Pyrroloquinolines; Part II[1]. Synthesis of 1*H*-Pyrrolo[2,3-*b*]quinolines

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In connection with our syntheses of seleno-[2] and tellurolo[2,3-*b*]quinolines[3], we prepared several 2-chloro-3-(2-chloroethyl)-quinolines (**1**) from 2-quinolone-3-acetic acids, which were obtained as a result of a one-step conversion of *N*-arylaconamides[4]. We have now evolved a convenient synthesis of pyrrolo[2,3-*b*]quinolines based on the use of the above mentioned dichloro compounds. Interest in the pyrrolo[2,3-*b*]quinoline-ring system stems from the fact that it constitutes the 'aza'-analogue of furo[2,3-*b*]quinoline, the parent ring feature of the dictamine group of alkaloids which occur widely in the *Rutaceae*[5] and from its antiinflammatory, antibacterial, antihypertensive, antipyretic, and anticonvulsant properties, and interferon inducing activity, reported[6] in the literature.

Among the successful methods hitherto reported for the construction of the title heterocyclic system, the one due to Tanaka[7] proceeded through 2,3,4,5-tetrahydrofuro[3,2-*c*]quinolines which were earlier recognised[8] as precursors for the synthesis of the furoquinoline alkaloids. An improved version of the method was reported later for the synthesis of 7-chloro-4-methoxy-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]quinoline[9]. Zimmer et al.[10] obtained 1-acetyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]quinolines by the photolysis of 1-acetyl-*trans*-3-(2-aminobenzylidene)-pyrrolidin-2(1*H*)-ones. Another method appeared in patent reports[11] for the synthesis of 1-substituted 2,3-dihydropyrrolo[2,3-*b*]quinolines. It involved cyclization of 3-(2-diethylaminoethyl)-quinolin-2(1*H*)-ones with phosphorus halides. Another method[12] involved pyrrolysis of an azepine derivative to give 1-alkyl-2-oxo-4-phenyl-2,3,3a,4-tetrahydropyrrolo[2,3-*b*]quinoline.

The method we now describe is convenient and provides the feasibility of obtaining 1*H*-pyrrolo[2,3-*b*]quinolines with different substitution patterns than is possible through the other methods reported in the literature.

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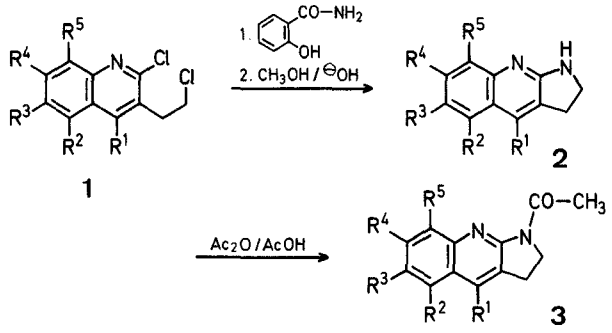
The 2-chloro-3-(2-chloroethyl)-quinoline (**1a**) was fused with salicylamide and the resulting mass was dissolved in hot methanol and digested with aqueous alkali to give the dihydropyrrolo[2,3-*b*]quinoline (**2a**) in 83% yield. Its properties (m.p., solubility, I.R.) correspond to that reported for the authentic sample[7b]. Extension of this technique to the dichloro-compounds **1b** to **1i** afforded the dihydropyrroloquinolines **2b** to **2i**, respectively, which were characterised as the 1-acetyl derivatives **3b** to **3i**.



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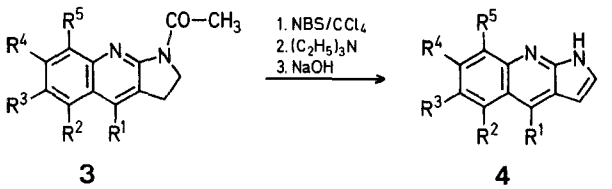
Product	R^1	R^2	R^3	R^4	R^5
a	H	H	H	H	H
b	C_6H_5	H	H	H	H
c	C_6H_5	H	Cl	H	H
d	CH_3	H	H	H	H
e	H	Cl	H	H	CH_3
f	H	Cl	H	H	OCH_3
g	C_6H_5	H	CH_3	H	H
h	C_6H_5	H	Br	H	H
i	H	H	H	—CH=CH—CH=CH—	

In an attempted dehydrogenation of the dihydropyrroloquinolines, the acetyl derivatives **3a** to **3d** were treated with *N*-bromosuccinimide and the resultant bromo compounds were, without characterisation, reacted with triethylamine to afford the pyrroloquinolines **4a** to **4d**, respectively.



3 4

Melting points were determined on a Boetius microheating table and are uncorrected. The N.M.R. Spectra were determined on a Varian T-60 spectrometer (TMS as internal standard).

2,3-Dihydro-1*H*-pyrrolo[2,3-*b*]quinolines 2:

An intimate mixture of 2-chloro-3-(2-chloroethyl)-quinoline (**1a**; 4 g) and pure salicylamide (8 g) is fused at 180° for 2 h, in an oil bath. The black solidified mass is cooled, and digested with hot methanol. The solution after cooling is poured into 10% aqueous sodium hydroxide (100 ml) and the aqueous solution is then heated for 30 min on a steam bath. It is cooled and the precipitated solid is filtered and recrystallised from methanol to give **2a** as colourless crystals (m.p., I.R., etc. see Table 1). Compounds **2b** to **2i** are obtained in a similar manner.

Table 1. 2,3-Dihydro-1*H*-pyrrolo[2,3-*b*]quinolines **2**

Product	Yield [%]	m.p. (recryst. solvent)	Molecular formula[a] or Lit. m.p.	I.R. (KBr) ν_{max} [cm^{-1}]
2a	83	204–206° (CH_3OH)	203–205°[7b]	3220, 2210
2b	82	253–255° ($CHCl_3/C_2H_5OAc$)	$C_{17}H_{14}N_2$ (170.2)	3115, 2265
2c	89	260° (CH_3OH)	$C_{17}H_{13}ClN_2$ (280.7)	3280, 2270
2d	83	272–274° (CH_3OH)	$C_{12}H_{12}N_2$ (184.2)	3280, 2260
2e	84	269–271° (C_2H_5OAc)	$C_{12}H_{11}ClN_2$ (218.7)	3270, 2280
2f	83	260° (AcOH)	$C_{12}H_{11}ClN_2O$ (234.5)	3265, 2270
2g	80	249–250° ($CHCl_3/C_2H_5OAc$)	$C_{18}H_{10}N_2$ (260.3)	3215, 2250
2h	93	300° ($CHCl_3/CH_3OH$)	$C_{17}H_{13}BrN_2$ (325.2)	3280, 2280
2i	82	271–273° ($CHCl_3/C_2H_5OAc$)	$C_{15}H_{12}N_2$ (220.3)	3260, 2275

[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.31, H ±0.30, N ±0.16).

1-Acetyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]quinolines 3:

The dihydropyrroloquinoline **2a** (1 g) is heated with a mixture of acetic anhydride (3 ml) and glacial acetic acid (3 ml) on a steam bath for 5 h. The mixture is cooled, poured into ice/water, and neutralised with ammonium hydroxide. The solid that separates is extracted with chloroform and the chloroform extract is washed with water (2 × 50 ml), dried (Na_2SO_4), and chromatographed over alumina using benzene as the eluent, to afford **3a** as colourless crystals. (For yield, m.p., etc., see Table 2). Compounds **3b** to **3i** are obtained in a similar manner.

1*H*-pyrrolo[2,3-*b*]quinolines 4:

A mixture of 1-acetyl 2,3-dihydro[2,3-*b*]quinoline (**3a**; 2.1 g, 0.01 mol), *N*-bromosuccinimide (1.8 g, 0.021 mol), and benzoyl peroxide (0.1 g) in carbon tetrachloride (100 ml) is refluxed for 1.5 h. It is cooled, filtered, and the residue obtained after evaporation of the solvent is mixed with freshly distilled triethylamine (4 ml) and heated under reflux for 7 h. The excess triethylamine is removed in vacuo and the residue dissolved in chloroform and filtered. The filtrate, after drying (Na_2SO_4), is evaporated and the residue obtained treated by dropwise addition of methanolic 10% sodium hydroxide (50 ml) and subsequent heating under reflux for 30 min on a steam bath. The solution, after cooling, is poured into ice/water and the solid that separates is collected, washed with water, and dried. The dried material is chromatographed over alumina using benzene/petroleum ether as eluent to give **4a** as colourless crystals (for m.p., yield, etc., see Table 3). The pyrroloquinoline **4b** to **4d** are obtained in a similar manner.

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Table 2. 1-Acetyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]quinolines **3**

Product	Yield [%]	m.p. (recryst. from)	Molecular formula[a]	I.R. (KBr) ν_{max} [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
3a	83	180–183° (C_6H_6)	$C_{13}H_{12}N_2O$ (212.2)	1635, 2270	3.01 (s, 3H, CO—CH_3); 3.23 (t, 2H, H—C-3, J = 8 Hz); 3.83 (t, 2H, H—C-2, J = 8 Hz); 7.33–8.33 (m, 5 H_{arom})
3b	85	212–213° (C_6H_6)	$C_{19}H_{16}N_2O$ (288.3)	1630, 2210	3.1 (s, 3H, CO—CH_3); 3.3 (t, 2H, H—C-3, J = 8 Hz); 4.1 (t, 2H, H—C-2, J = 8 Hz); 7.56–8.13 (m, 9 H_{arom})
3c	94	217–219° (C_6H_6/$CHCl_3$)	$C_{19}H_{15}ClN_2O$ (322.8)	1615, 2260	2.93 (s, 3H, CO—CH_3); 3.01 (t, 2H, H—C-3, J = 8 Hz); 4.16 (t, 2H, H—C-2, J = 8 Hz); 6.73–8.2 (m, 8 H_{arom})
3d	89	250–252° ($CHCl_3$)	$C_{14}H_{14}N_2O$ (226.3)	1630, 2250	2.70 (s, 3H, CH_3); 2.96 (s, 3H, CO—CH_3); 3.03 (t, 2H, H—C-3, J = 8 Hz); 4.18 (t, 2H, H—C-2, J = 8 Hz); 7.01–8.13 (m, 4 H_{arom})
3e	92	152–154° ($CHCl_3$)	$C_{14}H_{13}ClN_2O$ (260.7)	1615, 2280	2.46 (s, 3H, CH_3); 3.1 (s, 3H, CO—CH_3); 3.66 (t, 2H, H—C-3, J = 8 Hz); 4.70 (t, 2H, H—C-2, J = 8 Hz); 7.06 (d, H—C-7); 7.86 (d, H—C-6); 8.23 (s, H—C-4)
3f	89	186–187° (C_6H_6)	$C_{14}H_{13}ClN_2O_2$ (276.7)	1635, 2275	2.93 (s, 3H, CO—CH_3); 3.2 (t, 2H, H—C-3, J = 8 Hz); 4.03 (s, 3H, OCH_3); 4.2 (t, 2H, H—C-2, J = 8 Hz); 4.96 (d, 1H, H—C-6 or -7, J = 8 Hz); 7.43 (d, 1H, H—C-7 or -6, J = 8 Hz); 8.3 (t, 1H, H—C-4)
3g	82	203–205° (C_6H_6/$CHCl_3$)	$C_{20}H_{18}N_2O$ (302.4)	1635, 2210	2.3 (s, 3H, CH_3); 2.83 (s, 3H, CO—CH_3); 2.84 (t, 2H, H—C-3, J = 8 Hz); 4.00 (t, 2H, H—C-2, J = 8 Hz); 7.00–8.06 (m, 8 H_{arom})
3h	89	175–176° (C_6H_6/PE)	$C_{19}H_{15}BrN_2O$ (367.2)	1615, 2270	2.93 (s, 3H, CO—CH_3); 2.94 (t, 2H, H—C-3, J = 8 Hz); 4.13 (t, 2H, H—C-2, J = 8 Hz); 7.1–8.3 (m, 8 H_{arom})
3i	76	110–112° (C_6H_6)	$C_{17}H_{14}N_2O$ (262.3)	1620, 2215	2.83 (s, 3H, CO—CH_3); 3.26 (t, 2H, H—C-3, J = 8 Hz); 3.83 (t, 2H, H—C-2, J = 8 Hz); 7.3–8.03 (m, 7 H_{arom})

[a] The microanalyses of all products were in satisfactory agreement with the calculated values (C ±0.11, H ±0.06, N ±0.08).

Table 3. 1*H*-Pyrrolo[2,3-*b*]quinolines **4**

Product	Yield [%]	m.p. (recryst. from)	Molecular formula[a] or Lit. m.p.	I.R. (KBr) ν_{max} [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
4a	29	210–211° (C_6H_6)	Lit. [7b], 209–210°	3210, 2280	6.7 (d, 1H, H—C-3, J = 2.5 Hz); 7.31–8.33 (m, 6 H_{arom}); 8.55 (s, 1H, NH)
4b	35	180–182° (C_6H_6)	$C_{17}H_{12}N_2$ (244.3)	3280, 2270	6.76 (d, 1H, H—C-3, J = 3 Hz); 7.58–8.26 (m, 10 H_{arom}); 8.35 (d, 1H, NH)
4c	33	232–233° ($CHCl_3$)	$C_{17}H_{11}ClN_2$ (278.7)	3270, 2275	6.93 (d, 1H, H—C-3, J = 2.5 Hz); 7.02–8.46 (m, 10 H_{arom})
4d	35	218–220° ($CHCl_3$)	$C_{12}H_{10}N_2$ (182.2)	3220, 2280	2.73 (s, 3H, CH_3); 6.63 (d, 1H, H—C-3, J = 3 Hz); 7.06–8.2 (m, 6 H_{arom})

[a] The microanalyses of all products were in satisfactory agreement with the calculated values (C ±0.1, H ±0.07, N ±0.07).

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