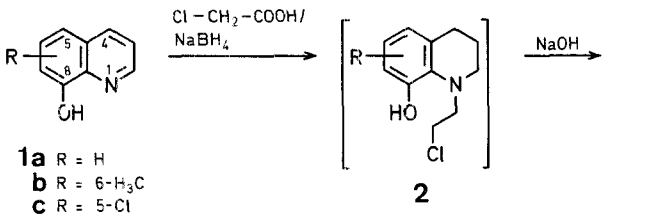
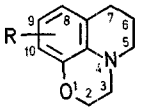


1a R = H
b R = 6-H_3C
c R = 5-Cl

2



3a R = H
b R = 9-H_3C
c R = 8-Cl

Convenient Preparation of 2,3,6,7-Tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazines (1-Oxajulolidines)

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There is a single report on the preparation of 2,3,6,7-tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine (**3a**; 1-oxajulolidine) because of its analgetic interest[1]. In that report, 1-oxajulolidine was prepared from 8-hydroxy-1,2,3,4-tetrahydroquinoline (tetrahydroxine) by a several-step process. We have been concerned with the reductive acylation of quinoline[2] and became interested in the reductive alkylation of quinolines[3] by a combination of sodium borohydride and the corresponding carboxylic acid. We have extended the reductive alkylation for the preparation of 1-oxajulolidines **3** and now report on the convenient preparation of 1-oxajulolidines **3** from 8-hydroxyquinolines **1** by a two step process which gives practically useful yields.

A mixture of 8-hydroxyquinoline **(1a)** and monochloroacetic acid dissolved in tetrahydrofuran was reduced by the gradual addition of sodium borohydride. The progress of the reduction was monitored by T.L.C. and the reaction was stopped when the starting material disappeared. Evaporation, neutralization, and extraction of the reaction mixture gave the reductive alkylation product **2a** which contained a large amount of *β*-chloroethyl monochloroacetate as the major contaminant. Column chromatography of this crude product allowed the isolation of pure 1-*β*-chloroethyl-8-hydroxy-1,2,3,4-tetrahydroquinoline **(2a)** but this procedure is not required for the following cyclization reaction. The treatment of reductive alkylation product **2** with sodium hydroxide gave the cyclized product **3** in a high state of purity. The purification of the crude product was carried out either by column chromatography on silica gel, eluting with ethyl acetate or by Kugelrohr distillation. 6-Methyl-8-hydroxyquinoline **(1b)** was reduced somewhat slower than the other two compounds **1a** and **1c**. 2-Methyl-8-hydroxyquinoline resisted the reaction and resulted in the recovery of starting material (63%) without giving the reductive alkylation product **2** in a preparatively useful quantity.

Considering the difficulties to prepare 6-substituted 8-hydroxyquinolines, the easy access to a large quantity of 1-oxajulolidine by this method may provide a useful pathway for the preparation of 9-substituted 1-oxajulolidines and thus to expand the chemistry of 1-oxajulolidines.

2,3,6,7-Tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazines 3; General Procedure:

A solution of 8-hydroxyquinoline **1** (0.04 mol) and monochloroacetic acid (75.6 g, 0.8 mol) dissolved in tetrahydrofuran (100 ml) is cooled in

Table. 2,3,6,7-Tetrahydro-5*H*-pyrido[1,2,3-*de*]-1,4-benzoxazines **3a–c**

Product	Yield[a] [%]	m.p. [°C]	I.R. (film) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]	**3** · Hydrobromide		
					m.p. [°C] (solvent)	I.R. (KBr) ν [cm^{-1}]	Molecular formula[b]
3a	68	oil	1585, 1495, 1085	1.99 (m, 2H); 2.77 (t, 2H, J=6.5 Hz); 3.04 (t, 2H, J=6 Hz); 3.09 (t, 2H, J=5 Hz); 4.25 (m, 2H), 6.54 (s, 3H)	212–221° (CH_3OH/acetone)	2350, 1597, 1106, 800	$C_{11}H_{14}BrNO$ (256.2)
3b	45	oil	1580, 1503, 1162	2.02 (m, 2H); 2.19 (s, 3H); 2.76 (t, 2H, J=6.5 Hz); 3.05 (t, 2H, J=5.5 Hz); 3.11 (t, 2H, J=4.5 Hz); 4.31 (t, 2H, J=4.5 Hz); 6.43 (s, 2H)	213–223° (CH_2Cl_2/acetone)	2250, 1613, 1118, 848	$C_{12}H_{16}BrNO$ (270.2)
3c	53	oil	1595, 1063	2.03 (m, 2H); 2.77 (t, 2H, J=6.5 Hz); 3.04 (t, 2H, J=5 Hz); 3.14 (t, 2H, J=6.5 Hz); 4.25 (t, 2H, J=5 Hz); 6.55 (s, 2H)	184–190° (CH_3OH/acetone)	2240, 1595, 1067, 824	$C_{11}H_{13}BrClNO$ (290.6)

[a] Yield of purified product.
[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.10; H, ±0.03; N, ±0.07; Br, ±0.09.

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a water bath and stirred vigorously with mechanical stirrer. Into this solution, sodium borohydride (6.8 g, 0.18 mol) is gradually added over a period of 50 min. Then the reaction mixture is warmed at 80 °C (bath temperature) for 2–3 h while monitoring the disappearance of starting material by T.L.C. on silica plates with ethyl acetate. The reaction solution is evaporated in vacuo, the residue is diluted with water (250 ml), neutralized with 8% sodium hydrogen carbonate solution, and extracted with ether (3 × 250 ml). The organic extracts are washed with saturated brine (2 × 80 ml), dried with anhydrous sodium sulfate, and evaporated to give the reductive alkylation product **2**. This product is subsequently treated with 2 normal sodium hydroxide in 80% aqueous methanol (200 ml) at room temperature for 18 h. The reaction mixture is evaporated and the residue is diluted with water (300 ml). Extractions with ether (3 × 100 ml) and workup by Kugelrohr distillation at 105°C/31 torr gives the 1-oxajulolidine **3** in analytical purity.

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