueous 1 *N* sodium hydroxide solution was allowed to stand at room temperature for a half-hour. The solution was acidified with aqueous hydrochloric acid solution, saturated with sodium chloride and extracted with chloroform. Removal of the chloroform by distillation left 0.3 g. of 3-acetyl-1-hydroxypyridazin-6-one (**16**), m.p. 191-192° dec. The product gave a dark red color when treated with aqueous ferric chloride solution. This was crystallized from benzene to colorless scales, m.p. 191-192°, dec, yield, 0.23 g. (84%); U. V. λ max (95% ethanol), 224 (ε, 11,300), 275 (ε, 6,200), 318 mμ (ε, 5,100); infrared cm^{-1}, 3095(m), 3020 broad(m), 2300 broad, 1680(s), 1555(w), 1500(s), 1455(m), 1425(m), 1385(s), 1360(m), 1300(s), 1284(s), 1201(m), 1185(m), 1170(w), 1120(s), 1087(w), 1017(w), 993(w), 958(m), 926(w), 848(s), 812(w), 800(w), 734(w), 702(w), 618(m), 595(m), 530(m), 438(w).

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.75; H, 3.93; N, 18.18. Found: C, 47.18; H, 3.96; N, 18.16.

3-(α-Ethylenedioxyethyl)pyridazine 1-Oxide (**18**).

A mixture containing 8.5 g. (0.0615 mole) of 3-acetylpyridazine 1-oxide (**7**), 5.7 g. (0.092 mole) of ethyleneglycol, 15 g. (0.079 mole) of *p*-toluenesulfonic acid monohydrate and 200 ml. of benzene was heated under reflux for 8 hours. The mixture was poured into water containing enough sodium bicarbonate to neutralize the acid, stirred and the benzene layer was separated.

The aqueous layer was extracted further with chloroform, the chloroform extract was combined with the benzene solution described above and dried over sodium sulfate. Removal of the solvent left an oily residue which solidified on standing. The crystalline mass was digested with ether and filtered to yield 8.2 g. (73%) of the ketal, m.p. 105-106°. Recrystallization from isopropyl ether formed colorless needles, m.p. 104.5-105.5°.

Anal. Calcd. for $C_8H_{10}N_3O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.92; H, 5.67; N, 15.31.

3,4-Bis(3′-pyridazinoyl)furoxan 1′,1′-Dioxide (**19**).

(A) From 3-(α-Ethylenedioxyethyl)pyridazine 1-Oxide (**18**).

To a solution containing 0.9 g. (0.005 mole) of the ketal and 9 ml. of concentrated sulfuric acid was added 1.0 ml. of 90% nitric acid with initial cooling. The resulting mixture was heated at 50° for 6 hours, cooled and poured into ice water (100-150 ml.). The solution was adjusted to *p*H 1.5-2.0 by the addition of sodium bicarbonate and set aside overnight. The yellow crystalline solid was filtered, washed with water and dried in air to give 0.47 g. (44%) of the product, m.p. 210° (violently decomposed). The product was dissolved in boiling acetone, the solution was filtered and the filtrate was concentrated. The yellow prisms which separated were collected by filtration, m.p. 219° dec; infrared cm^{-1}, 3120(m), 3085(m), 1710(s), 1600(s), 1580(s), 1480(m), 1450(m), 1430(s), 1360(s), 1330(m), 1265(m), 1160(s), 1115(w), 1070(w), 1013(m), 963(s), 892(m), 824(m), 808(w), 783(w), 765(m), 700(w), 693(m), 675(w), 615(w), 593(w), 585(w), 571(m), 557(w), 510(w), 468(w), 450(w), 425(w).

Anal. Calcd. for $C_{12}H_6N_6O_3$: C, 43.65; H, 1.83; N, 25.45. Found: C, 43.60; H, 1.78; N, 25.17.

B. From 3-Acetylpyridazine 1-Oxide (**7**).

A mixture containing 0.7 g. (0.0051 mole) of 3-acetylpyridazine 1-oxide (**7**), 9 ml. of concentrated sulfuric acid and 1.9 ml. of 90% nitric acid was heated at 50° for 5 hours, and worked up as described in (A) above to give 0.58 g. (70%) of 3,4-bis(3′-pyridazinoyl)furoxan 1′,1′-dioxide (**19**), m.p. 219° dec.

Reaction of 3,4-Bis(3′-pyridazinoyl)furoxan 1′,1′-Dioxide (**19**) with Alcohols.

A. Methyl Pyridazine-3-carboxylate 1-Oxide (**20**).

A mixture containing 0.7 g. (0.0021 mole) of 3,4-bis(3′-pyridazinoyl)-furoxan 1′,1′-dioxide (**19**) and 30 ml. of methanol was refluxed for one hour. The methanol was removed by distillation and the residue was purified by passing through a silica gel column using chloroform-methanol mixture (10:1) as the eluent. The product was recrystallized from acetone to give 0.36 g. (55%) of colorless scales, m.p. 195-196°; U. V. λ max (95% ethanol), 211 (ε, 14,250), 273 (ε, 10,800), 334 mμ (ε, 2,300); infrared cm^{-1}, 3095(m), 3045(m), 1725(s), 1680(w), 1590(s), 1545(w), 1460(m), 1440(s), 1420(s), 1350(s), 1300(s), 1198(m), 1191(m), 1172(m), 1153(s), 1068(w), 1003(s), 967(w), 930(m), 837(m), 808(s), 772(s), 690(s), 595(m), 576(w), 540(w), 437(m).

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.52; H, 3.85; N, 18.39.

B. Ethyl Pyridazine-3-carboxylate 1-Oxide (**21**).

A mixture containing 0.5 g. (0.0015 mole) of 3,4-bis(3′-pyridazinoyl)furoxan 1′,1′-dioxide (**19**) and 30 ml. of ethanol was refluxed for 6 hours. After the ethanol was removed under reduced pressure, the residue was dissolved in chloroform-ethanol mixture (10:1) and passed through a silica gel column, which was eluted with the same solvent mixture. Removal of the solvent from the eluates and recrystallization of the residue from isopropyl ether gave 0.15 g. (30%) of colorless needles, m.p. 120°; U. V. λ max (95% ethanol), 212 (ε, 11,900), 273 (ε, 10,200), 335 mμ (ε, 2,200); infrared cm^{-1}, 3120(w), 3095(m), 3065(m), 2980(w), 1740(s), 1580(s), 1550(m), 1475(w), 1430(s), 1375(s), 1330(s), 1282(s), 1190(s), 1170(m), 1120(w), 1077(w), 1040(m), 995(m), 960(w), 870(w), 845(m), 823(w), 775(m), 694(m), 600(w), 573(w), 538(w), 457(w), 428(w).

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.30; H, 4.80; N, 16.70.

Ethyl Pyridazine-3-carboxylate 1-Oxide (**21**) from Ethyl Pyridazine-3-carboxylate (**3**).

A mixture containing 3.6 g. (0.0236 mole) of ethyl pyridazine-3-carboxylate, 8.4 g. (0.742 mole) of 30% hydrogen peroxide and 40 ml. of acetic acid was heated at 65-70° for 6 hours. The reaction mixture was treated with palladium on charcoal to decompose the excess hydrogen peroxide and kept overnight. After removal of the palladium on charcoal by filtration, the filtrate was concentrated under reduced pressure to a small volume. The residual liquid was poured in a cooled aqueous sodium bicarbonate solution. The resultant solution was extracted with chloroform, the extracts were dried over anhydrous sodium sulfate and concentrated to dryness. The residue was digested with ether, filtered and washed with ether to give 3.3 g. (83%) of colorless scales, m.p. 119-120°. This was recrystallized from isopropyl ether to form colorless needles, m.p. 120-120.5°, undepressed on admixture with a sample of ethyl 3-pyridazinecarboxylate 1-oxide (**21**) prepared from 3,4-bis-[3′-pyridazinoyl)furoxan 1′,1′-dioxide (**19**). The infrared spectra of the two samples were identical.

Methyl Pyridazine-3-carboxylate 1-Oxide (**20**).

A mixture containing 0.6 g. (0.0036 mole) of ethyl pyridazine-3-carboxylate 1-oxide (**21**), 0.2 g. (0.0037 mole) of sodium methoxide and 30 ml. of methanol was refluxed for 15 minutes. The methanol was removed by distillation, the residue was dissolved in water and the aqueous solution was extracted with chloroform. After being dried over anhydrous sodium sulfate, the chloroform extract was evaporated to dryness. Recrystallization of the residue from acetone yielded 0.25 g. (45% of colorless scales, m.p. 195-196°, undepressed when mixed with a sample of methyl pyridazine-3-carboxylate 1-oxide (**20**) prepared from 3,4-bis(3′-pyridazinoyl)-furoxan 1′,1′-dioxide (**19**). The infrared spectra of the two samples were identical.

3,4-Bis(3′-pyridazinoyl)furoxan (**22**).

To a solution containing 1.85 g. (0.015 mole) of 3-acetylpyridazine (**6**) and 27 ml. of concentrated sulfuric acid was added 5.7 ml. of 90% nitric acid with stirring and cooling. The mixture was kept at room temperature for 45 minutes, then heated at 50° for 5 hours, and poured into ice water. Sodium bicarbonate was added to the resulting solution to *p*H 1.5-2.0. The crystalline precipitate was collected by filtration, washed with water and dried, yielding 1.35 g. (60%) of 3,4-bis(3′-pyridazinoyl)furoxan, m.p. 201° dec.

The analytical sample was prepared by dissolving it in boiling acetone followed by concentrating the solution, yellow prisms, m.p. 204° (decomposed violently); infrared cm^{-1}, 3055(w), 1705(s), 1595(s), 1575(m), 1535(w), 1480(m), 1450(m), 1430(w), 1390(m), 1335(m), 1280(m), 1247(w), 1190(w), 1150(w), 1083(w), 1054(w), 1044(w), 1016(m), 932(s), 897(w), 835(w), 812(w), 762(m), 725(w), 705(m), 675(w), 630(w).

Anal. Calcd. for $C_6H_3N_3O_2$: C, 48.33; N, 28.19. Found: C, 48.48; H, 1.93; N, 28.47.

Molecular weight (osmometer) 295, (Calcd. 298).

3,4-Bis(6′-methoxy-3′-pyridazinoyl)furoxan (**23**).

To a solution containing 1.0 g. (0.0066 mole) of 3-acetyl-6-methoxypyridazine (**10**) and 14 ml. of concentrated sulfuric acid was added 2.7 ml. (8 equivalents) of 90% nitric acid with ice cooling. The resulting solution was heated at 50° for 5 hours, cooled and poured into ice water (300 ml.). Sodium bicarbonate was added to adjust *p*H of the solution to 1.5-2.0. The precipitate was filtered, washed with water, dried in air and recrystallized from acetone-isopropyl ether yielding 0.7 g. of pale yellow needles, m.p. 181° dec. The filtrate was further concentrated and 0.15 g. of the second crop, m.p. 181° dec., was obtained. Total yield, 0.85 g. (72%); infrared cm^{-1}, 3075(m), 3000(w), 2955(w), 1695(s), 1605(s) (shoulder), 1590(s), 1485(m) (shoulder), 1470(s), 1440(m), 1415(s), 1370(s), 1365(s), 1310(s), 1266(s), 1233(m), 1190(w), 1118(m), 1089(m), 1029(m), 1006(s), 932(s), 855(m), 823(w), 790(m), 728(m), 686(w), 675(m), 625(m), 547(w), 515(w), 496(w), 488(w), 448(w).

Anal. Calcd. for $C_{14}H_{10}N_6O_6$: C, 46.94; H, 2.81; N, 23.46. Found: C, 47.05; H, 2.82; N, 23.74.

Reaction of 3,4-Bis(3′-pyridazinoyl)furoxan (**22**) with Ethanol.

A slurry containing 0.2 g. (0.672 mmole) of 3,4-bis(3′-pyridazinoyl)furoxan (**22**) and 20 ml. of ethanol was refluxed for 4 hours. The ethanol was distilled *in vacuo*, the residue was dissolved in chloroform, and the solution was passed through a silica gel column to decolorize it. The chloroform was removed by distillation from the eluate and the residue was recrystallized from petroleum ether (b.p. 60-90°) to give 0.08 g. (39%) of colorless rhombs, m.p. 67-68°, undepressed when mixed with an authentic sample of ethyl pyridazine-3-carboxylate (**3**). The infrared spectra of the two samples were identical.

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