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POLYNUCLEAR ISOXAZOLE TYPES—II

ISOXAZOLO[4,5-d]PYRIDAZINES[1]

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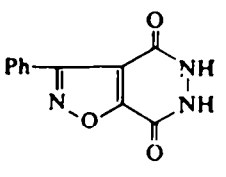
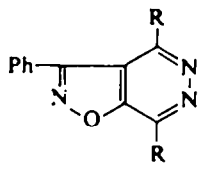
Abstract—A number of isoxazolo[4,5-d]pyridazine derivatives have been prepared. Condensation of diethyl 3-phenylisoxazole-4,5-dicarboxylate with hydrazine hydrate gave 3-phenylisoxazolo[4,5-d]-pyridazin-4,7(5H,6H)-dione; from the latter several 4,7-disubstituted derivatives have been obtained through the dichloro compound. In addition several methylation products (mono- and di-, N- and O-methyl derivatives) have been described and their structures investigated.

ALTHOUGH pyrazolo[3,4-d]pyridazine derivatives have been prepared, the related isoxazolopyridazines, apart from some isoxazolo[3,4-d]pyridazine derivatives[2-4] have not been studied.

The most convenient intermediate for the synthesis of the isoxazolo[4,5-d]-pyridazine ring diethyl is 3-phenylisoxazole-4,-5-dicarboxylate.[5] The reaction with hydrazine hydrate led to a high-melting product, readily soluble in weak bases but not in acids. The structure, 3-phenylisoxazolo[4,5-d]pyridazin-4,7(5H,6H)-dione (I), was assigned on the basis of the IR spectrum, 1670 (CO) and chemical evidence. Treatment of I with $POCl_3$ gave a good yield of the dichloro compound IIa, which upon treatment with $POBr_3$ yielded the dibromo derivative IIb. The two halogen atoms in positions 4 and 7 showed a different reactivity toward acidic hydrolysis: heating



I



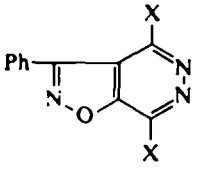
IIa: R = Cl
b: R = Br
c: R = OMe

II d: R = OPh
e: R = $S(CH_2)_6Me$
f: R = SPh

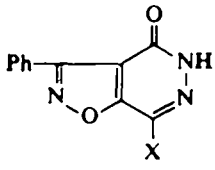
with acetic acid yielded halogen-containing products, whose IR spectrum still showed the carbonyl amide band at 1670. Selective hydrolysis of dihalogeno derivatives is well-known in phthalazine chemistry. The easier hydrolysis of the halogen atom in 4 position was expected because of the lower interaction of the isoxazole oxygen atom toward the *meta* as compared with the *ortho* position.

[1] Part I; *Tetrahedron* **23**, 675 (1967).
[2] C. Musante, *Gazz. Chim. Ital.* **69**, 523 (1939)
[3] V. Sprio and J. Fabra, *Gazz. Chim. Ital.* **86**, 1059 (1956).
[4] V. Sprio and E. Ajello, *Ric. Sci.* **35**, Rend. A, **8**, 676 (1965).
[5] A. Quilico and R. Fusco, *Gazz Chim. Ital.* **67**, 589 (1937).

Structure IIIb for the hydrolysis products of the dibromo derivative was confirmed by X-ray analysis.[6]

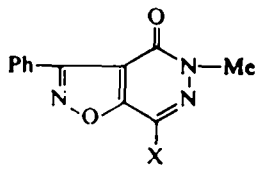


II



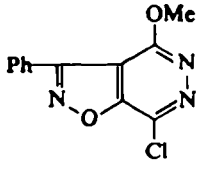
III

(a: X = Cl; b: X = Br)

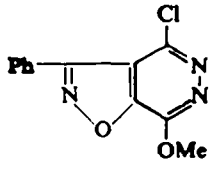


IV

A selective reactivity of the two chlorine atoms towards nucleophilic reagents could not be detected: reactions with sodium methoxide, phenoxide, thiobutoxide and thiophenoxide led to the expected 4,7-di-substituted derivatives (II c–f). When IIa was treated with only one mole of sodium methoxide, two isomers were isolated, both of which still contained chlorine and gave the dimethoxy derivative IIc with excess of sodium methoxide. The structure V was assigned to one isomer because of easy hydrolysis to IIIa. The second isomer was therefore identified as VI. This structural assignment was confirmed by the following two-step synthesis from the dimethoxy



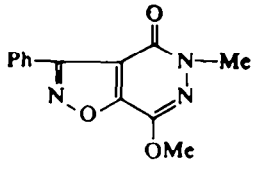
V



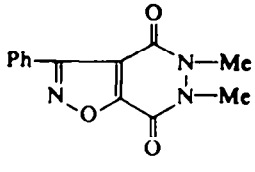
VI

derivative IIc: hydrolysis of the methoxy group in position 4 led to 3-phenyl-7-methoxyisoxazolo[4,5-d]pyridazin-4(5H)-one (IX) and subsequent treatment of the latter with $POCl_3$ yielded a product identical with the second isomer.

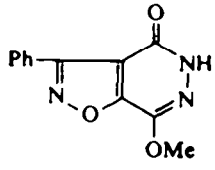
Methylation of I yielded three dimethyl-derivatives out of the four theoretically possible. Dimethyl sulfate reacted with II to yield two isomeric dimethyl compounds, both different from IIc. One isomer was identified as VII, having been synthesized by an independent route: methylation of IIIa or IIIb with diazomethane gave the N-methyl derivatives (IVa or IVb) which on nucleophilic substitution with sodium methoxide led to the same product obtained by methylation of I. The second isomer was therefore assigned structure VIII, since it did not hydrolyse easily (absence of methoxy group in position 4).



VII



VIII



IX

[6] B. Bovio, S. Locchi and V. Riganti: in press.

Methylation of I with diazomethane yielded besides a very low yield of the dimethyl derivative VII, a 47% yield of the O-monomethyl derivative IX. Its structure was ascertained by its identity with the product obtained by partial hydrolysis of the dimethoxy compound IIc.

EXPERIMENTAL

All m.ps are uncorrected. UV spectra: 95% EtOH, Perkin–Elmer Model 137 UV spectrophotometer; IR spectra: nujol mulls, Perkin–Elmer Model Infracord spectrophotometer. Microanalyses: by Dr. Lucia Maggi Dacrema.

3-Phenylisoxazolo[4,5-d]*pyridazin*-4,7(5H,6H)-*dione* (I)

A soln of crude diethyl 3-phenylisoxazole-4,5-dicarboxylate (37 g), prepared from benzohydroxamyl chloride and sodium diethyl oxalacetate,[8] and 100% hydrazine hydrate (30 ml) in MeOH (80 ml) was refluxed for 8 hr, then left at room temp overnight. The crude brown crystalline product (24 g), upon treatment with sat. $NaHCO_3$aq (100 ml) left undissolved a small amount (1·5 g) of diphenylfuroxan as impurity. Acidification of the filtrate yielded 18 g (61%) of a white crystalline product, which upon recrystallization from AcOH melted at 315° dec. (Found: C, 57·62; H, 3·58; N, 18·47. Calc. for $C_{11}H_7N_3O_3$: C, 57·64; H, 3·08; N, 18·34%.) IR: 1670 (CO.)

3-Phenyl-4,7-dichloroisoxazolo[4,5-d]*pyridazine* (IIa).

A mixture of I (0·7 g), $POCl_3$ (7 ml) and N,N-diethylaniline (0·7 ml) was refluxed at 130° for 7 hr. After vacuum concentration the residue was poured on ice; the separated oil soon solidified and was washed with $NaHCO_3$aq and water, the solid was recrystallized from MeOH, yielding a product (0·6 g), m.p. 159–160°. (Found: C, 49·91; H, 1·83; N, 15·87; Cl, 26·47; Calc. for $C_{11}H_5Cl_2N_3O$: C, 49·65; H, 1·89; N, 15·81; Cl, 26·63%.) UV spectrum: 276 mμ (log ε 3·74).

3-Phenyl-4,7-dibromoisoxazolo[4,5-d]*pyridazine* (IIb)

A soln of IIa (3·5 g), $POBr_3$ (10·0 g) and N,N-diethylaniline (7 ml) in benzene (100 ml) was heated under reflux at 130° for 5 hr. The reaction mixture was then poured onto ice and extracted with ether. After washing with $NaHCO_3$aq and drying, the solvent was evaporated and the residue boiled with MeOH (50 ml). On cooling to room temp, a yellow solid separated. Filtration and concentration of the filtrate gave 4·0 g (85% yield) of a product, which upon crystallization from MeOH yielded light yellow needles, m.p. 189·5–191·5°. (Found: C, 37·33; H, 1·45; N, 11·90; Br, 44·65. Calc. for $C_{11}H_5Br_2N_3O$: C, 37·21; H, 1·42; N, 11·84; Br, 45·02%.) UV spectrum: 219, 283 mμ (log ε 4·35, 3·76).

3-Phenyl-4,7-dimethoxyisoxazolo[4,5-d]*pyridazine* (IIc)

(a) A soln of IIa (1·0 g) in MeOH (40 ml) was heated under reflux for 7 hr with a methanolic soln of MeONa (from 0·5 g Na). The resulting milky suspension was concentrated to dryness *in vacuo*, and the residue suspended in water and filtered off. Recrystallization of the crude product (0·9 g), m.p. 114–116°, from MeOH gave white crystals. m.p. 116–117°. (Found: C, 61·16; H, 4·32; N, 16·31. Calc. for $C_{13}H_{11}N_3O_3$: C, 60·69; H, 4·31; N, 16·34%.) UV spectrum: 223, 247 mμ (log ε 4·25, 4·07).

(b) Analogous treatment of IIb with MeONa gave the same product and this was also obtained on treatment of both isomers V and VI (see below) with MeONa.

3-Phenyl-4,7-diphenoxyisoxazolo[4,5-d]*pyridazine* (IId).

Finely triturated IIa (1·0 g) was added to a soln of PhONa (prepared from 0·3 g of Na and 15 ml of phenol) and the mixture was heated at 40–50° for 8 hr and poured into water (200 ml). The mixture was made alkaline (NaOH) and stirred for 1 hr. The white precipitate was washed with water and crystallized from AcOEt yielded 0·8 g (57%) m.p. 183–184°. (Found: C, 72·09; H, 4·19; N, 11·01, Calc. for $C_{23}H_{15}N_3O_3$: C, 72·43; N, 3·96; N, 11·02%.)

3-Phenyl-4,7-di-n-butylisoxazolo[4,5-d]*pyridazine* (IIe)

A mixture of IIa (1·0 g) and sodium n-butylmercaptide (prepared from 0·3 g Na in 15 ml n-butylmercaptan) was heated at 60° for 4 hr. After evaporation to dryness *in vacuo*, the residue was triturated with dil. MeOH and filtered off. Crystallization from MeOH gave 0·8 g (57%) m.p. 50°, which recrystallized as soft needles, m.p. 59–60°. (Found: C, 60·94; H, 6·29; N, 11·52; S, 16·95. Calc. for $C_{19}H_{23}N_3OS_2$: C, 61·09; H, 6·21; N, 11·25; S, 17·17%.) UV spectrum: 279, 343 mμ (log ε 4·15, 3·86).

3-Phenyl-4,7-diphenylthioisoxazolo[4,5-d]*pyridazine* (IIf)

A mixture of Na thiophenoxide (from 0·3 g Na and 20 ml thiophenol) and IIa (1·0 g) was heated at 60° for 4 hr, then poured with stirring into 10% NaOHaq (100 ml). The product (0·5 g; 32%) was recrystallized from MeOH as white soft needles, m.p. 168°. (Found: C, 66·69; H, 3·82; N, 10·31; S, 15·61. Calc. for $C_{23}H_{15}N_3OS_2$: C, 66·80; H, 3·83; N, 10·17; S, 15·51%.) UV spectrum: 290 mμ (log ε 3·92).

3-Phenyl-7-chloroisoxazolo[4,5-d]*pyridazin-4(5H)-one* (IIIa)

A soln of IIa (1·0 g) in AcOH (10 ml) was refluxed for 1 hr (evolution of HCl). Concentration to a small volume and refrigeration gave a practically pure product (0·8 g; 86%), m.p. 244–245°. (Found: C, 53·51; H, 2·53; N, 17·05; Cl, 14·15. Calc. for $C_{11}H_6ClN_3O_2$: C, 53·35; H, 2·44; N, 16·97; Cl, 14·32%.) IR spectrum: 3200 NH; 1670 (CO). UV spectrum: 238, 294 mμ (log ε 4·21, 3·66).

3-Phenyl-7-bromoisoxazolo[4,5-d]*pyridazin-4(5H)-one* (IIIb)

Analogous heating of IIb with AcOH gave a 89% of colourless prisms, m.p. 236°. (Found: C, 45·19; H, 2·38; N, 14·35; Br. 27·40. Calc. for $C_{11}H_6BrN_3O_2$: C, 45·23; H, 2·07; N, 14·39; Br, 27·36%.) IR spectrum 3200 (NH); 1670 (CO). UV spectrum: 238, 296 mμ (log ε 4·24. 3·75).

3-Phenyl-5-methyl-7-chloroisoxazolo[4,5-d]*pyridazin-4(5H)-one* (IVa)

This was obtained in 95% yield from IIIa and a slight excess of diazomethane in ethereal soln. Recrystallization from MeOH gave white crystals m.p. 138·5°. (Found: C, 54·83; H, 3·00; N, 16·06; Cl, 13·56. Calc. for $C_{12}H_8ClN_3O_2$: C, 55·08; H, 3·08; N, 16·06; Cl, 13·55%.) IR spectrum: 1670 (CO). UV spectrum: 239, 307 mμ (log ε 4·19, 3·70).

3-Phenyl-5-methyl-7-bromoisoxazolo[4,5-d]*pyridazin-4(5H)-one* (IVb)

Analogous treatment of IIIb with diazomethane yielded nearly quantitatively colourless crystals, m.p. 171–172°. (Found: C, 46·91; H, 2·69; N, 13·78; Br, 26·21. Calc. for $C_{12}H_8BrN_3O_2$: C, 47·08; H, 2·63; N, 13·73; Br, 26·10%.) UV spectrum: 239, 309 mμ (log ε 4·15, 3·56).

3-Phenyl-4-methoxy-7-chloroisoxazolo[4,5-d]*pyridazine* (V) *and 3-phenyl-4-chloro-7-methoxyisoxazolo*[4,5-d]*pyridazine* (VI)

A soln of IIa (0·84 g) in anhydrous MeOH (80 ml) was heated under reflux for 5 hr with MeONa (from 73 mg Na). Concentration to dryness *in vacuo* left a residue (0·8 g), m.p. 95°–120°. TLC on silica gel, eluent cyclohexane–AcOEt = 5:1. showed this to be a mixture of at least two compounds. The residue was then dissolved in hot MeOH (15 ml) and the soln left for 12 hr yielding heavy cream-coloured crystals, (0·25 g; 13%) which recrystallized from MeOH as colourless plates, m.p. 154–155°. (Found: C, 54·98; H, 3·25; N, 16·01; Cl, 13·63. Calc. for $C_{12}H_8ClN_3O_2$: C, 55·08; H, 3·08; N, 16·06; Cl, 13·35%.) UV spectrum: (fl) 241 mμ (log ε 3·98).

The product was also synthesized by the following route and therefore assigned structure V: a mixture of IX (0·65 g, see below), $POCl_3$ (15 ml) and N,N-diethylaniline (0·5 ml) was heated under reflux for 5 hr at 130°. Concentration *in vacuo* and pouring onto ice gave a crude brown product, which was eluted through a small alumina column, yielding 0·3 g (46%) m.p. 154–155°, identical (mixed m.p. and IR) with the above product.

The methanolic filtrate was concentrated and refrigerated, yielding 0·4 g (48%) of a second product, m.p. 124–128°. Recrystallization from MeOH gave shiny platelets, m.p. 130·5–131°. (Found: C, 55·42; H, 3·36; N, 16·20; Cl, 13·68. Calc. for $C_{12}H_8ClN_3O_2$: C, 55·08; H, 3·08; N, 16·06; Cl, 13·55%.) UV spectrum: 230, 280 mμ (log ε 4·25, 3·75).

This product was identified as VI because hydrolysis with boiling AcOH afforded a 54% of IIIa, m.p. 244–245°, identical with the product described above.

3-Phenyl-7-methoxyisoxazolo[4,5-d]*pyridazin-4*(5H)*-one* (IX)

A soln of IIc (0·15 g) in AcOH (15 ml) was refluxed for 6 hr, then concentrated *in vacuo* to dryness The residue was recrystallized from MeOH to give a good yield m.p. 263–265°. (Found: C, 59·38; H, 3·93; N, 17·38. Calc. for $C_{13}H_9N_3O_3$; C, 59·26; H, 3·73; N, 17·28%.) IR spectrum: 3150 (NH); 1670 (CO). UV spectrum: 233 mμ (log ε 4·18).

3-Phenyl-5-methyl-7-methoxyisoxazolo[4,5-d]*pyridazin-4*(5H)*-one* (VII)

(a) A soln of IVa (0·15 g) in hot MeOH (15 ml) was treated with MeONa (from 0·05 g Na). After refluxing for 6 hr, the solvent was evaporated *in vacuo* and the residue suspended in cold water. Filtration gave 0·13 g (90%) m.p. 142–145°, which recrystallized from MeOH in shiny needles, m.p. 147–148°. (Found: C, 60·53; H, 4·38: N, 16·33. Calc. for $C_{14}H_{11}N_3O_3$: C, 60·69; H, 4·31; N, 16·34%.) IR spectrum: 1660 (CO). UV spectrum: 234, 309 mμ (log ε 4·19, 3·48).

(b) The same product was obtained from IVb and MeONa; and in lower yield (28%) by treatment of IX with excess diazomethane in ether, followed by an elution with benzene through a grade I alumina column.

Methylation of 3-phenylisoxazolo[4,5-d]*pyridazin-4,7*(5H,6H)*-dione*

A soln of I (1·0 g) in 5% NaOH (25 ml) was treated at 40° with dimethyl sulfate (1·5 ml) and stirred for 6 hr. The resulting white solid was filtered and dissolved in cyclohexane–benzene (1:1 v/v). Chromatography on neutral alumina yielded 0·2 g (25%) VII, m.p. 147–148°, and, upon elution with benzene–ether, an isomeric product (0·15 g; 19%), which recrystallized from MeOH in colourless needles, m.p. 148–149°. (Found: C, 60·76; H, 4·48; N, 16·32. Calc. for $C_{14}H_{11}N_3O_3$: C, 60·69; H, 4·31; N, 16·34%.) IR spectrum: 1670 (CO). UV spectrum: 229, 305 mμ (log ε 4·28, 3·54). The product was insoluble in acids and bases and was not easily hydrolysed. Structure VIII was therefore assigned.

Upon acidification of the alkaline filtrate 0·3 g of unchanged starting material was recovered.

(b) Treatment of I with excess diazomethane in ether and fractional crystallization from MeOH gave a 47% of IX and 4·5% of VII.

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