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POLYNUCLEAR ISOXAZOLE TYPES—I

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

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Abstract—The Hofmann degradation of 3-phenylisoxazole-4,5-dicarboxamide gave 3-phenylisoxazolo[4.5-d]pyrimidin-5,7(4H, 6H)-dione. Starting from this compound a number of derivatives of the little-known isoxazolo[4.5-d]pyrimidine ring system have been prepared and their structures authenticated. The reactions with dimethyl sulfate and with diazomethane have been also studied, O- and N-methylderivatives obtained were interconverted.

THE polynuclear systems, containing an isoxazole ring fused with another heterocyclic ring, described include some derivatives of isoxazolo[3,4-d]pyridazine,[2-4] isoxazolo-[4,3-d]pyrimidine[5] and isoxazolo[5,4-d]pyrimidine.[6,7]

The synthesis and chemical properties of some isoxazolo[4.5-d]pyrimidine derivatives are now reported. The synthesis of this ring system could either start from an isoxazole derivative containing functional groups suitable for ring closure to pyrimidine, or from a pyrimidine derivative and subsequent addition of the isoxazole ring. The former method was adopted starting with 3-phenyl-isoxazole-4,5-dicarboxamide (I), obtained from the corresponding diester.[8]

The Hofmann degradation of the diamide (I) with a diamide–hypobromite (1:2 molar ratio) gave a 77% yield of 3-phenylisoxazolo[4,5-d]pyrimidin-5,7(4H,6H)-dione (II). When the reaction was carried out in 1:1 molar ratio, the above product was obtained in only 17% yield, whereas 31% of 3-phenyl-4-carboxamidoisoxazole-5-carboxylic acid and 36% of 3-phenyl-4-aminoisoxazole-5-carboxylic acid were obtained.[9] Structure IIa was supported since the amide group in position 5 of the isoxazole ring[9] is readily hydrolysed and the IR spectrum shows broad bands at 3560–3400 (NH) and at 1710–1690 (CO). Clearly the intermediate 3-phenyl-4-isocianatoisoxazole-5-carboxamide cyclizes immediately. The behaviour of the isoxazole-4,5-dicarboxamide (I) in the Hofmann reaction is analogous to pyrazole-4,5-dicarboxamide, which gives pyrazolo[3,4-d]pyrimidindione and not the [4,3-d] isomer.[10]

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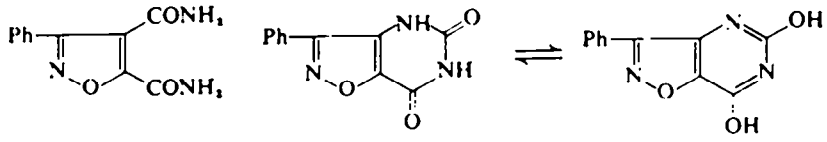


I IIa IIb

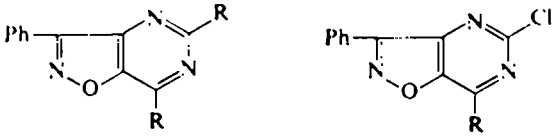
The following chemical evidence confirmed the above structure.

Treatment of II with $POCl_3$–$PhNEt_2$ gave a good yield of the dichloro derivative IIIa, whereas treatment with $POBr_3$ gave likewise IIIb. The reactivity of the two halogen atoms towards nucleophilic substitution is notably different: whereas sodium methoxide in excess afforded the dimethoxy derivative IIIc, heating with an equimolecular amount of sodium methoxide gave, beside 33% IIIc, a 42·5% yield of a monochloromonomethoxy derivative. The structure, 3-phenyl-5-chloro-7-methoxyisoxazolo[4,5-d]pyrimidine, was assigned to IVa on the following evidence:

(a) Subsequent treatment with sodium methoxide yielded quantitatively the dimethoxy derivative IIIc, which could in turn be hydrolysed with 1:1 HCl to the diketoisoxazolopyrimidine (IIa).

(b) The lower reactivity of the chlorine atom between the two nitrogen atoms towards nucleophilic reagents is well known in 2,4-dichloropyrimidine[11,12] and in 5,7-dichloropyrazolo[3,4-d]pyrimidine.[13]

(c) Treatment of IIIa with $POBr_3$ gave 3-phenyl-5-chloro-7-bromoisoxazolo[4,5-d]-pyrimidine (IVc), whose structure has been confirmed by X-ray analysis.[14] Heating IVc with an equimolecular amount of sodium methoxide yielded the same chloromethoxy derivative IVa, prepared from IIIa. Sodium methoxide in excess gave the dimethoxy derivative IIIc.



III IV

(a) R = Cl
(b) R = Br
(c) R = OMe

(a) R = OMe
(b) R = OPh
(c) R = Br
(d) R = NH_2

(e) R = NHMe
(f) R = $N(Et)_2$
(g) R = NHPh
(h) R = SH

All the nucleophilic substitution reactions on IIIa led to the substitution of only one chlorine atom: treatment with sodium phenoxide gave 3-phenyl-5-chloro-7-phenoxyisoxazolo[4.5-d]pyrimidine (IVb), whereas analogous treatment with ammonia or amines led to the appropriately 7-substituted isoxazolopyrimidines (IV d-g). Their structures were confirmed by their identity with the products obtained from the bromochloro derivative IVc. The UV spectra of all these compounds, being essentially identical, are consistent with the structures assigned. Selective hydrolysis on IVd led directly to the diketo-compound IIa.

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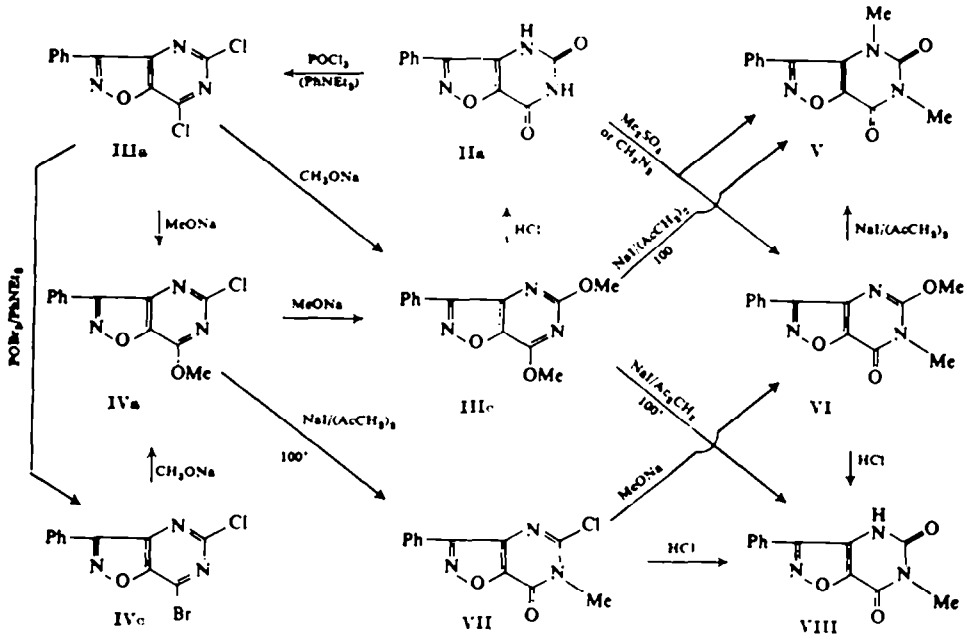
Treatment of IIIa or IVc with thiourea led to the substitution of the halogen atom in 7-position, IVh being obtained.

The methylation of II has been studied in some detail, and three dimethyl derivatives out of the four theoretically possible were obtained:

CHART I



Reaction of IIa with diazomethane or dimethyl sulfate yielded a mixture of two isomeric dimethyl derivatives, both different from IIIc. One was identified as 3-phenyl-5-methoxy-6-methylisoxazolo[4,5-d]pyrimidin-7(6H)-one (VI) through the following two-step sequence: starting from IVa, heating with NaI and acetonylacetone at 100° gave the N-methyl derivative VII; the migration of the methyl group from O to N is a well-known procedure in pyrimidine field. Treatment of VII with sodium methoxide afforded VI; from both compounds (VI and VII) acidic hydrolysis led to N-methylisoxazolopyrimidindione (VIII). The latter compound could also be obtained on heating IIIc with NaI in acetylacetone; when the same reaction was carried out in acetonylacetone, besides 15% of VIII, a double migration yielded 71% of N,N'-dimethyl derivative (V). This second isomer could also be prepared starting from VI with NaI–acetonylacetone, thus confirming its structure.

EXPERIMENTAL

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

3-Phenylisoxazole-4,5-dicarboxamide (I)

Crude diethyl 3-phenylisoxazole-4,5-dicarboxylate and aq. ammonia (*d* 0·886) were left in a tightly stoppered flask for 3 days. Filtration, washing with water and ether and recrystallization from EtOH afforded pure I (58%) m.p. 226° dec (reported:[8] m.p. 225° dec).

3-Phenylisoxazolo[4,5-d]pyrimidin-5,7(4H,6H)-dione (II)

Bromine (6·94 g) was added at −8° to a 10% KOHaq (60 ml) and to the cooled mixture, after dilution with water (60 ml), 3-phenylisoxazole-4,5-dicarboxamide (5·0 g) was added under vigorous stirring (1·5 hr). The mixture was heated at 70° for 1 hr and after cooling the pH was adjusted at 8 with dil. HCl and the crude precipitate filtered off (3·7 g; 77%). Recrystallization from AcOH afforded a light yellow crystalline solid, m.p. 360° dec (reported:[9] m.p. 362° dec).

3-*Phenyl*-5,7-*dichloroisoxazolo*[4,5-d]pyrimidine (IIIa)

A mixture of II (1·8 g), $POCl_3$ (9 ml) and N,N-diethylaniline (0·8 ml) was heated in a sealed tube at 130° for 3 hr and then poured onto ice and the precipitate filtered off. After grinding with 5% Na_2CO_3aq a product (1·9 g; 95%), m.p. 167–169° (EtOH) was obtained. (Found: C, 49·49; H, 2·05; N, 15·74; Cl, 26·45. Calc. for $C_{11}H_5Cl_2N_3O$: C, 49·65; H, 1·89; N, 15·79; Cl, 26·65%.) UV-spectrum: 228, 313 mμ (log ε 4·21, 3·94).

3-*Phenyl*-5,7-*dibromoisoxazolo*[4,5-d]*pyrimidine* (IIIb)

A soln of II (1·0 g), $POBr_3$ (10·0 g) and N,N-diethylaniline (1·0 ml) in dry toluene (15 ml) was refluxed for 3 hr on an oil bath (140°). After pouring onto ice and extraction with ether, the organic layer was dried and evaporated. The residue was eluted with benzene through a short column of alumina, and colourless needles (0·5 g), m.p. 216–218° (MeOH) were obtained. (Found: C, 37·10; H, 1·46; N, 11·83; Br, 45·05. Calc. for $C_{11}H_5Br_2N_3O$: C, 37·21; H, 1·42; N, 11·84; Br, 45·02.) UV: 227, 315 mμ (log ε 4·34, 4·01).

3-*Phenyl*-5-*chloro*-7-*bromoisoxazolo*[4,5-d]pyrimidine (IVc)

A solution of IIIa (0·9 g) in benzene (50 ml) was added with $POBr_3$ (5·0 g) and N,N-diethylaniline (2·0 ml) and refluxed for 5 hr. After standing at room temp for 12 hr, the mixture was poured onto ice and extracted with ether. Upon evaporation of the solvents, the residue was recrystallized from MeOH, (0·8 g) yellow needles, m.p. 190–191°. (Found: C, 43·21; H, 1·81; N, 13·24. Calc. for $C_{11}H_5BrClN_3O$: C, 42·54; H, 1·62; N, 13·53%.) UV: 229, 314 mμ (log ε 4·31, 4·05).

3-*Phenyl*-5-*chloro*-7-*methoxyisoxazolo*[4,5-d]*pyrimidine* (IVa)

(a) To a solution of IIIa (0·5 g) in warm MeOH (120 ml) a methanolic soln of MeONa (from 45 mg Na and 10 ml MeOH) was added, and the mixture refluxed for 5 hr. After standing 12 hr, the solvent was evaporated and the residue triturated with water. Filtration and recrystallization gave a product, m.p. 135–138°, which was a mixture of two compounds (TLC) . These were separated by column chromatography on neutral alumina: elution with cyclohexane–benzene gave white crystals (0·2 g; 42%), m.p. 165·5–167° (MeOH). (Found: C, 55·05; H, 3·00; N, 15·98; Cl, 13·65. Calc. for $C_{12}H_8ClN_3O_2$: C, 55·08; H, 3·08; N, 16·06; Cl, 13·55%.) UV: 223, 290, 300 mμ (log ε 4·26, 4·05, 4·06).

Further elution with benzene–ether yielded 0·15 g (33%) IIIc.

(b) The same product has been obtained under similar experimental conditions in 75% yield from IVc and equimolecular amounts of MeONa. Trace amounts of IIIc were identified on TLC plates.

3-*Phenyl*-5,7-*dimethoxyisoxazolo*[4,5-d]*pyrimidine* (IIIc)

(a) To a soln of IIIa (1·0 g) in abs MeOH (250 ml) MeONa (from 0·15 g Na in 20 ml MeOH) was added with stirring. The resulting mixture was refluxed for 15 min and then left for 12 hr. Filtration and dilution of the filtrate with a double volume of water gave 0·95 g (89%) of a product, which upon recrystallization from AcOEt melted at 162·5–163·5°. (Found: C, 60·85; H, 4·63; N, 16·31. Calc. for $C_{13}H_{11}N_3O_3$: C, 60·69; H, 4·31; N, 16·34%.) UV: 218, 307 mμ (log ε 4·27, 4·00).

(b) The same product was obtained by refluxing IIIb for 5 hr with excess MeONa.

(c) Or from IVc using analogous conditions.

(d) Refluxing IVa with a 4-fold excess of MeONa afforded a 94% yield of a product, m.p. 162–163°, identical (mixed m.p. and IR spectrum) with that obtained under (a).

Acidic hydrolysis. Refluxing IIIc (0·26 g) with 1:1 HClaq for 36 hr gave II (0·15 g), m.p. 360° dec.

3-Phenyl-5-chloro-7-phenoxyisoxazolo[4,5-d]*pyrimidine* (IVb)

(a) Sodium (0·26 g) was added to melted phenol (15 ml), and to the cooled suspension finely ground IIIa (1·0 g) was aded with stirring. After standing 12 hr, the mixture was poured into water (300 ml) and rendered slightly alkaline with 5% NaOHaq. Filtration gave 1·0 g (84%) of a crystalline product, m.p. 163–164° (AcOH). (Found C, 62·94; H, 3·18; N, 12·98; Cl, 10·98. Calc. for $C_{17}H_{10}ClN_5O_2$: C, 63·07; H, 3·11; N, 12·98; Cl, 10·95%.) UV: 223, 303 mμ (log ε 4·30, 4·08).

(b) The same product was obtained from IVc by treatment with PhONa.

3-Phenyl-5-chloro-7-aminoisoxazolo[4,5-d]*pyrimidine* (IVd)

(a) To a warm soln of IIIa (0·5 g) in EtOH (20 ml) sat ethanolic ammonia (3 ml) was added, and the mixture refluxed for 10 min. Cooling at 0° and filtering gave 0·4 g (91%) white needles, m.p. 288° from EtOH. (Found C, 53·55; H, 3·16; N, 22·51; Cl, 14·44. Calc. for $C_{11}H_7ClN_4O$: C, 53·56; H, 2·81; N, 22·70; Cl, 14·39%.) IR: 3350, 3150 (NH); UV: 218, 257, 308 mμ (log ε 4·37, 3·88, 3·99).

(b) The same product was prepared from IVc and ethanolic ammonia.

When IVd (0·5 g) was refluxed with 1:1 HClaq (50 ml) for 2 hr the product (0·5 g) was identified as II by comparison with an authentic sample.

3-Phenyl-5-chloro-7-methylaminoisoxazolo[4,5-d]*pyrimidine* (IVe)

(a) A soln of IIIa (0·7 g) and 30% methylamine (3 ml) in EtOH (40 ml) was refluxed for 12 hr. Upon concentration and cooling, the product (0·48 g; 72%) upon recrystallization from MeOH melted at 239–240°. (Found: C, 54·94; H, 3·64; N, 21·50; Cl, 13·46. Calc. for $C_{12}H_9ClN_4O$: C, 55·23; H, 3·48; N, 21·49; Cl, 13·60%.) IR: 3300 (NH); UV: 220, 260, 313 mμ (log ε 4·36, 3·98, 4·05).

(b) Analogous treatment of IVc with methylamine led to the same product.

3-Phenyl-5-chloro-7-diethylaminoisoxazolo[4,5-d]*pyrimidine* (IVf)

(a) A soln of IIIa (0·7 g) and diethylamine (2 ml) in EtOH (40 ml) was refluxed for 12 hr. After vacuum concentration and cooling to room temp, a light brown solid precipitated. Recrystallization from MeOH yielded white crystals (0·65 g; 83%), m.p. 129–130°. (Found: C, 58·86; H, 5·24; N, 18·49; Cl, 12·00. Calc. for $C_{16}H_{16}ClN_4O$: C, 59·50; H, 4·99; N, 18·51; Cl, 11·71%.) UV: 223, 265, 328 mμ (log ε 4·34, 3·98, 4·07).

(b) Similarly from IVc and diethylamine, the product, m.p. 129–130°, was identical with the compound described under (a).

3-Phenyl-5-chloro-7-phenylaminoisoxazolo[4,5-d]*pyrimidine* (IVg)

(a) A soln of IIIa (0·5 g) and aniline (0·5 ml) in EtOH (75 ml) was refluxed for 2–3 hr and yielded 0·4 g (69%) of a white crystalline product, m.p. 243° from EtOH. (Found: C, 62·70; H, 3·41; N, 17·31; Cl, 11·03. Calc. for $C_{17}H_{11}ClN_4O$: C, 63·26; H, 3·44; N, 17·36; Cl, 10·99%.) IR: 3150 (NH); UV: 225, 254 349 mμ (log ε 4·37, 4·14, 4·25).

(b) The same product could be obtained in lower yield from IVc and aniline.

3-Phenyl-5-chloroisoxazolo[4,5-d]*pyrimidin*-7(6H)-*thione* (IVh)

(a) A soln of IIIa (0·6 g) and thiourea (0·4 g) in 95% EtOH (60 ml) was refluxed for 3 hr. After evaporation to dryness, the residue was triturated with water and filtered off. The solid was then boiled briefly with water and finally dissolved in hot MeOH. Upon cooling at 0° and elimination of some brown polymeric material, the soln was diluted with cold water and the precipitate collected (0·3 g; 50%) yellow needles, m.p. 174°. Recrystallization from MeOH raised the m.p. to 183–183·5°. (Found: C, 49·70; H, 2·58; N, 15·92; Cl, 13·35; S, 12·28. Calc. for $C_{11}H_6ClN_5OS$: C, 50·10; H, 2·29; N, 15·93; Cl, 13·44; S, 12·16%.) UV: 225, 264, 367 mμ (log ε 4·19, 4·14, 4·07.)

(b) The same product was obtained from IVc and thiourea.

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

To an ethereal soln of diazomethane (about 1·0 g) finely ground II (1·0 g) was added in small portions with stirring. After 4 hr, the insoluble solid was filtered off and washed with very dil NaOHaq yielding (0·28 g) colourless needles, which upon recrystallization from MeOH melted at 194–195°.

The product was identified as *3-phenyl-5-methoxy-6-methylisoxazolo*[4,5-d]*pyrimidin-7(6H)-one* (VI) by comparison with a sample prepared as described below.

The ethereal filtrate, evaporated to dryness, left a mixture of two products (TLC). These could be separated by fractional crystallization from MeOH: a further amount (0·2 g), m.p. 194–195°, was recovered and in addition a 18% yield of *3-phenyl-4,6-dimethylisoxazolo*[4,5-d]*pyrimidin-5,7(4H,6H)-dione* (V), m.p. 167–168°, was obtained. The latter was identical in every respect with an authentic sample prepared as below described.

(b) Methylation of II with dimethyl sulfate gave 17% of VI and 17% of V.

3-Phenyl-4,6-dimethylisoxazolo[4,5-d]*pyrimidin-5,7(4H,6H)-dione* (V)

(a) A mixture of IIIc (0·35 g), NaI (0·35 g) and acetonylacetone (9·0 ml) was heated at 100° for 16 hr. Upon cooling to room temp, the insoluble solid was filtered off and washed on the filter with water, yielding light brown crystals (0·05 g; 15%), m.p. 310° dec. The product was identified as VIII by comparison with a sample prepared as described below.

Dilution of the filtrate with water (100 ml) yielded a white solid (0·25 g; 71%), which recrystallized from MeOH in small, hard prisms, m.p. 167·5–168·5°. (Found: C, 60·59; H, 4·57; N, 16·58; Calc. for $C_{13}H_{11}N_3O_3$: C, 60·69; H, 4·31; N, 16·30%.) IR: 1720, 1670 (CO); UV: 299 mμ (log ε 3·88).

(b) Similarly heating VI (see below) with NaI and acetonylacetone at 100° for 6 hr gave a 18% of VIII, m.p. 310° dec, and a 67% of V, m.p. 167·5–168·5°.

3-Phenyl-5-chloro-6-methylisoxazolo[4,5-d]*pyrimidin-7(6H)-one* (VII)

A mixture of IVa (0·55 g), NaI (0·55 g) and acetonylacetone (7·0 ml) was heated at 100° for 8 hr, then cooled to room temp and left aside for 12 hr. Upon dilution with water and filtration, 0·50 g (91%) of a product, m.p. 203–204°, were collected. Recrystallization from MeOH yielded light yellow needles, m.p. 209°. (Found: C, 54·87; H, 3·27; N, 16·07; Cl, 13·53. Calc. for $C_{13}H_8ClN_3O_3$: C, 55·08; H, 3·08; N, 16·06; Cl, 13·55%.) IR: 1700 (CO); UV: 222, 298 mμ (log ε 4·25, 3·85).

3-Phenyl-5-methoxy-6-methylisoxazolo[4,5-d]*pyrimidin-7(6H)-one* (VI)

A soln of VII (0·1 g) in abs MeOH (7 ml) was refluxed for 5 hr with MeONa (from 0·03 g Na) yielding 0·08 g (81%) white crystals, which upon recrystallization from MeOH melted at 194–195°. (Found: C, 60·80; H, 4·64; N, 16·37. Calc. for $C_{13}H_{11}N_3O_3$: C, 60·69; H, 4·31; N, 16·34%.) IR: 1700 (CO); UV: 221, 300 mμ (log ε 4·32, 3·94).

3-Phenyl-6-methylisoxazolo[4,5-d]*pyrimidin-5,7-(4H,6H)-dione* (VIII)

(a) A mixture of VII (0·10 g) and 1:1 HClaq (10 ml) was heated under reflux for 8 hr yielding a white solid (0·08 g) which recrystallized from MeOH, m.p. 310° dec. (Found: C, 59·19; H, 3·43; N, 17·55. Calc. for $C_{13}H_9N_3O_3$: C, 59·26; H, 3·73; N, 17·28%.) IR: 3150 (NH); 1720, 1670 (CO).

(b) Analogous treatment of VI with HCl led to the same product identical with the one obtained by method (a).

(c) A mixture of IIIc (0·50 g), NaI (0·50 g) and acetylacetone (15 ml) was heated at 100° for 24 hr. Dilution with water and filtration gave 0·40 g, m.p. 310° dec, identical (IR and mixture m.p.) with the product obtained by method (a).

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