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Preparation of 2*H*-Pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-ones and of the Corresponding Dihydropyridooxazines

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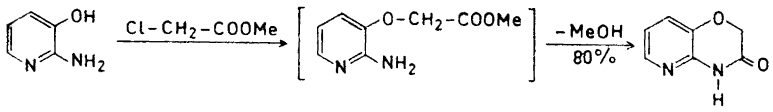
Seven 2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-ones have been prepared from 2-amino-3-pyridinol. Reduction of these with lithium aluminium hydride gave the corresponding dihydropyridooxazines. No dihydropyrido[3,2-*b*]-1,4-oxazines are known from the literature.

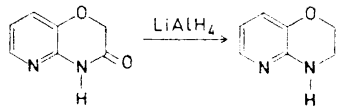
It has been found that a suspension of the sodium salt of 2-amino-3-pyridinol (I) in dimethyl sulfoxide (DMSO) reacts with chloroacetic acid methyl ester to give 2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one. We believe the reaction is initiated by an *O*-alkylation of the pyridinol (*cf.* Ref. 1) and thus proceeds through the intermediate 3-alkoxypyridine II.



I II III

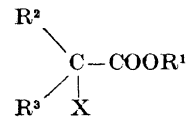
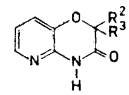
Six substituted halogenoacetic acid esters were found to react in the same way. The esters and the resulting 2-substituted pyridooxazin-3(4*H*)-ones are listed in Table 1.

Each of the pyridooxazin-3(4*H*)-ones were reduced by lithium aluminium hydride (LAH) to the corresponding dihydropyridooxazines (X—XVI) in good yields.



III X

Table 1. Syntheses of pyridooxazin-3(4*H*)-ones.

Alkylating agents				Pyridooxazin-3(4*H*)-ones	
					
X	R^1	R^2	R^3	No.	Yield %
Br	C_2H_5	H	CH_3	IV	74
Br	C_2H_5	H	C_2H_5	V	64
Br	CH_3	H	n-C_4H_9	VI	80
Br	C_2H_5	CH_3	CH_3	VII	46
Br	CH_3	H	C_6H_5	VIII	71
Cl	CH_3	C_6H_5	C_6H_5	IX	61

All fourteen compounds described above are new. None of them gave a color reaction with iron(III) chloride solution. This, together with the syntheses and the analytical evidence, proves the proposed structures. No other dihydropyrido[3,2-*b*]-1,4-oxazines are known from the literature.

EXPERIMENTAL

*2H-Pyrido[3,2-*b*]-1,4-oxazin-3(4H)-one (III).* 2-Amino-3-pyridinol (I) (11.0 g, 0.100 mol) is dissolved in a solution of sodium methoxide in methanol [from sodium (2.30 g, 0.100 mol) and methanol (50 ml)]. DMSO (100 ml) is added and the clear solution distilled under 10 mm, until pure DMSO begins to distil (b.p.$_{10}$ 69°). The remaining methanol-free suspension of the sodium salt of I is cooled to 20°. Methyl chloroacetate (10.9 g, 0.100 mol) is added in one portion and the mixture shaken. The mixture rapidly becomes dark and almost homogeneous, while the temperature rises to about 50°. After shaking for 15 min the mixture is evaporated to dryness from a water bath (100°) under 10 mm. The hot, semisolid residue is shaken with methanol (20 ml) and then with water (50 ml). The resulting suspension of crystals is cooled to 10°. Filtration, washing with water and methanol, and drying (100°) gives III (12.0 g; 80 %) as slightly grey needles, m.p. 205—206°. [Found: C 55.8; H 4.3; N 18.7. Calc. for $C_7H_6N_2O_2$ (150.1): C 56.0; H 4.0; N 18.7]. Crystallization from methanol gives white needles with the same m.p.

The six 2-substituted pyridooxazin-3(4*H*)-ones were prepared in the same way as described above for the parent compound.

*2-Methyl-2H-pyrido[3,2-*b*]-1,4-oxazin-3(4H)-one (IV).* From ethyl 2-bromopropionate (18.1 g, 0.100 mol); yield 12.2 g (74 %) of IV, m.p. 169—171°. Crystallization from 99 % ethanol (250 ml) gave 11.2 g with the same m.p. [Found: C 58.5; H 5.2; N 17.2. Calc. for $C_8H_8N_2O_2$ (164.2): C 58.5; H 4.9; N 17.1].

*2-Ethyl-2H-pyrido[3,2-*b*]-1,4-oxazin-3(4H)-one (V).* From ethyl 2-bromobutyrate (19.5 g, 0.100 mol); the reaction mixture was kept below 30° during the first 15 min of

the reaction. Yield 11.4 g (64 %) of V, m.p. 141–142° (from ethanol). [Found: C 60.8; H 5.7; N 15.6. Calc. for $C_9H_{10}N_2O_2$ (178.2): C 60.7; H 5.7; N 15.7].

*2-Butyl-2*H-*pyrido*[*3,2*-b]-*1,4-oxazin-3*(*4*H)-*one* (*VI*). From methyl 2-bromohexanoate (20.9 g, 0.100 mol), using 170 ml of DMSO. Yield 16.4 g (80 %) of VI, m.p. 137–138°. [Found: C 64.3; H 7.0; N 13.5. Calc. for $C_{11}H_{14}N_2O_2$ (206.2): C 64.1; H 6.8; N 13.6].

*2,2-Dimethyl-2*H-*pyrido*[*3,2*-b]-*1,4-oxazin-3*(*4*H)-*one* (*VII*). From ethyl 2-bromo-2-methylpropionate (19.5 g, 0.100 mol); yield 8.2 g (46 %) of VII, m.p. 146–148° (from methanol). [Found: C 60.6; H 5.9; N 15.8. Calc. for $C_9H_{10}N_2O_2$ (178.2): C 60.7; H 5.7; N 15.7].

*2-Phenyl-2*H-*pyrido*[*3,2*-b]-*1,4-oxazin-3*(*4*H)-*one* (*VIII*). From methyl bromophenylacetate (22.9 g, 0.100 mol); the reaction mixture was cooled during the reaction. Yield 16.0 g (71 %) of VIII, m.p. 201–202° (from methanol). [Found: C 69.1; H 4.4; N 12.2; O 14.2. Calc. for $C_{13}H_{10}N_2O_2$ (226.2): C 69.0; H 4.5; N 12.4; O 14.1].

*2,2-Diphenyl-2*H-*pyrido*[*3,2*-b]-*1,4-oxazin-3*(*4*H)-*one* (*IX*). From methyl chlorodiphenylacetate (26.1 g, 0.100 mol); the reaction mixture was left standing at room temperature overnight, before being worked up. Yield 18.5 g (61 %), m.p. in an evacuated tube 239–241° (from methanol). [Found: C 75.5; H 4.9; N 9.5. Calc. for $C_{19}H_{14}N_2O_2$ (302.3): C 75.5; H 4.7; N 9.3].

*3,4-Dihydro-2*H-*pyrido*[*3,2*-b]-*1,4-oxazine* (*X*). III (15.0 g, 0.100 mol) is added in small portions with stirring to LAH (5.7 g, 0.15 mol) in ether (200 ml) and the mixture heated with stirring under reflux for 90 h. Water is added dropwise with cooling and stirring, until a coarse powder or a stiff paste (aqueous phase) is obtained. The ethereal layer is removed by decantation and the aqueous phase washed with ether. Distillation of the ethereal extract gives 11.6 g (85 %) of X, b.p.$_{0.5}$ 115°. Crystallization from ether gives 10.4 g of white needles, m.p. 86–87°. [Found: C 61.8; H 6.2; N 20.6. Calc. for $C_7H_8N_2O$ (136.2): C 61.8; H 5.9; N 20.6].

The six 2-substituted dihydropyridooxazines were prepared in the same way as described above for the parent compound.

*3,4-Dihydro-3-methyl-2*H-*pyrido*[*3,2*-b]-*1,4-oxazine* (*XI*). From IV; yield 12.3 g (82 %) of XI, m.p. 102–103° (from ether). [Found: C 63.9; H 6.9; N 18.4. Calc. for $C_8H_{10}N_2O$ (150.2): C 64.0; H 6.7; N 18.7].

*2-Ethyl-3,4-dihydro-2*H-*pyrido*[*3,2*-b]-*1,4-oxazine* (*XII*). From V; yield 13.6 g (83 %) of XII, m.p. 89–93° (from ether). Another crystallization gave material with m.p. 92–93°. [Found: C 65.8; H 7.5; N 17.0. Calc. for $C_9H_{12}N_2O$ (164.2): C 65.8; H 7.4; N 17.1].

*2-Butyl-3,4-dihydro-2*H-*pyrido*[*3,2*-b]-*1,4-oxazine* (*XIII*). From VI; yield 14.8 g (77 %) of XIII, m.p. 61–63° [from benzine (b.p. 40–65°)]. [Found: C 68.6; H 8.4; N 14.5. Calc. for $C_{11}H_{16}N_2O$ (192.3): C 68.7; H 8.4; N 14.6].

*3,4-Dihydro-2,2-dimethyl-2*H-*pyrido*[*3,2*-b]-*1,4-oxazine* (*XIV*). From VII; yield 11.0 g (67 %) of XIV, m.p. 97–99° (from ether). [Found: C 65.6; H 7.3; N 16.9. Calc. for $C_9H_{12}N_2O$ (164.2): C 65.8; H 7.4; N 17.1].

*3,4-Dihydro-2-phenyl-2*H-*pyrido*[*3,2*-b]-*1,4-oxazine* (*XV*). From VIII; yield 14.6 g (69 %) of XV, m.p. 118–120° [from methanol-benzine (b.p. 100–140°)]. [Found: C 73.8; H 5.7; N 13.2. Calc. for $C_{13}H_{12}N_2O$ (212.2): C 73.6; H 5.7; N 13.2].

*3,4-Dihydro-2,2-diphenyl-2*H-*pyrido*[*3,2*-b]-*1,4-oxazine* (*XVI*). From IX; the solubility of the reaction product in ether is so small that continuous extraction (Soxhlet apparatus) of the aqueous phase (coarse powder) with ether is necessary. Yield 18.6 g (65 %) of XVI, m.p. 169–171° (from methanol). [Found: C 79.0; H 5.7; N 9.8. Calc. for $C_{19}H_{16}N_2O$ (288.3): C 79.1; H 5.6; N 9.7].

Iron(III) chloride reactions. All new compounds gave no color reaction with iron(III) chloride in aqueous alcoholic solution.

REFERENCE

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