Tetrahedron, 1967, Vol. 23, pp. 687 to 691. Pergamon Press Ltd. Printed in Northern Ireland

POLYNUCLEAR ISOXAZOLE TYPES—III

THE SYNTHESIS OF ISOXAZOLO[5,4-d]PYRIMIDINES[1]

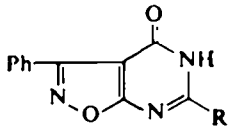
G. DESIMONI, P. GRÜNANGER and P. VITA FINZI
Istituto di Chimica Organica, Università di Pavia, Italy

(*Received* 17 *May* 1966)

Abstract—The reaction of 3-phenyl-5-aminoisoxazole-4-carboxamide with acyl chlorides gave variable amounts of 3-phenyl-4-cyano-5-acylaminoisoxazoles and 3-phenyl-6-alkyl(or aryl)isoxazolo-[5,4-d]pyrimidin-4(5H)-ones. Some reactions of the latter and transformations in the pyrazolo[3,4-d]-pyrimidine ring system have been described.

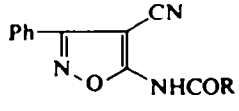
ALTHOUGH the pyrazolo[3,4-d]pyrimidine ring system has received much attention, the structurally analogous isoxazolo[5,4-d]pyrimidine system, apart from several 4-amino derivatives[2] and the synthesis of the 3-phenyl-4,6-diamino compound[3] has been neglected.

The reaction of 3-phenyl-5-aminoisoxazole-4-carboxamide with acetyl chloride gave 80% of a high-melting product, whose structure Ia was confirmed by IR analysis and the chemical evidence reported. The UV spectrum is very similar to that of 3-phenylisoxazolo[5,4-d]pyrimidin-4(5H)-one.[2] The behaviour of other acyl chlorides is different in that besides the high-melting isoxazolo[5,4-d]pyrimidinones (Ib–e) variable amounts of 3-phenyl-4-cyano-5-acylaminoisoxazoles (IIb–e) were isolated. The yield ratios of the two products varied according to the nature of R and to reaction temperature: use of aroyl chloride raised the yield of II

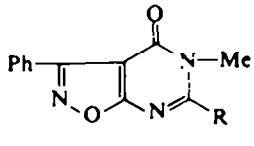


I

(a) R = Me
(b) R = Et
(c) R = Ph
(d) R = *p*-$CH_3C_6H_4$
(e) R = *p*-ClC_6H_4



II



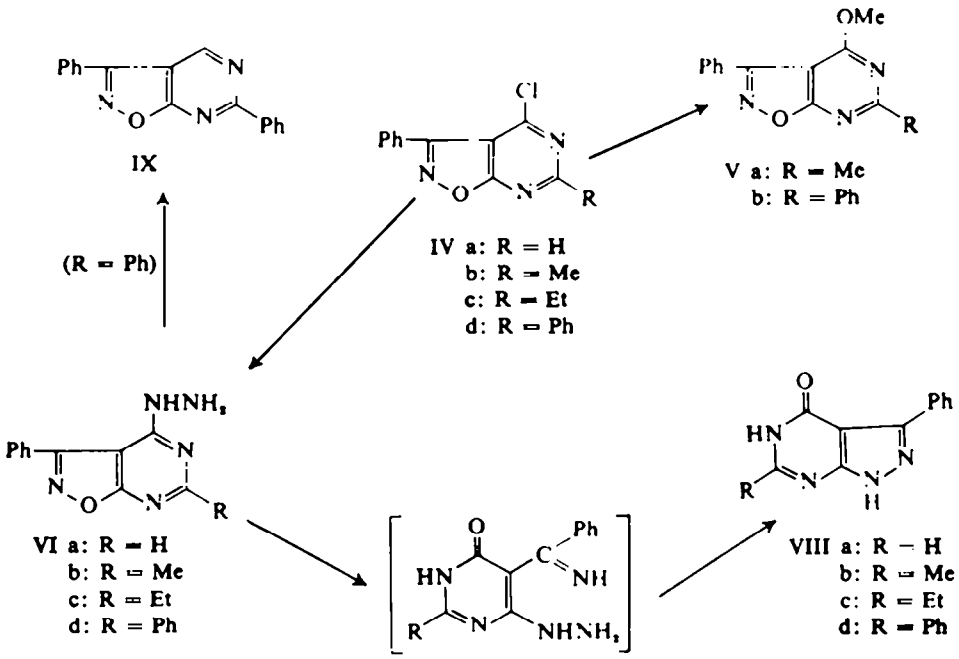
III

(a) R = Me
(b) R = Ph

and higher temperatures raised the yield of I. The structures of IIc–e have been confirmed by independent synthesis from 3-phenyl-4-cyano-5-aminoisoxazole and the appropriate aroyl chloride.

The isoxazolopyrimidinones (Ia–c) as well as the known 3-phenylisoxazolo-[5,4-d]pyrimidin-4(5H)-one[2] have been converted in good yield to the 4-chloro derivatives (IVa–d). The chlorine atom of these compounds can be readily displaced

[1] Part II, *Tetrahedron* **23**, 681 (1967).
[2] E. C. Taylor and E. E. Garcia, *J. Org. Chem.* **29**, 2116 (1964).
[3] A. Dornow and H. Teckenberg, *Chem. Ber.* **93**, 1103 (1960).



by sodium methoxide to give Va–b or by hydrazine to give VIa–d. Oxidation of the hydrazinodiphenyl derivative (VId) with cupric sulfate in acetic acid gave low yield of 3,6-diphenylisoxazolo[5,4-d]pyrimidine (IX); the other hydrazino compounds (VIa–c) could not be oxidized in the same manner because of their higher tendency to hydrolyse to 3-phenyl-(6-alkyl)isoxazolo[5,4-d]pyrimidin-4(5H)-ones.

Catalytic hydrogenation of VIa–d in ethanolic solution resulted in a rapid uptake of one mole of hydrogen and treatment of the reduction mixture with acetic acid led to compounds, for which structures VIIIa–d of pyrazolo[3,4-d]pyrimidin-4(5H)-ones were established by IR evidence and by independent synthesis.[4] The intermediate imines of type VII or the corresponding ketones were not easily isolated.

The methylation of Ia and Ic with diazomethane yielded in both cases a mixture of the O-methyl-(Va–b) and of the N-methyl-derivatives (IIIa–b); Ia giving higher yield of the latter compound and the more bulky Ic affording mostly the former isomer. Methylation of Ia with dimethyl sulfate yielded only the N-methyl compound (IIIa).

Conversion of the O-methyl (Va–b) into the N-methyl derivatives (IIIa–b) was accomplished in good yields by following the well-known procedure in pyrimidine chemistry.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra: nujol mulls. Microanalyses: by Dr. Lucia Maggi Dacrema.

Reaction of 3-phenyl-5-aminoisoxazole-4-carboxamide with acyl chlorides

(a) A mixture of 3-phenyl-5-aminoisoxazole-4-carboxamide[5] (3·0 g) and acetyl chloride (100 ml) was refluxed for 8 hr, then left overnight at room temp. Concentration *in vacuo* left a residue, which

[4] G. Desimoni and C. Ticozzi, *Gazz. Chim. Ital.* in press.

[5] A. Quilico and R. Fusco, *Rend. Ist. Lomb. Sc. Lett.* **69**, 439 (1936).

was treated with 10% NaOH aq (100 ml). The unchanged amide was filtered off and the filtrate acidified with HCl yielded Ia (2·7 g; 80%), m.p. 300°. This crystallized from AcOH as white crystals, m.p. 325° dec. (Found: C, 63·41; H, 4·44; N, 18·26. Calc. for $C_{18}H_9N_3O_3$: C, 63·43; H, 3·99; N, 18·49%.) IR: 3275 (NH); 1680 (CO). UV: 249 mμ (log ε 4·22).

(b) A mixture of 3-phenyl-5-aminoisoxazole-4-carboxamide (3·0 g) and propionyl chloride (30 ml) was heated to 90° for 8 hr. After evaporation *in vacuo*, the residue was treated with 5% NaOH aq (100 ml), some unchanged amide being left undissolved. Acidification of the filtrate yielded a white solid (3·3 g), which was crystallized from AcOH. *3-Phenyl-6-ethylisoxazolo*[5,4-d]*pyrimidin*-4(5H)-*one* (Ib; 2·0 g; 57%), m.p. 260–262°, was recrystallized m.p. 262–263°. (Found: C, 64·63; H, 4·68; N, 17·39. Calc. for $C_{13}H_{11}N_3O_2$: C, 64·72; H, 4·60; N, 17·42%.) IR: 3125 (NH); 1690 (CO).

Concentration of the acetic mother liquor to a small volume (10 ml) and cooling afforded IIb (1·0 g; 28·5%), m.p. 199–200°. (Found: C, 64·87; H, 5·03; N, 17·35. Calc. for $C_{13}H_{11}N_3O_2$: C, 64·72; H, 4·60; N, 17·42%.) IR: 3225, 3150 (NH); 2225 (CN); 1730, 1700 (CO).

(c) A mixture of 3-phenyl-5-aminoisoxazole-4-carboxamide (5·0 g) and benzoyl chloride (60 ml) was heated at 100° for 4 hr, then at 160° for further 4 hr. After cooling to room temp, the precipitate was filtered off and extracted several times with hot MeOH. From the methanolic soln, IIc (3·2 g; 45%), m.p. 200°, separated and was recrystallized from MeOH, m.p. 211–212°, identical with the product described below.

The product insoluble in MeOH, when recrystallized from AcOH, yielded shiny cream plates of *3,6-diphenylisoxazolo*[5,4-d]*pyrimidin*-4(5H)-*one* (Ic, 0·8 g; 11%), m.p. 313° dec. (Found: C, 70·68; H, 4·02; N, 14·60. Calc. for $C_{17}H_{11}N_3O_2$: C, 70·58; H, 3·83; N, 14·53%) IR: 3175 (NH); 1700 (CO).

When the reaction was carried out by heating in an oil bath at 160°, followed by heating for 8 hr, only Ic was obtained in 35% yield. If the reaction mixture was first left at room temp for 3 hr, then slowly heated to 110° and kept at this temp for 5 hr, cooling and standing overnight afforded only IIc in 62% yield.

(d) A mixture of 3-phenyl-5-aminoisoxazole-4-carboxamide (2·0 g) and *p*-tolyl chloride (20 ml) was heated at 160° for 8 hr. After cooling to room temp and diluting with ether (200 ml), a yellow solid (2·2 g) was obtained and extracted several times with 5% NaOH aq until the insoluble fraction did not show CN-band at 2225 cm^{-1}. Acidification of the alkaline solution yielded IId (1·35 g; 45%), m.p. 230–231°, identical with the product described below.

The solid was recrystallized from AcOH, yielding *3-phenyl-6-p-tolylisoxazolo*[5,4-d]*pyrimidin*-4(5H)-*one* (Id; 0·5 g; 17%), m.p. 322° dec. (Found: C, 71·02; H, 4·48; N, 13·77. Calc. for $C_{18}H_{13}N_3O_2$: C, 71·27; H, 4·32; N, 13·86%.) IR: 3125 (NH); 1665 (CO).

(e) A mixture of 3-phenyl-5-aminoisoxazole-4-carboxamide (3·0 g) and *p*-chlorobenzoyl chloride (30 ml) was heated at 160° for 8 hr. The suspension was filtered off and the cream-coloured solid washed with sat $NaHCO_3$ aq to eliminate *p*-chlorobenzoic acid (1·2 g) from the acidified filtrate. Extraction of the solid with three portions (100 ml each) of 5% NaOH aq and acidification of the filtrate yielded IIe (0·6 g; 13%), m.p. 210–212°, identical with the product obtained below. The residue, after removal of *p*-chlorobenzoyl anhydride (1·2 g) by extraction with MeOH, was recrystallized from AcOH to yield white crystals of *3-phenyl-6-p-chlorophenyl-isoxazolo*[5,4-d]*pyrimidin*-4(5H)-*one* (Ie; 0·7 g; 15%), m.p. 331° dec. (Found: C, 63·07; H, 3·21; N, 12·95; Cl, 10·99. Calc. for $C_{17}H_{10}ClN_3O_2$: C, 63·07; H, 3·11; N, 12·98; Cl, 10·95%.) IR: 3125 (NH); 1680 (CO).

3-Phenyl-4-cyano-5-aminoisoxazole

This compound[8,9] has been prepared by the following new procedure. To a stirred soln of MeONa (from 1·2 g Na) and malononitrile (3·3 g) in abs EtOH (55 ml) a soln of benzohydroxamyl chloride (7·8 g) in EtOH (20 ml) was added dropwise. After standing at room temp for 3 hr, followed by evaporation, the residue was treated with water and the crude product recrystallized from MeOH as colourless needles (8·0 g; 81%), m.p. 190–192° (reported[9] m.p. 193°).

3-Phenyl-4-cyano-5-aroylaminoisoxazoles (IIc e)

The following compounds have been prepared from 3-phenyl-4-cyano-5-aminoisoxazole with the appropriate aroyl chloride by a Schotten-Baumann procedure:

Compound IIc. Shiny colourless needles (MeOH), m.p. 211–212°. (Found: C, 70·98; H, 4·10; N, 14·68. Calc. for $C_{17}H_{11}N_3O_2$: C, 70·58; H, 3·83; N, 14·53%.)

Compound IId. Soft colourless needles (MeOH), m.p. 230–231°. (Found: C, 71·00; H, 4·49; N, 14·03. Calc. for $C_{18}H_{13}N_3O_2$: C, 71·27; H, 4·32; N, 13·86%.)

Compound IIe. Soft colourless needles (MeOH), m.p. 210–212°. (Found: C, 63·34; H, 3·28; N, 13·12; Cl, 10·93. Calc. for $C_{17}H_{10}ClN_3O_2$: C, 63·07; H, 3·11; N, 12·98; Cl, 10·95%.)

The reaction afforded 40–50% yields, and the IR spectra of the products showed the following bands: about 3200 (NH); 2225 (CN); 1695–1690 (CO).

3-*Phenyl*-4-*chloroisoxazolo*[5,4-d]*pyrimidine* (IVa)

A mixture of 3-phenylisoxazolo[5,4-d]pyrimidin-4(5H)-one[2] (3·28 g), $POCl_3$ (33 ml) and $PhNEt_2$ (3·3 ml) was heated at 140° for 4 hr. After concentration, the red-coloured residue was poured onto ice (300 g). Filtration of the crude product and purification by elution through an alumina column yielded 2·9 g (77%), m.p. 90–92°, which was recrystallized from diisopropyl ether in colourless platelets, m.p. 96–97°. (Found: C, 56·47; H, 2·86; N, 18·15; Cl, 15·53. Calc. for $C_{11}H_6ClN_3O$: C, 57·03; H, 2·61; N, 18·16; Cl, 15·31%.)

3-*Phenyl*-4-*chloro*-6-*methylisoxazolo*[5,4-d]*pyrimidine* (IVb)

A mixture of Ia (0·9 g), $POCl_3$ (8 ml) and $PhNEt_2$ (0·5 ml) was heated at 130° for 3 hr. After pouring onto ice, the precipitate was recrystallized from MeOH to give lightly cream-coloured needles (0·8 g; 82%), m.p. 111–112°. (Found: C, 58·97; H, 3·51; N, 17·14; Cl, 14·40. Calc. for $C_{12}H_8ClN_3O$: C, 58·66; H, 3·28; N, 17·12; Cl, 14·45%.)

3-*Phenyl*-4-*chloro*-6-*ethylisoxazolo*[5,4-d]*pyrimidine*(IVc)

This was obtained from Ib in 65% yield and recrystallized from MeOH, needles, m.p. 125°. (Found: C, 58·76; H, 3·71; N, 16·18; Cl, 13·78. Calc. for $C_{13}H_{11}ClN_3O$: C, 58·76; H, 3·88; N, 16·20; Cl, 13·65%.)

3,6-*Diphenyl*-4-*chloroisoxazolo*[5,4-d]*pyrimidine* (IVd)

This was obtained from Ic in 85% as needles (MeOH), m.p. 123–124°. (Found: C, 66·67; H, 3·37; N, 13·78; Cl, 11·77. Calc. for $C_{17}H_{10}ClN_3O$: C, 66·35; H, 3·28; N, 13·67; Cl, 11·52%.)

3-*Phenyl*-4-*methoxy*-6-*methylisoxazolo*[5,4-d]*pyrimidine* (Va)

A soln of IVb (0·7 g) and MeONa (from 0·1 g Na) in MeOH (50 ml) was refluxed for 4 hr. Evaporation to dryness left a white solid, which was suspended in water and filtered off yielding 0·6 g which recrystallized from MeOH as white needles, m.p. 116–117°. (Found: C, 64·44; H, 4·73; N, 17·45. Calc. for $C_{13}H_{11}N_3O_2$: C, 64·72; H, 4·60; N, 17·42%.)

3,6-*Diphenyl*-4-*methoxyisoxazolo*[5,4-d]*pyrimidine* (Vb)

Using a similar procedure, IVd gave a quant. yield of m.p. 145–150°, which recrystallized from MeOH as white needles, m.p. 153·5–154·5°. (Found: C, 71·71; H, 4·32; N, 13·58. Calc. for $C_{18}H_{13}N_3O_2$: C, 71·27; H, 4·32; N, 13·86%.)

3-*Phenyl*-5-*hydrazinoisoxazolo*[5,4-d]*pyrimidines* (VI)

To a stirred soln of the appropriate 3-phenyl-4-chloroisoxazolopyrimidine (IVa–d) in dioxan excess of hydrazine hydrate was added dropwise and under refrigeration with ice. After standing for 1–4 hr, the precipitate was washed with water and recrystallized from MeOH.

Physical data and yields of the compounds prepared by this procedure are reported in Table 1.

3-*Phenylpyrazolo*[3,4-d]*pyrimidin*-4(5H)-*ones* (VIII)

A soln of the appropriate hydrazinoisoxazolopyrimidine (VI) in abs EtOH was hydrogenated at room temp and press in the presence of 10% Pd–C. After uptake of one mole H, the boiling suspension was clarified by addition of AcOH and filtered hot from the catalyst. Upon cooling the corresponding VIII crystallized out, and some additional amount could be recovered by evaporation of the mother liquor.

All of the compounds were identical in every respect with the corresponding products prepared by another route.[4] Physical data and yields are reported in Table 1.

3,6-*Diphenylisoxazolo*[5,4-d]*pyrimidine* (IX)

To a stirred soln of $CuSO_4$ (2·0 g) in water (100 ml) a soln of VId (0·5 g) in AcOH (100 ml) was added dropwise: gas evolution and cloudiness of the mixture were noticed.

After standing overnight, the mixture was diluted with water (500 ml) and the precipitate was filtered off and dried. The brown solid was triturated with benzene (50 ml), and the filtrate was eluted through a short alumina column. From the first fractions a white product (0·11 g; 27%), m.p. 158–159°, was collected. Recrystallization from MeOH yielded colourless needles, m.p. 161–162°. (Found: C, 74·46; H, 4·26; N, 15·38. Calc. for $C_{17}H_{11}N_3O$: C, 74·71; H, 4·06; N, 15·38%.)

TABLE 1

Compound	M.p.	Yield %	Analysis % Found C	Found H	Found N	Calc. C	Calc. H	Calc. N
VIa	201–202°	92	57·93	3·98	31·07	58·14	3·99	30·82
VIb	176–178°	93	59·33	4·78	28·90	59·74	4·60	29·03
VIc	155–156°	90	61·07	5·55	27·44	61·16	5·13	27·44
VId	235° dec.	93	67·05	4·55	22·72	67·13	4·32	23·09
VIIIa	360°	87	62·12	4·00	26·23	62·25	3·80	26·40
VIIIb	360°	84	63·59	4·71	24·71	63·70	4·46	24·77
VIIIc	>360°	77	64·66	5·02	23·50	64·98	5·03	23·32
VIIId	>360°	81	79·74	4·42	19·24	70·82	4·20	19·44

Methylation of Ia

(a) To an ethereal solution of slight excess diazomethane Ia (1·0 g) was added in small portions. After standing for 24 hr, the solvent was evaporated and the residue, m.p. 100–150°, showed by TLC to be a mixture of at least two products. Fractional crystallization from MeOH and column chromatography separated 28% of Va, m.p. 116–117°, identical (mixed m.p. and IR) with the product described above and a 57% of IIIa, m.p. 202–203°, identical with the product prepared below.

(b) A stirred soln of Ia (1·0 g) in 5% NaOH aq (200 ml), dimethyl sulfate (3·0 ml) was added. A second portion (3·0 ml) of dimethyl sulfate was added after 1 hr, then the mixture was left for 24 hr. Filtration of the white precipitated solid gave a 75% of IIIa, m.p. 202–203° (see below).

Methylation of Ic

This (1·0 g) was methylated with diazomethane yielding a mixture of isomers from which a 61% of Vb, m.p. 153·5–154·5° (see above), together with a 25% of IIIb, m.p. 168–169° (see below), could be separated.

3-*Phenyl*-5,6-*dimethylisoxazolo*[5,4-d]*pyrimidin*-4(5H)-*one* (IIIa)

A mixture of Va (0·7 g), NaI (0·7 g) and freshly distilled acetonylacetone (8·0 ml) was heated at 100° for 8 hr. After dilution with water the precipitate (0·7 g) was filtered off and recrystallized from MeOH, m.p. 202–203°. (Found: C, 64·40; H, 4·74, N, 17·47; Calc. for $C_{13}H_{11}N_3O_2$: C, 64·72; H, 4·60; N, 17·42%.) IR: 1690 (CO).

3,6-*Diphenyl*-5-*methylisoxazolo*[5,4-d]*pyrimidin*-4(5H)-*one* (IIIb)

Analogous treatment of Vb (0·7 g) with NaI and acetonylacetone at 100° gave 0·7 g, m.p. 160–162°, which upon recrystallization from MeOH yielded soft needles, m.p. 168–169°. (Found: C, 70·80; H, 4·33; N, 14·06; Calc. for $C_{18}H_{13}N_3O_2$: C, 71·27; H, 4·32; N, 13·86%.) IR: 1690 (CO).

A small amount (0·05 g) of Ic, m.p. 313° dec, was recovered as a product insoluble in hot MeOH.

Acknowledgement—Financial aid from the Consiglio Nazionale delle Ricerche (Rome) is gratefully acknowledged.