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SYNTHESIS OF 4-HYDROXY-, 4-CHLORO-. 4-AMINO- AND 4-SUBSTITUTED AMINOISOXAZOLO [5.4-d] PYRIMIDINES*

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Abstract—Treatment of 4-hydroxyisoxazolo [5.4-d] pyrimidines (II) with phosphorous oxychloride furnishes the 4-chloro analogues (III) which react readily with ammonia, primary and secondary amines yielding the corresponding 4-amino, 4-mono and 4-disubstituted amino derivatives (IV) respectively.

TAYLOR and Garcia[1] recently described an elegant synthesis of 4-hydroxy and 4-amino derivatives of isoxazolo [5.4-d] pyrimidines of the types II and IV respectively. When this publication appeared we had already synthesized a number of derivatives of this interesting condensed heterocyclic system. Our approach to the synthesis of compounds of type II, differed from that of Taylor and Garcia[1] in that the key intermediate (I) was prepared by the reaction of hydroximoyl chlorides with the sodium salt of cyanoacetamide[2] while they obtained this type of compound (I) by the partial hydrolysis of the isoxazoloaminonitriles (VI) which were in turn prepared from suitably substituted ethoxymethylenemalononitrile (V) and hydroxylamine. The isoxazoloaminoamides (I), on being refluxed with triethyl orthoformate in the presence of acetic anhydride, underwent smooth cyclization to yield 4-hydroxy-isoxazolo [5.4-d] pyrimidines (II).[1]

Treatment of the 4-hydroxy compounds (II) with phosphorous oxychloride furnished the corresponding 4-chloro analogues (III) which reacted readily with ammonia, primary and secondary amines yielding the corresponding 4-amino (IV, $R_1 = R_2 = H$), 4-monosubstituted amino (IV, $R_2 = H$) and 4-disubstituted amino (IV) isoxazolo [5.4-d] pyrimidines respectively. This route to the compounds of the type IV is different from the one employed by Taylor and Garcia[1] who prepared such compounds (IV) starting with the isoxazoloaminonitriles (VI), converting them to the ethoxymethyleneamino intermediate (VII) and cyclizing the latter with ammonia and primary amines. It is relevant to mention here that secondary amines may not bring about the cyclization of Taylor and Garcia's intermediate (VII), the reaction stopping at the stage of the amidines of the type VIII, if the mechanism of cyclization of the compounds of the type VII with ammonia and primary amines as proposed by Taylor and Loeffler[3] is operative. As such the 4-disubstituted amino-isoxazolo [5.4-d] pyrimidines (IV) may not directly be accessible by their route.

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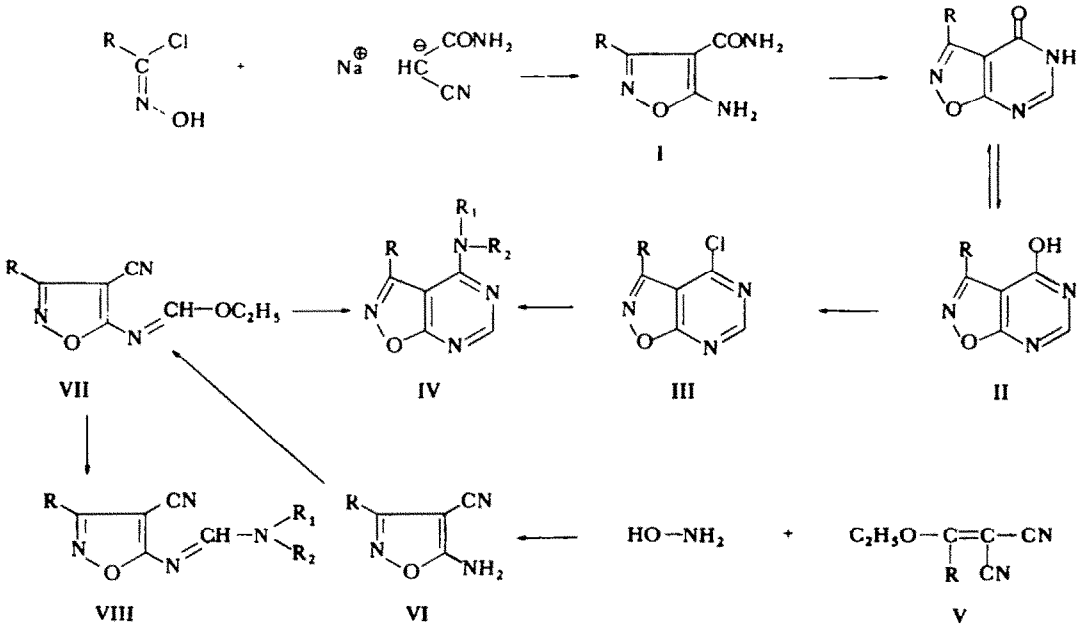
[1] E. C. Taylor and E. E. Garcia, *J. Org. Chem.* **29**, 2116 (1964).
[2] A. Quilico and R. Fusco, *Rend. ist. lombardo. Sci.* **69** [2], 439 (1936); *Chem. Abstr.* **32**, 7454 (1938).
[3] E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.* **82**, 3147 (1960).



EXPERIMENTAL

All m.ps were determined in open capillary tubes and are uncorrected.

5-Amino-3-(4-chlorophenyl)isoxazole-4-carboxamide. A warm soln of cyanoacetamide (16·4 g) in abs EtOH (125 ml) was added to a stirred soln of freshly prepared EtONa (from 4·6 g Na) in abs EtOH (125 ml) and the resulting clear soln was cooled to −5° and treated with a soln of 4-chlorobenzhydroximoyl chloride (38·0 g) in abs EtOH (200 ml) added at such a rate as to maintain the temp below 20°. After addition of the hydroximoyl chloride, the mixture was stirred at room temp for 1·5 hr and then refluxed for 2·5 hr, cooled and poured into crushed ice and water. The mixture was filtered after 30 min and the residue washed with water and recrystallized from MeOH as colourless crystals, m.p. 212–216°, yield 36 g (76%). (Found: C, 50·85; H, 3·71; N, 17·42. $C_{10}H_8ClN_3O_2$ requires: C, 50·54; H, 3·39; N, 17·68%.)

The isoxazoloaminoamides listed below were prepared by a similar method.

5-Amino-3-phenylisoxazole-4-carboxamide—colourless crystals from MeOH, m.p. 182–185° (reported[1]: 178–180°), yield 45%. (Found: C, 59·62; H, 4·42; N, 20·20. $C_{10}H_9N_3O_2$ requires: C, 59·10; H, 4·46; N, 20·68%.)

5-Amino-3-(3-nitrophenyl)isoxazole-4-carboxamide—yellow crystals from MeOH, m.p. 170–173°, yield, 62%. (Found: C, 48·47; H, 3·28; N, 22·67. $C_{10}H_8N_4O_4$ requires: C, 48·39; H, 3·25; N, 22·58%.)

5-Amino-3-t-butylisoxazolo-4-carboxamide—colourless crystals from acetone–hexane, m.p. 153–155. yield 42%. (Found: C, 52·24; H, 6·99; N, 23·11. $C_8H_{13}N_3O_2$ requires: C, 52·44; H, 7·15; N, 22·94%.)

3-(4-Chlorophenyl)-4,5-dihydro-4-oxoisoxazolo [5,4-d] *pyrimidine.* This and the following 4-oxoisoxazolo [5,4-d] pyrimidines were prepared essentially according to the procedure of Taylor and Garcia.[1]

A mixture of 5-amino-3-(4-chlorophenyl)isoxazole-4-carboxamide (21 g), triethyl orthoformate (125 ml) and Ac_2O (125 ml) was refluxed for 3 hr and then concentrated to a small bulk, diluted with EtOH and cooled. The solid that separated was filtered off, washed with a small quantity of EtOH and recrystallized from the same solvent as colourless crystals, m.p. 253–256°, yield 15·9 g (73%). (Found: C, 53·66, H, 2·76; N, 16·67. $C_{11}H_6ClN_3O_2$ requires: C, 53·35; H, 2·44; N, 16·97%.)

4,5-Dihydro-3-(3-nitrophenyl)-4-oxoisoxazolo [5,4-d] *pyrimidine*—colourless crystals from EtOH, m.p. 250° (dec) (reported[1]: 239–241° (dec), yield 48%. (Found: C, 61·92; H, 3·08; N, 20·07. $C_{11}H_7N_3O_2$ requires: C, 61·97; H, 3·31; N, 19·71%.)

4,5-Dihydro-3-(3-nitrophenyl)-4-oxoisoxazolo [5,4-d] *pyrimidine*—colourless crystals from EtOH, m.p. 260–262° (dec), yield 52%. (Found: C, 51·37; H, 2·43; N, 21·68. $C_{11}H_6N_4O_4$ requires: C, 51·17; H, 2·34; N, 21·70%.)

3-t-*Butyl*-4,5-*dihydro*-4-*oxoisoxazolo* [5.4-d] *pyrimidine*—colourless crystals from benzene–hexane, m.p. 259–263° (dec), yield 45%. (Found: C, 56·28; H, 5·43; N, 21·68. $C_9H_{11}N_3O_2$ requires: C, 55·95; H, 5·74; N, 21·75%.)

4-*Chloro*-3-(4-*chlorophenyl*)*isoxazolo* [5.4-d] *pyrimidine*. A mixture of 3-(4-chlorophenyl)4,5-dihydro-4-oxoisoxazolo-[5.4-d] pyrimidine (8·3 g) and pure $POCl_3$ (83 ml) was refluxed for 2·5 hr, cooled and evaporated to dryness under reduced press. The residue was triturated with a small quantity of benzene and the mixture again evaporated to dryness under reduced press. The residue was then treated with crushed ice and water and the solid that separated was filtered, washed thoroughly with water, dried and recrystallized from THF–pet. ether as colourless crystals, m.p. 190–192°, yield 5·4 g (61%). (Found: C, 50·08; H, 2·21; N, 15·79. $C_{11}H_5Cl_2N_3O$ requires: C, 49·65; H, 1·89; N, 15·79%.)

The following were similarly prepared.

4-*Chloro*-3-*phenylisoxazolo* [5.4-d] *pyrimidine*—colourless crystals from aqueous MeOH, m.p. 95–98°, yield 48%. (Found: C, 57·44; H, 2·89; N, 18·16. $C_{11}H_6ClN_3O$ requires: C, 57·03; H, 2·61; N, 18·14%.)

4-*Chloro*-3-(3-*nitrophenyl*)*isoxazolo* [5.4-d] *pyrimidine*—yellow crystals from THF, m.p. 163–167°, yield 50%. (Found: C, 47·76; H, 2·14; N, 20·24. $C_{11}H_5ClN_4O_3$ requires: C, 47·76; H, 1·82; N, 20·25%.)

4-*Amino*-3-(4-*chlorophenyl*)*isoxazolo* [5.4-d] *pyrimidine*. A mixture of 4-chloro-3-(4-chlorophenyl) isoxazolo [5.4-d] pyrimidine (7·9 g), 35% aqueous NH_4OH (50 ml) and EtOH (100 ml) saturated with NH_3 was refluxed for 5 hr, cooled and filtered. The residue was washed with water and recrystallized from MeOH as colourless crystals, m.p. 240–242°, yield 34%. (Found: C, 53·50; H, 3·10; N, 22·52. $C_{11}H_7ClN_4O$ requires: C, 53·56; H, 2·86; N, 22·71%.)

4-*Amino*-3-*phenylisoxazolo* [5.4-d] *pyrimidine* was prepared according to a similar procedure as colourless crystals from EtOH, m.p. 213–216° (reported[1]: 211–212°), yield 48%. (Found: C, 62·52; H, 4·07; N, 26·04. $C_{11}H_8N_4O$ requires: C, 62·25; H, 3·80; N, 26·40%.)

3-(4-*Chlorophenyl*)-4-(2-*dimethylaminoethyl*)*aminoisoxazolo*-[5.4-d] *pyrimidine*. A warm suspension of 4-chloro-3-(4-chlorophenyl)isoxazolo [5.4-d] pyrimidine (2·7 g) in anhyd benzene (200 ml) was added with agitation to a soln of 2-dimethylaminoethylamine (1·0 g) in anhyd benzene (15 ml). The resulting clear soln was refluxed for 3·5 hr, cooled and filtered. The filtrate was evaporated to dryness under reduced press and the residue triturated with sat $NaHCO_3$, filtered, washed with water, dried and recrystallized from hexane as colourless crystals, m.p. 140–143°, yield 1·1 g (36%). (Found: C, 56·72; H, 4·78. $C_{15}H_{16}ClN_5O$ requires: C, 56·69; H, 5·08%.)

3-(4-*Chlorophenyl*)-2-*diethylaminoisoxazolo* [5.4-d] *pyrimidine*. Powdered 4-chloro-3-(4-chlorophenyl) isoxazolo [5.4-d] pyrimidine (2·7 g) was added slowly with agitation to diethylamine (10 g). The mixture became hot and when it had cooled it was poured into water containing crushed ice. The solid that separated was filtered off, washed thoroughly with water and recrystallized from MeOH as colourless crystals, m.p. 139–143°, yield 1·7 g (57%). (Found: C, 59·42; H, 5·15; N, 18·23. $C_{15}H_{15}ClN_4O$ requires: C, 59·50; H, 4·99; N, 18·51%.)

3-(4-*Chlorophenyl*)-4-(1-*pyrrolidino*)*isoxazolo* [5.4-d] *pyrimidine*. The procedure was similar to that for the 4-diethylamino analogue. Colourless crystals from MeOH, m.p. 151–153°, yield 72% (Found: C, 60·16; H, 4·69; N, 18·56. $C_{15}H_{13}ClN_4O$ requires: C, 59·90; H, 4·36; N, 18·63%.)

3-(4-*Chlorophenyl*)-4-(1-*piperidino*)*isoxazolo* [5.4-d] *pyrimidine*. The method was similar to that for the 4-diethylamino analogue and it was obtained as colourless crystals from MeOH, m.p. 124–127°, yield 62%. (Found: C, 61·27; H, 4·84; N, 17·55. $C_{16}H_{15}ClN_4O$ requires: C, 61·05; H, 4·80; N, 17·80%.)

4-(1-*Methylpiperazin*-4-*yl*)-3-(3-*nitrophenyl*)*isoxazolo* [5.4-d] *pyrimidine*. The procedure was similar to that used for 3-(4-chlorophenyl)-4-diethylaminoisoxazolo [5.4-d] pyrimidine and was obtained as yellow crystals from MeOH, m.p. 155–157°, yield 35%. (Found: C, 56·70; H, 4·63; N, 24·83. $C_{16}H_{16}N_6O_3$ requires: C, 56·46; H, 4·74; N, 24·70%.)

4-(N-*Benzyl*-N-*methyl*)*amino*-3-(4-*chlorophenyl*)*isoxazolo*-[5.4-d] *pyrimidine*. A soln of 4-chloro-3-(4-chlorophenyl)isoxazolo [5.4-d] pyrimidine (500 mg) in anhyd THF (5 ml) was added to a soln of N-methylbenzylamine (500 mg) in anhyd ether (25 ml). The mixture was set aside for 30 min and then evaporated to dryness under reduced press. The sticky residue was washed with water and triturated with MeOH and filtered. The solid was recrystallized from the same solvent. Colourless crystals, m.p. 129–130°, yield 300 mg (43%). (Found: C, 65·43; H, 4·29; N, 15·74. $C_{19}H_{15}ClN_4O$ requires: C, 65·04; H, 4·31; N, 15·97%.)

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