ACTA CHEMICA SCANDINAVICA 25 (1971) 3135–3143

Reactions of 3,4-Dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazines

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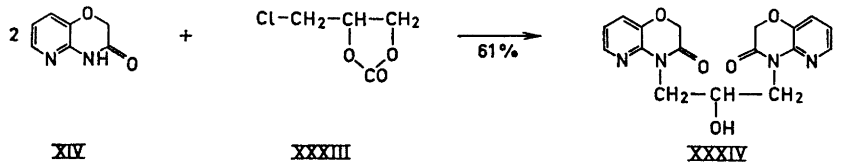
Dihydropyrido[3,2-*b*]-1,4-oxazines have recently been prepared.[1] Reactions of members of this new series of compounds with alkylating agents, lithium aluminium hydride, bromine, copper(I) cyanide, and phosphorus sulfide have been investigated.

3,4-Dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazines and 2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-ones have recently been prepared for the first time.[1] This paper describes a number of reactions carried out with these new bicyclic compounds.

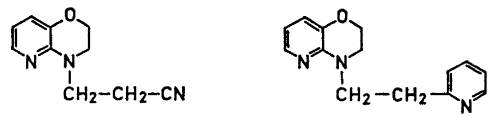
Both the dihydropyridooxazines and the pyridooxazinones have, as sodium salts in dimethyl sulfoxide, been alkylated in 4-position with alkylhalides. 23 4-substituted compounds have been prepared in this way (Tables 1 and 2).

Alkylation of the parent pyridooxazinone (XIV) with 3-chloro-1,2-propanediol cyclic carbonate (XXXIII) under the same conditions gave reaction at both ends of the propane derivative (compound XXXIV).



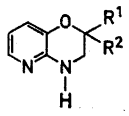
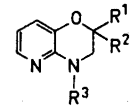
XIV XXXIII XXXIV

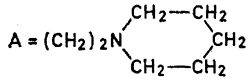
The parent dihydropyridooxazine (I) was also alkylated in 4-position by reaction with acrylonitrile and with 2-vinylpyridine to give, respectively, compounds XXXV and XXXVI.



XXXV (yield 75 %) XXXVI (yield 44 %)

Table 1. 4-Alkylation of 3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazines.

Starting material			Alkylating agent XR^3		Reaction product	
						
No.	R^1	R^2	X	R^3	No.	Yield %
I	H	H	Br	$CH_2CH=CH_2$	IV	41
I	H	H	Br	$(CH_2)_3CH_3$	V	28
I	H	H	Br	$CH_2C_6H_5$	VI	56
I	H	H	Cl	A	VII	35
I	H	H	Cl	$(CH_2)_3N(CH_3)_2$	VIII	52
II	H	C_6H_5	I	CH_3	IX	56
III	C_6H_5	C_6H_5	Cl	$(CH_2)_2N(CH_3)_2$	X	47
III	C_6H_5	C_6H_5	Cl	$(CH_2)_2N(C_2H_5)_2$	XI	44
III	C_6H_5	C_6H_5	Cl	$(CH_2)_3N(CH_3)_2$	XII	57
III	C_6H_5	C_6H_5	Cl	B	XIII	25



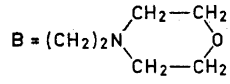
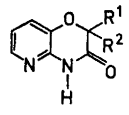
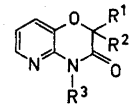


Table 2. 4-Alkylation of 2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-ones.

Starting material			Alkylating agent XR^3		Reaction product	
						
No.	R^1	R^2	X	R^3	No.	Yield %
XIV	H	H	I	CH_3	XX	75
XIV	H	H	Br	$CH_2CH=CH_2$	XXI	55
XIV	H	H	Br	$CH_2C_6H_5$	XXII	70
XIV	H	H	Cl	$(CH_2)_3N(CH_3)_2$	XXIII	65
XV	H	CH_3	Br	$CH_2C_6H_5$	XXIV	86
XVI	H	C_2H_5	I	CH_3	XXV	75
XVI	H	C_2H_5	Cl	$(CH_2)_3N(CH_3)_2$	XXVI	79
XVII	H	C_6H_5	I	CH_3	XXVII	70
XVIII	CH_3	CH_3	I	CH_3	XXVIII	66
XVIII	CH_3	CH_3	Br	$CH_2CH=CH_2$	XXIX	68
XVIII	CH_3	CH_3	Cl	$(CH_2)_3N(CH_3)_2$	XXX	76
XIX	C_6H_5	C_6H_5	Br	$CH_2C_6H_5$	XXXI	62
XIX	C_6H_5	C_6H_5	Cl	$(CH_2)_3N(CH_3)_2$	XXXII	57

Heating of 4-substituted pyridooxazinones with lithium aluminium hydride (LAH) under reflux in ether for a short period (20 min) gave the corresponding 3-hydroxy derivatives, five of which have been prepared (Table 3).

When similar reactions were carried out for 48 h, mixtures of the 3-hydroxy derivatives and the corresponding des-hydroxy compounds were obtained. Three reactions of this type have been carried out (Table 4).

Table 3. Short-period reduction of 4-substituted 2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-ones with LAH.

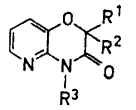
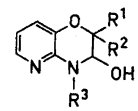
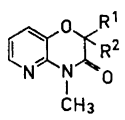
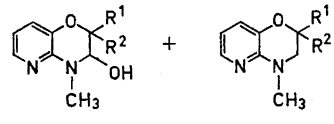
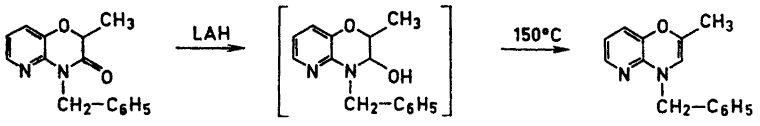
Starting material				Reaction product	
					
No.	R^1	R^2	R^3	No.	Yield %
XXIII	H	H	$(CH_2)_3N(CH_3)_2$	XXXVII	85
XXIX	CH_3	CH_3	$CH_2CH=CH_2$	XXXVIII	95
XXX	CH_3	CH_3	$(CH_2)_3N(CH_3)_2$	XXXIX	94
XXXI	C_6H_5	C_6H_5	$CH_2C_6H_5$	XL	60
XXXII	C_6H_5	C_6H_5	$(CH_2)_3N(CH_3)_2$	XLI	86

Table 4. Long-period reduction of 4-methyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-ones with LAH.

Starting material			Reaction products			
						
No.	R^1	R^2	No.	Yield %	No.	Yield %
XX	H	H	XLII	18	XLV	53
XXV	H	C_2H_5	XLIII	15	XLVI	34
XXVIII	CH_3	CH_3	XLIV	18	XLVII	38

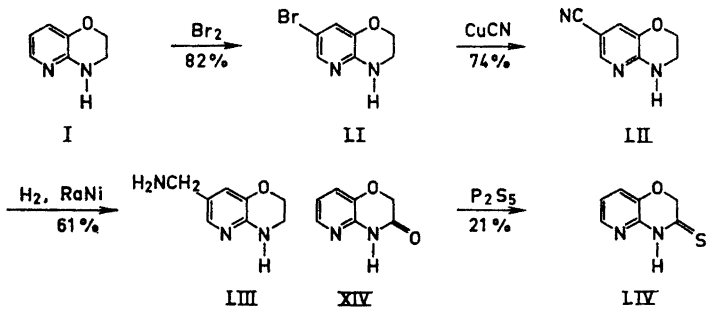
It was further found that short-period reduction of 4-benzyl-2-methylpyridooxazinone (XXIV) with LAH and distillation of the reaction product gave a 93 % yield of a mixture of the expected 3-hydroxy compound (XLVIII) and its dehydration product (XLIX). By heating this mixture to 150°C for 2 h pure XLIX was obtained. 4-(3-Dimethylaminopropyl)-2-ethyl-



XXIV XLVIII XLIX

pyridooxazinone (XXVI) similarly gave the dehydration product L (yield 92 %).

Finally the reaction sequences shown below were carried out starting from the parent compounds I and XIV.



I LI LII LIII XIV LIV

All reaction products (43 compounds) mentioned above are new. Their structures follow from the syntheses and from analyses, and additionally, in the case of compound LI, from the ^{1}H NMR spectrum. IR spectra of XXVII – XXXIX confirmed the structures proposed for these compounds.

EXPERIMENTAL

*4-Allyl-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine (IV) hydrochloride.* From 3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine [1] (I) (13.6 g, 0.100 mol) and 3-bromopropene (12.1 g, 0.100 mol) after the general recipe published recently [2] for the *O*-alkylation of 3-pyridinols. Impure IV (12.3 g) was isolated by distillation, b.p.$_{0.3}$ about 80°C. The base was dissolved in ether (150 ml) and the crystalline hydrochloride precipitated with hydrogen chloride. Isolation of the hydrochloride by filtration followed by two crystallizations from 2-propanol gave 8.80 g (41 %) of IV hydrochloride, m.p. 149 – 150°C. [Found: C 56.6; H 6.2; Cl 16.5; N 13.1. Calc. for $C_{10}H_{13}ClN_2O$ (212.7): C 56.5; H 6.2; Cl 16.7; N 13.2.]

The following 22 alkylations were all carried out after the recipe mentioned above.

*4-Butyl-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine (V) hydrochloride.* From I and 1-bromobutane. Impure V (15.6 g) was isolated by distillation, b.p. $_{0.1}$ 79°C. Transformation of the base into the hydrochloride as above, and crystallization from ether – 2-propanol (2:1) and then from acetone gave 6.5 g (28 %) of V hydrochloride, m.p. 120 – 121°C. [Found: C 57.8; H 7.4; Cl 15.7; N 12.4. Calc. for $C_{11}H_{17}ClN_2O$ (228.7): C 57.8; H 7.5; Cl 15.5; N 12.2.]

*4-Benzyl-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine (VI) hydrochloride.* From I and α-bromotoluene. VI (16.5 g) was isolated by distillation, b.p.$_{0.2}$ 125 – 126°C, n_D^{25} 1.6148. The base was dissolved in 2-propanol (110 ml) and the crystalline hydrochloride precipitated with hydrogen chloride. Filtration and drying gave 14.8 g (56 %) of VI

hydrochloride with constant m.p. (167–169°C). [Found: C 63.9; H 6.0; Cl 13.6; N 10.7. Calc. for $C_{14}H_{15}ClN_2O$ (262.7): C 64.0; H 5.8; Cl 13.5; N 10.7.]

*3,4-Dihydro-4-(2-piperidinoethyl)-2*H*-pyrido[3,2-*b*]-1,4-oxazine (VII) dihydrochloride.* From I and 1-(2-chloroethyl)-piperidine. Impure VII (10.7 g) was isolated by distillation, b.p. $_{0.1}$ 122–126°C. The base was dissolved in an excess of hydrochloric acid. The solution was evaporated to dryness from a water bath (90°C) under 10 mm. Crystallization of the residue from 2-propanol (225 ml) gave 11.2 g (35 %) of VII dihydrochloride, m.p. in an evacuated tube 238–242°C. [Found: C 52.1; H 7.4; Cl 22.0; N 13.0. Calc. for $C_{14}H_{23}Cl_2N_3O$ (320.3): C 52.6; H 7.2; Cl 22.1; N 13.1.]

*3,4-Dihydro-4-(3-dimethylaminopropyl)-2*H*-pyrido[3,2-*b*]-1,4-oxazine (VIII) dihydrochloride.* From I and 1-chloro-3-dimethylaminopropane. VIII (15.8 g) was isolated by distillation, b.p.$_{0.2}$ 101–103°C, n_D^{25} 1.5470. The base was transformed into the dihydrochloride as described in the preceding preparation. Crystallization from 2-propanol and then from ethanol gave 15.4 g (52 %) of VIII dihydrochloride as white, hygroscopic needles, m.p. >200°C. [Found: C 48.1; H 7.6; Cl 24.6; N 14.2. Calc. for $C_{12}H_{21}Cl_2N_3O$ (294.2): C 49.0; H 7.2; Cl 24.1; N 14.3.]

*3,4-Dihydro-4-methyl-2-phenyl-2*H*-pyrido[3,2-*b*]-1,4-oxazine (IX).* From 3,4-dihydro-2-phenyl-2*H*-pyrido[3,2-*b*]-1,4-oxazine (II) and iodomethane; yield 12.7 g (56 %) of IX, b.p.$_{0.1}$ 160°C, m.p. 75–76°C [from ether–benzine (b.p. 40–65°C) (1:5)]. [Found: C 74.4; H 6.4; N 12.2. Calc. for $C_{14}H_{14}N_2O$ (226.3): C 74.3; H 6.2; N 12.4.]

*3,4-Dihydro-4-[2-(dimethylamino)ethyl]-2,2-diphenyl-2*H*-pyrido[3,2-*b*]-1,4-oxazine (X).* From 3,4-dihydro-2,2-diphenyl-2*H*-pyrido[3,2-*b*]-1,4-oxazine (III) and 1-chloro-2-dimethylaminoethane; yield 16.8 g (47 %), m.p. 119–121°C (from methanol). [Found: C 77.0; H 7.1; N 11.8. Calc. for $C_{23}H_{25}N_3O$ (359.5): C 76.9; H 7.0; N 11.7.]

*4-[2-(Diethylamino)ethyl]-3,4-dihydro-2,2-diphenyl-2*H*-pyrido[3,2-*b*]-1,4-oxazine (XI) dihydrochloride.* From III and 1-chloro-2-diethylaminoethane. Impure XI (39.2 g) was isolated by evaporation to dryness of a chloroform extract from a water bath (100°) under 10 mm. The base was dissolved in an excess of hydrochloric acid. The solution was evaporated to dryness from a water bath (100°C) under 10 mm. Two crystallizations of the residue from ethanol gave 20.2 g (44 %) of XI dihydrochloride, m.p. 240–244°C (decomp.). [Found: C 64.8; H 7.0; Cl 15.1; N 9.2. Calc. for $C_{25}H_{31}Cl_2N_3O$ (460.4): C 65.2; H 6.8; Cl 15.4; N 9.1.]

*3,4-Dihydro-4-[3-(dimethylamino)propyl]-2,2-diphenyl-2*H*-pyrido[3,2-*b*]-1,4-oxazine (XII) dihydrochloride.* From III and 1-chloro-3-dimethylaminopropane. Impure XII (28.2 g) was isolated by distillation, b.p.$_{0.2}$ 201–202°C. The base was transformed into the dihydrochloride as described in the preceding preparation. Crystallization from 2-propanol and then from ethanol gave 25.4 g (57 %) of XII dihydrochloride as white crystals, m.p. >250°C. [Found: C 64.4; H 6.7; Cl 15.8; N 9.2. Calc. for $C_{24}H_{29}Cl_2N_3O$ (446.4): C 64.6; H 6.5; Cl 15.9; N 9.4.]

*3,4-Dihydro-2,2-diphenyl-4-(2-morpholinoethyl)-2*H*-pyrido[3,2-*b*]-1,4-oxazine (XIII) dihydrochloride.* From III and 4-(2-chloroethyl)morpholine. Impure XIII (40.0 g) was isolated by evaporation to dryness of a chloroform extract from a water bath (100°C) under 10 mm. Crystallization from methanol–water (5:1) (120 ml) and then from ether (180 ml) gave 16.8 g of material, m.p. 70–100°C. Dissolution in methanol (40 ml) and 2-propanol (90 ml), addition of conc. hydrochloric acid (13.4 ml), and cooling of the solution to −20°C gave crystals of XIII dihydrochloride. The crystals were isolated by filtration and crystallized from methanol, yielding 11.8 g (25 %) of XIII dihydrochloride, m.p. 252–254°C (decomp.). [Found: C 63.1; H 6.2; Cl 14.3; N 8.7. Calc. for $C_{25}H_{29}Cl_2N_3O_2$ (474.4): C 63.3; H 6.2; Cl 14.9; N 8.9.]

*4-Methyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XX).* From 2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XIV) and iodomethane; yield 12.3 g (75 %), m.p. 70–71°C. [Found: C 58.7; H 4.8; N 17.2. Calc. for $C_8H_8N_2O_2$ (164.2): C 58.5; H 4.9; N 17.1.]

*4-Allyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XXI).* From XIV and 3-bromopropene; yield 10.4 g (55 %), b.p.$_{0.1}$ 91°C. n_D^{25} 1.5749, m.p. 27–30°C. [Found: C 62.9; H 5.5; N 14.6; O 17.0. Calc. for $C_{10}H_{10}N_2O_2$ (190.2): C 63.2; H 5.3; N 14.7; O 16.8.]

*4-Benzyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XXII).* From XIV and α-bromotoluene; yield 16.8 g (70 %), m.p. 59–60°C (from methanol). [Found: C 70.2; H 5.2; N 11.6. Calc. for $C_{14}H_{12}N_2O_2$ (240.3): C 70.0; H 5.0; N 11.7.]

*4-[3(Dimethylamino)propyl]-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XXIII).* From XIV and 1-chloro-3-dimethylaminopropane; yield 15.4 g (65 %), b.p.$_{0.1}$ 114–116°C,

n_D^{25} 1.5465. [Found: C 61.2; H 7.4; N 18.0. Calc. for $C_{12}H_{17}N_3O_2$ (235.3): C 61.3; H 7.3; N 17.9.]

*4-Benzyl-2-methyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XXIV).* From 2-methyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XV) and α-bromotoluene; yield 21.9 g (86 %), m.p. 75–76°C (from methanol). [Found: C 71.0; H 5.7; N 11.1. Calc. for $C_{15}H_{14}N_2O_2$ (254.3): C 70.9; H 5.6; N 11.0.]

*2-Ethyl-4-methyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XXV).* From 2-ethyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XVI) and iodomethane; yield 14.4 g (75 %), $b.p._{0.04}$ 73°C, n_D^{25} 1.5532. [Found: C 62.5; H 6.2; N 14.5. Calc. for $C_{10}H_{12}N_2O_2$ (192.2): C 62.5; H 6.3; N 14.6.]

*4-[3(Dimethylamino)propyl]-2-ethyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XXVI).* From XVI and 1-chloro-3(dimethylamino)propane. The alkylation was carried out at 70°C over a period of 40 h. XXVI was isolated by distillation; yield 20.8 g (79 %), $b.p._{0.06}$ 115–120°C, n_D^{25} 1.5308. [Found: C 64.0; H 8.1; N 16.3. Calc. for $C_{14}H_{21}N_3O_2$ (263.3): C 63.9; H 8.0; N 16.0.]

*4-Methyl-2-phenyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XXVII).* From 2-phenyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XVII) and iodomethane; yield 16.8 g (70 %), m.p. 72–73°C (from ether). [Found: C 69.9; H 5.1; N 11.7. Calc. for $C_{14}H_{12}N_2O_2$ (240.3): C 70.0; H 5.0; N 11.7.]

*2,2,4-Trimethyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XXVIII).* From 2,2-dimethyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XVIII) and iodomethane; yield 12.7 g (66 %), $b.p._{0.5}$ 74°C, m.p. 42–44°C (from ether). [Found: C 62.6; H 6.2; N 14.6. Calc. for $C_{10}H_{12}N_2O_2$ (192.2): C 62.5; H 6.3; N 14.6.]

*4-Allyl-2,2-dimethyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XXIX).* From XVIII and 3-bromopropene; yield 14.8 g (68 %), $b.p._9$ 137°C, n_D^{25} 1.5444. [Found: C 66.1; H 6.6; N 13.0. Calc. for $C_{12}H_{14}N_2O_2$ (218.3): C 66.0; H 6.5; N 12.8.]

*2,2-Dimethyl-4[3(dimethylamino)propyl]-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XXX).* From XVIII and 1-chloro-3(dimethylamino)propane. The alkylation was carried out at 70°C over a period of 40 h. XXX was isolated by distillation, yield 20.0 g (76 %), $b.p._{0.2}$ 106–107°C, n_D^{25} 1.5272. [Found: C 64.2; H 8.1; N 16.2. Calc. for $C_{14}H_{21}N_3O_2$ (263.3): C 63.9; H 8.0; N 16.0.]

*4-Benzyl-2,2-diphenyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XXXI).* From 2,2-diphenyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XIX) and α-bromotoluene; yield 24.3 g (62 %), m.p. 115–116°C (from methanol). [Found: C 79.6; H 5.2; N 6.9. Calc. for $C_{26}H_{20}N_2O_2$ (392.4): C 79.6; H 5.1; N 7.1.]

*4-[3(Dimethylamino)propyl]-2,2-diphenyl-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (XXXII) hydrochloride.* From XIX and 1-chloro-3(dimethylamino)propane. Impure XXXII (43 g) was isolated by evaporation of a chloroform extract from a water bath (100°C) under 10 mm. Two crystallizations from cyclohexane gave 29 g of material, m.p. 79–87°C. Dissolution in 2-propanol (500 ml), water (150 ml), and conc. hydrochloric acid (26 ml), and evaporation of the solution to dryness from a water bath (100°C) under 10 mm gave impure XXXII hydrochloride (34 g). Crystallization from methanol (1300 ml) gave 24.0 g (57 %) of XXXII hydrochloride, m.p. >250°C. [Found: C 67.6; H 6.1; Cl 8.0; N 9.8. Calc. for $C_{24}H_{26}ClN_3O_2$ (423.9): C 68.1; H 6.2; Cl 8.4; N 9.9.] Liberation of XXXII from the hydrochloride in the usual way gave pure XXXII, m.p. 91–92°C.

*1,3-Bis{2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-on-4-yl}-2-propanol (XXXIV).* XIV (7.5 g, 0.050 mol) was added to a solution of sodium methoxide in methanol [from sodium (1.15 g, 0.050 mol) and methanol (20 ml)]. DMSO (75 ml) was added and the mixture distilled from a water bath under 10 mm, until DMSO began to distil ($b.p._{10}$ 69°C). A solution of 3-chloro-1,2-propanediol cyclic carbonate (3.4 g, 0.025 mol) in DMSO (10 ml) was added to the methanol-free suspension of the sodium salt of XIV in DMSO. The mixture was kept at 80° for 60 h. Some carbon dioxide was evolved during the reaction. After cooling to 20°C water (400 ml) was added to the reaction mixture. The resulting precipitate of greyish brown crystals was isolated by filtration, washed with water, and dried (6.6 g). Crystallization from acetone (1000 ml) with carbon black gave 5.4 g (61 %) of XXXIV as almost white crystals, m.p. 214°C. [Found: C 57.3; H 4.6; N 15.8. Calc. for $C_{17}H_{16}N_4O_5$ (356.3): C 57.3; H 4.5; N 15.7.]

*4-(2-Cyanoethyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine (XXXV).* I (27.2 g, 0.200 mol) and a 40 % solution of Triton B in methanol (2 ml) were dissolved in benzene (200 ml). Acrylonitrile (30 ml, 0.45 mol) was added dropwise with stirring at 25°C over a

period of 30 min. The reaction mixture was heated under reflux (16 h). After cooling to room temperature the benzene solution was decanted from some sticky material, washed with water, dried with magnesium sulfate, and distilled. 28.3 g (75 %) of XXXV was hereby obtained, b.p.$_{0.1}$ 113°C, n_D^{25} 1.5700. [Found: C 63.7; H 5.9; N 22.5. Calc. for $C_{10}H_{11}N_3O$ (189.2): C 63.5; H 5.9; N 22.2.]

3,4-Dihydro-4-[2-(2-pyridyl)ethyl]-2H-pyrido[3,2-b]-1,4-oxazine (XXXVI) dihydrochloride. I (5.45 g, 0.0400 mol), 2-vinylpyridine (4.32 ml, 0.0400 mol), and sodium methoxide (0.22 g, 0.0040 mol) were mixed and the resulting suspension stirred (45 h) at 25°C. The very dark reaction mixture was heated to 100°C and kept at this temperature for 15 min. After cooling to room temperature 0.5 N sodium hydroxide (100 ml) was added and the mixture extracted with chloroform (50 ml). The chloroform extract was dried with magnesium sulfate and distilled. The fraction with b.p.$_{0.4}$ 148–152°C, n_D^{25} 1.6027 was collected (6.98 g). This fraction (probably pure XXXVI) was dissolved in an excess of 3 N hydrochloric acid and the solution evaporated to dryness from a water bath under 10 mm. Crystallization of the residue from ethanol, and drying of the resulting crystals (7 h, 70°C, 0.1 mm) gave 5.5 g (44 %) of XXXVI dihydrochloride as almost white, hydroscopic crystals, m.p. 196–199°C. [Found: C 52.9; H 5.7; Cl 22.4; N 13.2. Calc. for $C_{14}H_{17}Cl_2N_3O$ (314.2): C 53.5; H 5.5; Cl 22.6; N 13.4.]

3,4-Dihydro-4-[3-(dimethylamino)propyl]-2H-pyrido[3,2-b]-1,4-oxazin-3-ol (XXXVII). A solution of XXIII (7.2 g, 0.031 mol) in ether (20 ml) was added dropwise with stirring over a period of 2–3 min to a cooled mixture of LAH (1.2 g, 0.030 mol) in ether (50 ml). The reaction mixture was heated under reflux (20 min) and then cooled to 0°C. Water (5.5 ml) was added dropwise with stirring and cooling over a period of 5–10 min. The mixture was heated under reflux (30 min), whereafter evolution of hydrogen ceased. Filtration, and washing of the filter cake with ether (25 ml) gave an ethereal solution of XXXVII. Distillation of this solution gave 6.2 g (85 %) of XXXVII as a slightly yellow oil, b.p.$_{0.04}$ 117–119°C, n_D^{25} 1.5579. [Found: C 60.2; H 8.2; N 17.6. Calc. for $C_{12}H_{19}N_3O_2$ (237.3): C 60.7; H 8.1; N 17.7.] The IR spectrum showed no carbonyl group absorption.

4-Allyl-3,4-dihydro-2,2-dimethyl-2H-pyrido[3,2-b]-1,4-oxazin-3-ol (XXXVIII). From XXIX (10.9 g, 0.050 mol) as described in the preceding preparation. The final ethereal solution of XXXVIII was evaporated to dryness and the residue dried at 50°C, 0.1 mm; Yield 10.4 g (95 %) of XXVIII, white crystals, m.p. 69–70°C. [Found: C 65.5; H 7.3 N 12.7. Calc. for $C_{12}H_{16}N_2O_2$ (220.3): C 65.4; H 7.3; N 12.7.] The IR spectrum showed no carbonyl group absorption.

3,4-Dihydro-2,2-dimethyl-4-[3-(dimethylamino)propyl]-2H-pyrido[3,2-b]-1,4-oxazin-3-ol (XXXIX). From XXX (10.0 g, 0.038 mol) as described in the preparation of XXXVII. The yield was 9.5 g (94 %) of XXXIX, colorless oil, b.p.$_{0.04}$ 103–110°C, n_D^{25} 1.5446. [Found: C 63.0; H 8.8; N 15.7. Calc. for $C_{14}H_{23}N_3O_2$ (265.4): C 63.4; H 8.7; N 15.8.] The IR spectrum showed no carbonyl group absorption.

4-Benzyl-3,4-dihydro-2,2-diphenyl-2H-pyrido[3,2-b]-1,4-oxazin-3-ol (XL). XXXI (7.5 g, 0.019 mol) was added in small portions over a period of 2–3 min to a cooled mixture of LAH (0.75 g, 0.020 mol) in ether (70 ml). The reaction mixture was heated under reflux (20 min) and then cooled to 0°C. Water (4.0 ml) was added dropwise with stirring and cooling over a period of 5–10 min. The mixture was heated under reflux (30 min). Filtration and continuous extraction of the filter cake in a Soxhlet-type apparatus (5 h) gave, by combination of the ethereal solutions and evaporation, crystals (6.7 g) of crude XL. Crystallization from 2-propanol (200 ml) with carbon black gave 4.5 g (60 %) of XL as white crystals, m.p. 170–172°C (decomp.). [Found: C 79.0; H 5.8; N 7.1. Calc. for $C_{26}H_{22}N_2O_2$ (394.5): C 79.2; H 5.6; N 7.1.]

3,4-Dihydro-4-[3-(dimethylamino)propyl]-2,2-diphenyl-2H-pyrido[3,2-b]-1,4-oxazin-3-ol (XLI). XXXII (4.5 g, 0.012 mol) was added in small portions over a period of 2–3 min to a cooled mixture of LAH (0.46 g, 0.012 mol) and ether (75 ml). The reaction mixture was heated under reflux (20 min) and then cooled to 0°C. Ether (400 ml) was added in one portion. Water (2.5 ml) was added dropwise with stirring and cooling over a period of 5–10 min. The mixture was heated under reflux (30 min) and then worked up as described in the preceding preparation (yield 4.3 g of crude XLI). Crystallization from water (25 ml) and ethanol (30 ml) gave 3.9 g (86 %) of XLI as white crystals, m.p. 149–150°C. [Found: C 74.0; H 7.1; N 10.7. Calc. for $C_{24}H_{27}N_3O_2$ (389.5): C 74.0; H 7.0; N 10.8.]

*3,4-Dihydro-4-methyl-2*H-*pyrido*[*3,2*-b]-*1,4-oxazin-3-ol (XLII) and 3,4-dihydro-4-methyl-2*H-*pyrido*[*3,2*-b]-*1,4-oxazine (XLV)*. XX (16.7 g, 0.102 mol) and LAH (4.9 g, 0.13 mol) were stirred with ether (200 ml) under reflux (48 h). The reaction mixture was cooled to 0° and water added dropwise with stirring and cooling, until a rather stiff paste (aqueous phase) in ether was obtained. The ethereal layer was removed by decantation and the paste washed with ether by decantation. Evaporation of the ethereal extract and distillation of the residue gave 8.15 g (53 %) of XLV as a slightly yellow liquid, b.p.$_{0.7-0.8}$ 78 – 85°C, n_D^{25} 1.5793. [Found: C 63.9; H 6.5; N 18.8. Calc. for $C_8H_{10}N_2O$ (150.2): C 64.0; H 6.7; N 18.7.] The product turned stronger yellow on standing. The semisolid residue from the distillation was dissolved in boiling water (150 ml). The clear solution was evaporated by distillation over a free flame to about 50 ml. On cooling of this clear yellowish brown solution white crystals separated. They were isolated by filtration, washed with water, and dried (50°, 0.1 mm). 3.10 g (18 %) of XLII was hereby obtained, m.p. 116 – 119°C. [Found: C 58.0; H 5.9; N 17.1. Calc. for $C_8H_{10}N_2O_2$ (166.2): C 57.8; H 6.1; N 16.9.]

*3,4-Dihydro-2-ethyl-4-methyl-2*H-*pyrido*[*3,2*-b]-*1,4-oxazin-3-ol (XLIII) and 3,4-dihydro-2-ethyl-4-methyl-2*H-*pyrido*[*3,2*-b]-*1,4-oxazine (XLVI)*. XXV (24.0 g, 0.13 mol) was reduced with LAH (8 g, 0.21 mol) as described in the preceding preparation and the reaction products isolated in the same way. Yield of XLVI 7.5 g (34 %), b.p.$_{0.65}$ 86 – 89°C, n_D^{25} 1.5520. [Found: C 67.3; H 8.1; N 15.7. Calc. for $C_{10}H_{14}N_2O$ (178.2): C 67.4; H 7.9; N 15.7.] Yield of XLIII 3.6 g (15 %), m.p. 121 – 125°, after crystallization from water (250 ml). [Found: C 61.6; H 7.3; N 14.4. Calc. for $C_{10}H_{14}N_2O_2$ (194.2): C 61.8; H 7.3; N 14.4.]

*3,4-Dihydro-2,2,4-trimethyl-2*H-*pyrido*[*3,2*-b]-*1,4-oxazin-3-ol (XLIV) and 3,4-dihydro-2,2,4-trimethyl-2*H-*pyrido*[*3,2*-b]-*1,4-oxazine (XLVII)*. XXVIII (12 g, 0.060 mol) was reduced with LAH (4 g, 0.10 mol) as described in the preparation of XLII and XLV, and the reaction product isolated in the same way. Yield of XLVII 4.2 g (38 %), b.p.$_{12}$ 119 – 126°, n_D^{25} 1.5464. [Found: C 66.9; H 8.1; N 16.1. Calc. for $C_{10}H_{14}N_2O$ (178.2): C 67.4; H 7.9; N 15.7.] Yield of XLIV 2.1 g (18 %), m.p. 147 – 150°C (from water). [Found: C 62.1; H 7.5; N 14.4. Calc. for $C_{10}H_{14}N_2O_2$ (194.2): C 61.8; H 7.3; N 14.4.]

*4-Benzyl-2-methyl-4*H-*pyrido*[*3,2*-b]-*1,4-oxazine (XLIX)*. XXIV (7.0 g, 0.028 mol) was reduced with LAH (1.2 g, 0.03 mol) as described in the preparation of XL. The crude reaction product (7.5 g) was a light yellow oil which could not be brought to crystallize, nor could an analytically pure sample of a dihydrochloride be prepared. Distillation gave 6.5 g of an orange colored oil, b.p.$_{0.03}$ 160 – 141°C, n_D^{25} 1.6139, no infrared absorption corresponding to the presence of a carbonyl group in the molecule. The product was oxidized slowly on standing (darkening of the surface). [Found: C 72.2; H 6.2; N 11.2. Calc. for $C_{15}H_{16}N_2O_2$ (256.3) (XLVIII): C 70.3; H 6.3; N 10.9. Calc. for $C_{15}H_{14}N_2O$ (238.2) (XLIX): C 75.6; H 5.9; N 11.8.] Boiling point, analyses and spectrum of the product indicate that water has been partially split off during distillation to give a distillate consisting of 60 % of XLVIII and 40 % of XLIX. This corresponds to a combined yield of both compounds of 93 %.

1.28 g of the product was heated (2 h) at 150°C under 10 mm, and the reaction product distilled. 1.11 g (90 %) of XLIX was hereby obtained as an orange-yellow oil, b.p.$_{0.1}$ 118 – 119°C, n_D^{25} 1.6211. [Found: C 75.7; H 6.2; N 12.0.]

*4-[3-(Dimethylamino)propyl]-2-ethyl-4*H-*pyrido*[*3,2*-b]-*1,4-oxazine (L)*. XXVI (7.9 g, 0.030 mol) was reduced with LAH (1.2 g, 0.03 mol) as described in the preceding preparation. Distillation of the crude reaction product (7.4 g) gave 7.2 g of a light yellow oil, b.p.$_{0.04}$ 132 – 126°C, n_D^{25} 1.5448, no infrared absorption corresponding to the presence of a carbonyl group in the molecule, the product was oxidized slowly on standing (darkening of the surface). [Found: C 64.5; H 8.8; N 16.2. Calc. for $C_{14}H_{23}N_3O_2$ (265.4): C 63.4; H 8.7; N 15.8. Calc. for $C_{14}H_{21}N_3O$ (247.3): C 68.0; H 8.6; N 17.0.] Boiling point, analyses and spectrum of the product indicate that water has been partially split off during distillation to give a distillate consisting of 75 % of the hydroxy compound and 25 % of L. This corresponds to a combined yield of both compounds of 92 %.

1.16 g of the product was heated (2 h) at 150°C under 10 mm and the reaction product distilled. 0.90 g (82 %) of L was hereby obtained as a yellow oil, b.p.$_{0.1}$ 100 – 101°C, n_D^{25} 1.5490. [Found: C 68.2; H 8.9; N 17.2. Calc. for $C_{14}H_{21}N_3O$ (247.3): C 68.0; H 8.6; N 17.0.]

7-Bromo-3,4-dihydro-2H-pyrido[3,2-b]-1,4-oxazine (LI). A solution of −20°C of I (1.36 g, 0.0100 mol) in methanol (50 ml) was poured in one portion into a solution of −20° of bromine (0.50 ml, 0.0100 mol) in methanol (50 ml). The resulting, clear solution was left standing (30 min) at room temperature. Most of the methanol was distilled off from a water bath under reduced pressure. Ether (50 – 100 ml) was added to the suspension of the hydrobromide of LI in methanol to complete precipitation. The precipitate was isolated by filtration, washing with ether, and drying. The yield of LI hydrobromide was 2.42 g (82 %), yellowish-grey powder, no sharp m.p. [Found: C 28.5; H 2.7; Br 53.8; Br (ion) 27.0; N 9.5. Calc. for $C_7H_8Br_2N_2O$ (296.0): C 28.4; H 2.7; Br 54.0; one Br (ion) 27.0; N 9.5.]

The free base was prepared from the hydrobromide in the usual way (yield 1.55 g) and crystallized from methanol; yield 0.97 g (55 %) of LI, m.p. 122 – 123°C. [Found C 38.9; H 3.5; Br 37.0; N 13.0. Calc. for $C_7H_7BrN_2O$ (215.1): C 39.2; H 3.3; Br 37.2; N 13.0.]

3,4-Dihydro-2H-pyrido[3,2-b]-1,4-oxazine-7-carbonitrile (LII). LI (44 g, 0.21 mol), copper(I) cyanide (32 g, 0.36 mol) and 1-methyl-2-pyrrolidinone (125 ml) were mixed and heated under reflux (17 h). The hot reaction mixture was poured in a thin stream into a preheated (80°C), stirred solution of sodium cyanide (60 g) in water (300 ml). The resulting precipitate of crude LII was isolated by filtration, washing with methylpyrrolidinone – water, and then with water. The wet cake was dried and continuously extracted with ether in a Soxhlet-type apparatus. Evaporation of the ethereal suspension gave 21.3 g of LII, m.p. 221 – 222°C. Another 3.1 g (m.p. 221 – 222°C) of LII was isolated by extraction of the filtrate and washings from the isolation of crude LII. The total yield of LII was thus 24.4 g (74 %). A small portion was crystallized from benzene (yield 83 %, m.p. 222 – 223°C) and analysed. [Found: C 59.8; H 4.5; N 26.2. Calc. for $C_8H_7N_3O$ (161.2): C 59.6; H 4.4; N 26.1.]

7-Aminomethyl-3,4-dihydro-2H-pyrido[3,2-b]-1,4-oxazine (LIII) dihydrochloride. LII (9.7 g) was suspended in dry ethanol (125 ml) saturated with ammonia at 20°C. The suspension was shaken (4.5 h) under hydrogen (100 atm) at 85°C with Raney nickel (9 g) and the reaction product isolated as an oil in the usual way. The oil was dissolved in 2-propanol (100 ml). Addition of concentrated hydrochloric acid (20 ml), evaporation to dryness, and crystallization of the residue from methanol gave 8.7 g (61%) of LIII dihydrochloride, m.p. 270 – 280°C (decomp.). [Found: C 40.3; H 5.5; Cl (ion) 29.8; N 17.6. Calc. for $C_8H_{13}Cl_2N_3O$ (238.1): C 40.4; H 5.5; Cl 29.8; N 17.7.]

2H-Pyrido[3,2-b]-1,4-oxazine-3(4H)-thione (LIV). XIV (3.75 g 0.025 mol) was dissolved in pyridine (30 ml). Phosphorus pentasulfide (2.8 g, 0.013 mol) was added in one portion with stirring. The temperature of the reaction mixture rose rapidly to about 40°C. The mixture was heated under reflux (3 h) with stirring. Water (150 ml) was added and the mixture distilled with stirring, until 100 ml of distillate had been collected (removal of pyridine). The residue was cooled to 20°C and the crystals formed isolated by filtration, washing with water, and drying (50°C, 0.1 mm). Crystallization with carbon black from methanol (900 ml) (yield 1.20 g) and another crystallization from acetic acid (50 ml) gave 0.87 g (21 %) of LIV, m.p. above 250°C (decomp.). [Found: C 50.5; H 3.8; N 17.0; S 19.2. Calc. for $C_7H_6N_2OS$ (166.2): C 50.6; H 3.6; N 16.8; S 19.3.]

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Received January 30, 1971.