Synthesis and Photochemical Reactivity of 3-Methylisoxazolo[4,5-*d*]pyridazines [1]

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A synthetic pathway to 3-methylisoxazolo[4,5-*d*]pyridazine and some of its derivatives is described. Uv irradiation of 4,7-dimethoxy (XVII) and 7-chloro-4-hydrazino-3-methylisoxazolo[4,5-*d*]pyridazine (IX) shows that both intramolecular rearrangements and solvent involving reactions can occur.

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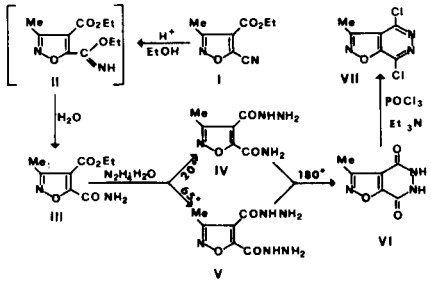
In the course of our previous studies on the aromatic azabenzoxazoles we have ascertained that, as a consequence of ring fusion, some interesting chemical [2], photochemical [3] and spectroscopic [4] properties can be observed.

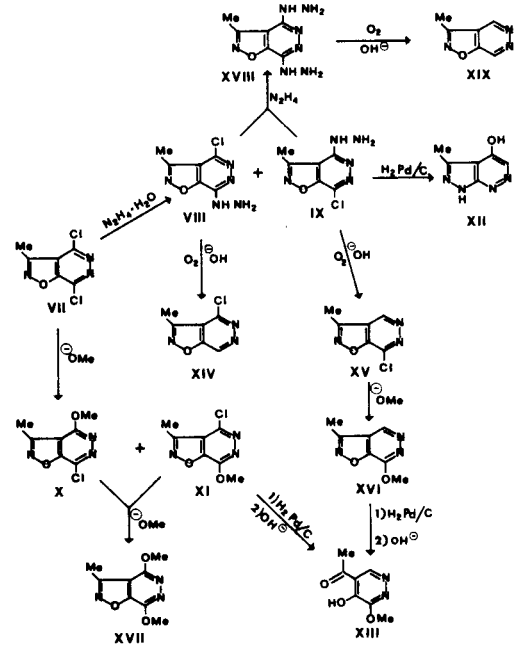
In order to obtain further insight into this field, we have prepared a series of 3-methylisoxazolo[4,5-*d*]pyridazines for comparative purposes. Only a few 3-phenyl derivatives of this system are known [5].

3-Methylisoxazolo[4,5-*d*]pyridazinedione VI was prepared from 5-cyanoisoxazole I, which gave the amide III through the iminoether II by reaction with ethanolic hydrochloric acid followed by treatment with water. With hydrazine at different temperatures the amide III was converted into the mono IV and the dihydrazide V. On heating, both compounds IV and V gave the dione VI. The high melting point and the ir spectrum with bands attributable to NH_2^+, C=O and C-O$^-$ suggest that VI exists in a dipolar form in the solid state [6]. Compound VI reacted with phosphorus oxychloride/triethylamine to give 4,7-dichloroisoxazolo[4,5-*d*]pyridazine (VII).



Scheme 1

A comparative study on the reactivity of the dichloro derivative VII and the corresponding dichloroisoxazolo-[4,5-*b*] and [4,5-*c*]pyridines with nucleophiles has been undertaken, showing that fusion of an isoxazole nucleus on a pyridazine ring is not sufficient to differentiate the reactivity of the two chlorine atoms. In fact, compound VII with a stoichiometric amount of hydrazine hydrate or sodium methoxide gave a mixture of 4- and 7-substituted isomers (VIII and IX or X and XI, respectively), whereas in the case of isoxazolopyridines only one substitution isomer was obtained [2a,c,d].

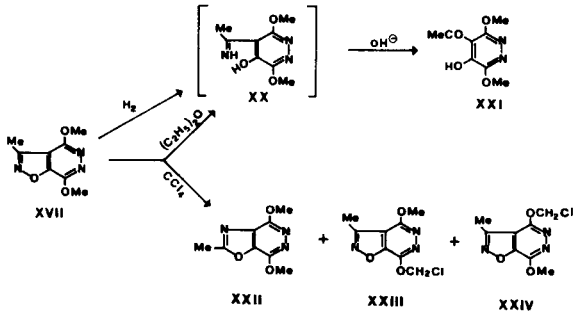


Scheme 2

The structures of the chlorohydrazino derivatives VIII and IX were assigned on the basis of their catalytic hydrogenation: only the isomer IX led to 4-hydroxy-3-methylpyrazolo[3,4-*c*]pyridazine (XII). This immediately permits unambiguous assignment of the structures X and XI to the respective chloromethoxy derivatives. In fact catalytic hydrogenation of the isomer XI gave 5-acetyl-4-hydroxy-3-

methylpyridazine (XIII), which could be unambiguously prepared from compound IX by oxidative removal of the hydrazino group to give 7-chloroisoxazolopyridazine XV, methoxydechlorination to the ether XVI followed by catalytic hydrogenolysis of the isoxazole moiety. Disubstituted compounds XVII and XVIII were obtained by treatment of the corresponding mixtures of monosubstituted isomers X, XI and VIII, IX with an excess of sodium methoxide or anhydrous hydrazine, respectively. 3-Methylisoxazolo-[4,5-*d*]pyridazine XIX was prepared from the dihydrazino derivative XVIII by alkaline oxidative degradation.

Photoreactivity of the isoxazolo[4,5-*d*]pyridazine system was also investigated. The dimethoxy derivative XVII showed solvent dependent photochemistry: uv irradiation in ether followed by alkaline hydrolysis gave compound XXI, whereas in carbon tetrachloride compounds XXII, XXIII and XXIV were obtained as the main products. The acetylpyridazine XXI was also unambiguously prepared by catalytic hydrogenation of the dimethoxy derivative XVII followed by alkaline hydrolysis.



Scheme 3

A comparison of ^{13}C nmr spectra of the starting material XVII, with those of compounds XXII, XXIII and XXIV allowed the attribution of oxazolo[4,5-*d*]pyridazine structure to XXII and isoxazolo[4,5-*d*]pyridazine structure to XXIII and XXIV. In fact, as previously reported for a series of 2-methyloxazolo and 3-methylisoxazolopyridines [4b], the signal attributable to the methyl group was more shielded (about 3 ppm) in the isoxazolo than in the oxazolo condensed system.

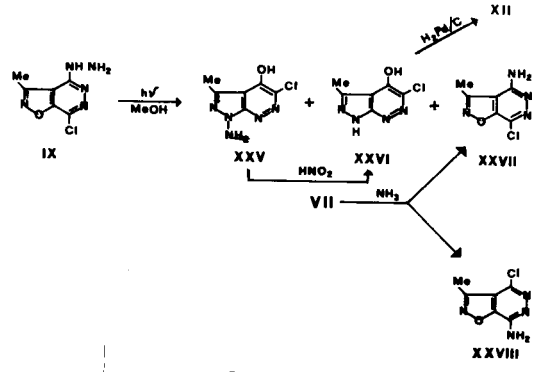
Table I

Some ^{13}C-NMR Data of Isoxazoles XVII, XXIII, XXIV and Oxazole XXII, Chemical Shift (δ) in Deuteriochloroform

	CH_3	4- and/or 7-OCH_3	OCH_2
XVII	10.86	54.91	—
XXIII or XXIV mp 95-97°	10.93	55.32	72.08
XXIV or XXIII mp 106-108°	10.86	55.32	72.02
XXII	14.39	54.92	—

Attempts to differentiate structures XXIII and XXIV by chemical and spectroscopic methods were inconclusive.

The uv irradiation of compound IX in methanol afforded 1-amino-5-chloro-4-hydroxy-3-methylpyrazolo[3,4-*c*]pyridazine (XXV) together with corresponding deaminated product XXVI.



Scheme 4

The assignment of their structures was supported by conversion of XXV to XXVI with nitrous acid followed by reductive dechlorination to give the 4-hydroxy-3-methylpyrazolo[3,4-*c*]pyridazine (XII). A third product was isolated from the reaction mixture and was identified as 4-amino-7-chloroisoxazolo[4,5-*d*]pyridazine (XXVII) on the basis of its synthesis from the dichloro derivative VII and ammonia.

Formation of the oxazolo[4,5-*d*]pyridazine XXII and 1-aminopyrazolo[3,4-*c*]pyridazine XXV can be rationalized through a rearrangement pathway analogous to that previously observed for the isoxazolo[4,5-*c*]pyridines [3]. But, whereas only intramolecular photorearrangements could be observed in the case of isoxazolopyridines, solvent involving reactions enter into competition with intramolecular processes for isoxazolo[4,5-*d*]pyridazines.

EXPERIMENTAL

Melting points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer 782 spectrophotometer for potassium bromide disks. The pmr and ^{13}C-nmr spectra were recorded on a Hitachi-Perkin Elmer R 600 and a Varian XL-200 instruments, respectively; chemical shifts (J in Hz) are reported in ppm downfield from internal tetramethylsilane. Column chromatography was carried out on Lobar Si 60 (40-63 μm) (Merck). The hplc analyses were performed on a Waters instrument equipped with a column "Li-chrosorb RP-8 (10 μm)" (Merck) eluted with methanol/water 1:1 (uv detector 290 nm). Photochemical reactions were carried out with a medium pressure mercury immersion lamp (125 Watt) filtered and cooled with copper(II) sulfate solution (cut off, ~300 nm); nitrogen was constantly bubbled through the solution during the photolysis.

Ethyl 5-Carbamoyl-3-methylisoxazole-4-carboxylate (III).

Gaseous hydrogen chloride was added, with stirring, to a cooled solution of ethyl 5-cyano-3-methylisoxazole-4-carboxylate (I) (5.0 g, 27.8 mmoles) in absolute ethanol until the solution was saturated. The solvent was then rotary evaporated at 20-30° and the residue was washed with aqueous sodium hydrogen carbonate to afford compound III (5.0 g, 91%) mp 137-139° (from water); ir: 3260, 3130 (NH_2), 1720 (COOEt), 1690

($CONH_2$) cm^{-1}; pmr (deuteriochloroform): δ 1.41 (t, J = 7.0, CH_2-CH_3), 2.48 (s, CH_3), 4.42 (q, J = 7.0, CH_2-CH_3), 7.03 and 9.32 (brs, NH_2).

Anal. Calcd. for $C_6H_{10}N_2O_4$: C, 48.48; H, 5.05; N, 14.14. Found: C, 48.18; H, 5.18; N, 13.80.

5-Carbamoyl-3-methylisoxazole-4-carbohydrazide (IV).

Hydrazine hydrate (1.8 ml, 37.4 mmoles) was added with stirring to a solution of compound III (3.55 g, 17.9 mmoles) in methanol (40 ml). The resultant mixture was kept at room temperature for 24 hours. the precipitate was filtered off to give compound IV (2.4 g, 73%), mp 184-186° (from ethanol); ir: 3400-2700 (br, NH_2 and $NHNH_2$), 1700 ($CONHNH_2$), 1640 ($CONH_2$) cm^{-1}; pmr (DMSO-d_6): δ 2.46 (s, CH_3), 4.61 (s, NHNH_2), 8.48, 8.76 (s, CONH_2), 10.59 (s, NHNH_2).

Anal. Calcd. for $C_6H_8N_4O_3$: C, 39.13; H, 4.38; N, 30.42. Found: C, 39.09; H, 4.29; N, 30.52.

3-Methylisoxazolo-4,5-dicarbohydrazide (V).

Hydrazine hydrate (1.0 ml, 20.8 mmoles) was added to a solution of compound III (1.0 g, 5.05 mmoles) in methanol (20 ml). The resultant mixture was refluxed for 2 hours. After cooling the precipitate was filtered off to give compound V (0.57 g, 57%), mp 185-188°; ir: 3400-2200 ($NHNH_2$), 1670, 1640 (CO) cm^{-1}; pmr (DMSO-d_6): δ 2.35 (s, CH_3), 5.0 brs, (2, $NHNH_2$).

Anal. Calcd. for $C_6H_9N_5O_3$: C, 36.18; H, 4.55; N, 35.16. Found: C, 36.40; H, 4.59; N, 35.12.

3-Methylisoxazolo[4,5-*d*]pyridazine-4,7(5*H*,6*H*)-dione (VI).

The compound IV (2.37 g, 12.9 mmoles) was heated at 180-190° for 3 hours to give compound VI as a yellow solid (2.13 g, 99%), mp 293-295° (from water); ir: 3200, 3150-2200 (br, NH_2^+), 1670 (CO), 1560 (C-O^-) cm^{-1}; pmr (DMSO-d_6): δ 2.57 (s, CH_3), 10.55 (brs, 2NH or OH).

Anal. Calcd. for $C_6H_5N_3O_3$: C, 43.12; H, 3.02; N, 25.14. Found: C, 42.96; H, 3.01; N, 25.22.

Compound VI was also obtained by heating the dihydrazide V under the same conditions.

4,7-Dichloro-3-methylisoxazolo[4,5-*d*]pyridazine (VII).

A mixture of compound VI (1.0 g, 6.0 mmoles), phosphorus oxychloride (10.0 ml) and triethylamine (1.2 ml) was heated at 100° for 3 hours. After vacuum concentration the residue was poured on ice, the solid was filtered off and was washed with aqueous sodium hydrogen carbonate and then with water. The crude product was sublimed at 50°, 0.02 mm Hg to give VII as a white solid (0.7 g, 57%), mp 95°; pmr (deuteriochloroform): δ 2.83 (s, CH_3).

Anal. Calcd. for $C_6H_3Cl_2N_3O$: C, 35.31; H, 1.47; N, 20.59. Found: C, 35.00; H, 1.61; N, 20.42.

4-Chloro-7-hydrazino-3-methylisoxazolo[4,5-*d*]pyridazine (VIII) and 7-Chloro-4-hydrazino-3-methylisoxazolo[4,5-*d*]pyridazine (IX).

Hydrazine hydrate (1.2 ml, 25 mmoles) was slowly added, with stirring, to a solution of the dichloro derivative VII (2.0 g, 9.8 mmoles) in dioxane (20 ml). The resultant mixture was stirred at room temperature for 24 hours. The solid was filtered off and was washed with water to give a crude product (1.6 g, 82%) containing the two isomers VIII and IX in a ratio 2:1 (pmr spectrum). This mixture was resolved by column chromatography (chloroform/methanol 95/5 as eluent) to give (in order of mobility):

a) Compound VIII had mp 155-156° (from chloroform); ir: 3310-2600 (NH, NH_2) cm^{-1}; pmr (pyridine-d_5): δ 2.55 (s, CH_3), 5.78 (brs, NH_2, NH).

Anal. Calcd. for $C_6H_6ClN_5O$: C, 36.10; H, 3.03; N, 35.08. Found: C, 36.34; H, 3.14; N, 35.18.

b) Compound IX had mp 171-172° (from chloroform); ir: 3290, 3270-3200 (NH, NH_2) cm^{-1}; pmr (pyridine-d_5): δ 2.76 (s, CH_3), 5.16 (brs, NH_2, NH).

Anal. Calcd. for $C_6H_6ClN_5O$: C, 36.10; H, 3.03; N, 35.08. Found: C, 36.20; H, 3.05; N, 35.10.

7-Chloro-4-methoxy-3-methylisoxazolo[4,5-*d*]pyridazine (X) and 4-Chloro-7-methoxy-3-methylisoxazolo[4,5-*d*]pyridazine (XI).

The dichloro derivative VII (0.5 g, 2.45 mmoles) was added to a solution of sodium (0.056 g, 0.0024 g-atom) in dry methanol (10 ml). The reaction mixture was kept at room temperature for 1 hour, then was rotary evaporated. The solid residue, treated with water, collected by filtration and dried, yielded a mixture (0.42 g, 86%) of the two isomers X and XI in a ratio 1:0.9 (pmr spectrum) which was resolved by column chromatography (chloroform as eluent) to give (in order of mobility):

a) Compound X had mp 99-100°; pmr (deuteriochloroform): δ 2.70 (s, CH_3), 4.30 (s, OCH_3).

Anal. Calcd. for $C_7H_6ClN_3O$: C, 42.10; H, 3.03; N, 21.06. Found: C, 42.17; H, 3.09; N, 21.13.

b) Compound XI had mp 121-123°; pmr (deuteriochloroform): 2.77 (s, CH_3), 4.32 (s, OCH_3).

Anal. Calcd. for $C_7H_6ClN_3O$: C, 42.10; H, 3.03; N, 21.06. Found: C, 41.85; H, 3.07; N, 21.32.

4-Hydroxy-3-methylpyrazolo[3,4-*c*]pyridazine (XII).

A mixture of compound IX (0.5 g, 2.5 mmoles), palladium on charcoal 10% (0.1 g) and ethanol (50 ml) was shaken under hydrogen at room temperature and 30 psi for 4 hours. The catalyst was then filtered off and the solvent was evaporated *in vacuo*. The white residue was dissolved in 1*N* sodium hydroxide (10 ml). Neutralization of the alkaline solution afforded compound XII (0.24 g, 64%), mp 332-334°; ir: 3250-2700 (br, NH, OH) cm^{-1}; pmr (DMSO-d_6): δ 2.56 (s, CH_3), 6.84 (brs, OH, NH), 7.42 (s, CH).

Anal. Calcd. for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.76; H, 3.97; N, 37.20.

,4-Chloro-3-methylisoxazolo[4,5-*d*]pyridazine (XIV) and 7-Chloro-3-methylisoxazolo[4,5-*d*]pyridazine (XV).

Benzene (165 ml) and 1*N* sodium hydroxide (22 ml) were added to a mixture of isomers VIII and IX (1.1 g, 5.5 mmoles). Air was bubbled into the reaction mixture while being vigorously stirred for about 3 hours. Evaporation of the organic layer afforded a mixture (0.47 g, 50% after sublimation) of the two isomers XIV and XV in a ratio 0.9:1 (pmr spectrum) which was resolved by column chromatography (chloroform as eluent) to give (in order of mobility):

a) Compound XIV had mp 79-81°; pmr (deuteriochloroform): δ 2.82 (s, CH_3), 9.60 (s, CH).

Anal. Calcd. for $C_6H_4ClN_3O$: C, 42.50; H, 2.38; N, 24.78. Found: C, 42.63; H, 2.27; N, 24.76.

b) Compound XV had mp 110-111°; pmr (deuteriochloroform): δ 2.75 (s, CH_3), 9.49 (s, CH).

Anal. Calcd. for $C_6H_4ClN_3O$: C, 42.50; H, 2.38; N, 24.78. Found: C, 42.61; H, 2.23; N, 24.75.

7-Methoxy-3-methylisoxazolo[4,5-*d*]pyridazine (XVI).

Compound XV (0.22 g, 1.3 mmoles) was added to a solution of sodium (0.033 g, 0.0014 g-atom) in dry methanol (5 ml). The reaction mixture was kept at room temperature for 15 minutes, then it was rotary evaporated. The solid residue, treated with water, collected by filtration and dried, yielded compound XVI (0.175 g, 82%) mp 128-129° (after sublimation); pmr (deuteriochloroform): δ 2.68 (s, CH_3), 4.35 (s, OCH_3), 9.17 (s, CH).

Anal. Calcd. for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44. Found: C, 51.03; H, 4.37; N, 25.20.

5-Acetyl-4-hydroxy-3-methoxypyridazine (XIII).

A mixture of compound XVI (0.1 g, 0.6 mmole), palladium on charcoal 5% (0.025 g) and ethanol (50 ml) was shaken under hydrogen at room temperature and 30 psi until the starting material disappeared. Then the catalyst was filtered off and the solvent was evaporated *in vacuo*. The residue was dissolved in 1*N* sodium hydroxide. Neutralization of the alkaline solution afforded compound XIII (0.030 g, 30%) mp 271-274° (from methanol); ir: 3130-2400 (OH), 1673 (CO) cm^{-1}; pmr (methanol-d_4): δ 2.63 (s, CH_3), 3.96 (s, OCH_3), 8.54 (s, CH).

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.79; N, 16.66. Found: C, 49.73; H, 4.79; N, 16.50.

This compound was also prepared from 4-chloro-7-methoxy derivative XI in an analogous way.

4,7-Dimethyloxy-3-methylisoxazolo[4,5-*d*]pyridazine (XVII).

A mixture of the chloromethoxy derivatives X and XI (1.0 g, 5.0 mmoles) was added to a solution of sodium (0.5 g, 0.022 g-atom) in dry methanol (50 ml). The reaction mixture was kept at room temperature for 24 hours, then it was rotary evaporated. The solid residue, treated with water, collected by filtration and dried, yielded compound XVII (0.85 g, 87%), mp 119-121° (from ethanol/water); pmr (deuteriochloroform): δ 2.65 (s, CH_3), 4.21, 4.23 (s, 2 OCH_3).

Anal. Calcd. for $C_8H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.25; H, 4.72; N, 21.77.

4,7-Dihydrazino-3-methylisoxazolo[4,5-*d*]pyridazine (XVIII).

Anhydrous hydrazine (2.0 ml) was added dropwise with cooling (ice-water bath) to a stirred mixture of the chlorohydrazino derivatives VIII and IX (1.0 g, 5.0 mmoles). The mixture was then heated at 100° for 30 minutes. The precipitate was filtered and was washed with cold ethanol to give compound XVIII (0.5 g, 51%) mp 284-286° dec; ir: 3315, 3265, 3150-2300 (2 $NHNH_2$) cm^{-1}; pmr (deuteriotrifluoroacetic acid): δ 2.89 (s, CH_3). An analytical sample of this compound (as the dihydrochloride) had mp 240-242° (from ethanol/water).

Anal. Calcd. for $C_6H_{11}Cl_2N_7O$: C, 26.88; H, 4.14; N, 36.57. Found: C, 26.75; H, 4.10; N, 36.70.

3-Methylisoxazolo[4,5-*d*]pyridazine (XIX).

Benzene (10 ml) and 2*N* sodium hydroxide (8 ml) were added to the dihydrazino-derivative XVIII (0.195 g, 1.0 mmoles). Air was bubbled into the reaction mixture, vigorously stirred, for 7 hours. Evaporation of the organic layer afforded compound XIX (0.078 g, 58% after sublimation) mp 143-144°; pmr (deuteriochloroform): δ 2.74 (s, CH_3), 9.59, 9.71 (s, 2 CH).

Anal. Calcd. for $C_6H_5N_3O$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.33; H, 3.72; N, 30.89.

Irradiation of 4,7-Dimethoxy-3-methylisoxazolo[4,5-*d*]pyridazine (XVII).

A) In Ether.

A solution of the dimethoxy derivative XVII (0.50 g, 2.56 mmoles) in anhydrous ether (100 ml) was irradiated for 60 hours, then was rotary evaporated. The residue (0.45 g) was treated with 1*N* sodium hydroxide and the insoluble starting material (0.25 g) was recovered by filtration. Neutralization of the alkaline solution with concentrated hydrochloric acid followed by extraction with chloroform gave a mixture (0.16 g) of the starting material and of compound XXI (yield 43% [7] based on the unrecovered starting material). The mixture, washed with ether, gave 5-acetyl-4-hydroxy-3,6-dimethoxypyridazine (XXI), mp 280° dec (from ethanol); ir: 1655 (CO) cm^{-1}; pmr (deuteriochloroform): δ 2.74 (s, CH_3), 4.13, 4.15 (s, 2 OCH_3), 13.98 (brs, OH).

Anal. Calcd. for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.08; N, 14.13. Found: C, 48.42; H, 5.04; N, 13.83.

The same product XXI was also obtained by catalytic hydrogenation of the dimethoxy derivative XVII, following the procedure reported above for compound XIII, yield 94%.

B) In Carbon Tetrachloride.

A solution of the dimethoxy derivative XVII (0.80 g, 4.1 mmoles) in anhydrous carbon tetrachloride (100 ml) was irradiated for 56 hours. The solution was rotary evaporated and the residue was chromatographed on column with ether/petroleum ether 1/3 as eluent to give the following compounds (in order of mobility):

a) Chlorinated isoxazolopyridazine XXIII or XXIV was obtained (14% [8]), mp 95-97° (after sublimation); pmr (deuteriochloroform): δ 2.63 (s, CH_3), 4.29 (s, OCH_3), 6.34 (s, OCH_2).

Anal. Calcd. for $C_8H_8ClN_3O_3$: C, 41.85; H, 3.51; N, 18.30. Found: C, 41.53; H, 3.28; N, 18.42.

b) Chlorinated isoxazolopyridazine XXIV or XXIII was obtained (10% [8]), mp 106-108° (after sublimation); pmr (deuteriochloroform): δ 2.68 (s, CH_3), 4.25 (s, OCH_3), 6.35 (s, OCH_2).

Anal. Calcd. for $C_8H_8ClN_3O_3$: C, 41.85; H, 3.51; N, 18.30. Found: C, 41.60; H, 3.30; N, 18.50.

c) Starting material XVII (61% [8]).

d) 4,7-Dimethoxy-2-methyloxazolo[4,5-*d*]pyridazine (XXII) was obtained (15% [8]), mp 197-200° (after sublimation); pmr (deuteriochloroform): δ 2.74 (s, CH_3), 4.23 (s, 2 OCH_3).

Anal. Calcd. for $C_8H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.08; H, 4.57; N, 21.25.

Irradiation of 7-Chloro-4-hydrazino-3-methylisoxazolo[4,5-*d*]pyridazine (IX).

A solution of the chlorohydrazino derivative IX (0.43 g, 2.15 mmoles) in anhydrous methanol (100 ml) was irradiated for 15 hours. The solution was rotary evaporated and the residue was chromatographed on column with chloroform/methanol 95/5 as eluent to give the following compounds (in order of mobility):

a) 5-Chloro-4-hydroxy-3-methylpyrazolo[3,4-*c*]pyridazine (XXVI) was obtained (15% [7]), mp 304-307°; ir: 3250-2200 (NH, OH); cm^{-1}; pmr (methanol-d_4): δ 2.66 (s, CH_3).

Anal. Calcd. for $C_6H_5ClN_4O$: C, 39.04; H, 2.73; N, 30.35. Found: C, 38.82; H, 2.85; N, 30.55.

b) 1-Amino-5-chloro-4-hydroxy-3-methylpyrazolo[3,4-*c*]pyridazine (XXV) (19% [7]); ir: 3330,3280-2100 (NH_2 and OH) cm^{-1}; pmr (DMSO-d_6): δ 2.42 (s, CH_3), 5.60 (brs, NH_2 and OH). This product was characterized as the corresponding benzal derivative, mp 315-317°.

Anal. Calcd. for $C_{13}H_{10}ClN_5O$: C, 54.26; H, 3.48; N, 24.34. Found: C, 54.36; H, 3.69; N, 24.62.

Treatment of the 1-amino derivative XXV with nitrous acid afforded compound XXVI.

c) 4-Amino-7-chloro-3-methylisoxazolo[4,5-*d*]pyridazine (XXVII) (7% [7]), mp 213-215°; ir: 3420, 3320, 3120 (NH_2) cm^{-1}; pmr (deuteriochloroform): δ 2.72 (s, CH_3), 5.65 (brs, NH_2).

Anal. Calcd. for $C_6H_5ClN_4O$: C, 39.04; H, 2.73; N, 30.35. Found: C, 38.82; H, 2.79; N, 30.12.

This compound was also prepared in the following manner.

Ammonia solution 33% (0.35 ml) was added with stirring to the dichloro derivative VII (0.5 g, 2.45 mmoles) in dioxan (1 ml) and the resultant mixture was kept at 50° for 4 hours. the precipitate was filtered and was washed with dioxan to give compound XXVII (0.30 g). The solution was rotary evaporated and the residue was chromatographed on column with chloroform/methanol 90/10 as eluent to give (in order of mobility):

a) Starting material VII (0.050 g) was obtained.

b) 7-Amino-4-chloro-3-methylisoxazolo[4,5-*d*]pyridazine (XXVIII) (0.035 g, 8.6% on the unrecovered starting material), mp 233-235° dec (from methanol/water); ir: 3380, 3320, 3130 (NH_2) cm^{-1}; pmr (deuteriochloroform): δ 2.75 (s, CH_3), 5.45 (brs, NH_2).

Anal. Calcd. for $C_6H_5ClN_4O$: C, 39.04; H, 2.73; N, 30.35. Found: C, 38.88; H, 2.50; N, 30.40.

c) Compound XXVII (0.045 g) (total yield 85%) was obtained.

Catalytic Hydrogenation of 5-Chloro-4-hydroxy-3-methylpyrazolo[3,4-*c*]-pyridazine (XXVI).

This reaction was carried out following the procedure reported above for compound IX, yielding 4-hydroxy-3-methylpyrazolo[3,4-*c*]pyridazine (XII), 0.020 g, 83%.

REFERENCES AND NOTES

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[7] Yield based on pmr analysis.

[8] Yield based on hplc analysis.