

Condensed Heterocycles; XI. Synthesis of 1,2,5-Thia(selena)diazolo[3,4-*b*]quinolines and 1,2,5-Thia(selena)diazolo[3,4-*h*]quinolines

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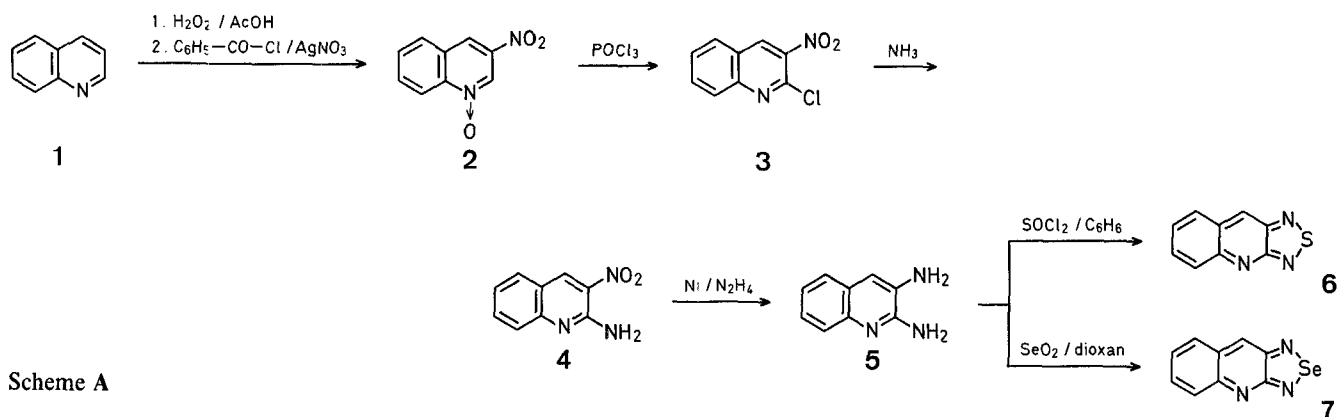
In view of the potential biological activity of the quinoline¹, 1,2,5-thiadiazole², and 1,2,5-selenadiazole³ moieties, it was thought worthwhile to prepare molecules containing both 1,2,5-thia(or seleno)diazole and quinoline moieties with the hope that these ring systems may prove to be potential biologically active systems.

Quinoline (**1**) was oxidised to quinoline *N*-oxide by treating the former with hydrogen peroxide and the latter was subjected to nitration by benzoyl nitrate (prepared from silver nitrate and

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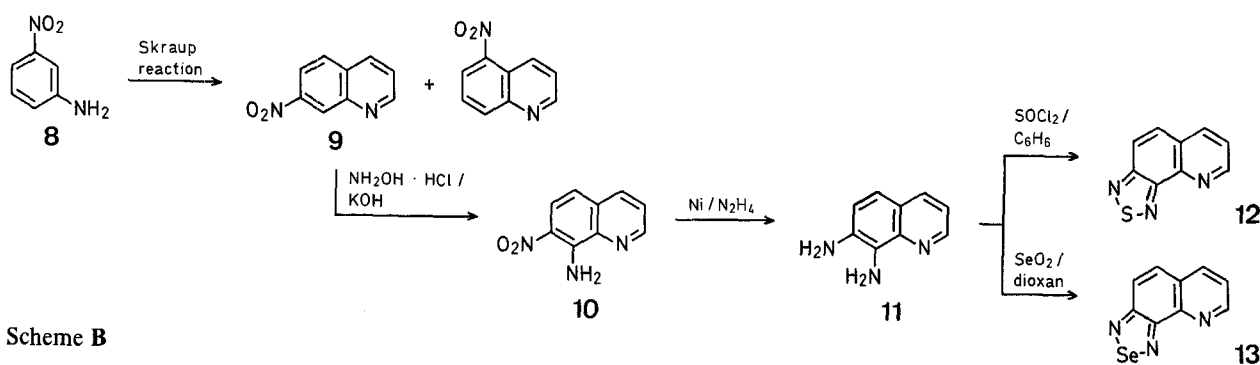
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benzoyl chloride) to give 3-nitroquinoline-*N*-oxide (**2**). Compound **2** was then reacted with phosphoryl chloride to give 2-chloro-3-nitroquinoline (**3**; 40% yield) which, on treatment with ammonia solution provided 2-amino-3-nitroquinoline (**4**; 75% yield). The latter underwent smooth reduction with 98% hydrazine hydrate in the presence of Raney-nickel catalyst; the resulting 2,3-diaminoquinoline (**5**) could not be characterised and was directly treated with thionyl chloride in dry benzene to give 1,2,5-thiadiazolo[3,4-*b*]quinoline (**6**; 24% yield). The diamine **5**, on treatment with selenium dioxide in dioxan, afforded 1,2,5-selenadiazolo[3,4-*b*]quinoline (**7**) in 20% yield (Scheme A).



Scheme A

m-Nitroaniline (**8**) was subjected to the Skraup reaction⁴ in the presence of arsenic pentoxide as an oxidant and 80% sulphuric acid and the resulting mixture of 7-nitro- and 5-nitroquinolines was separated by column chromatography. 7-Nitroquinoline (**9**), on reaction with hydroxylamine hydrochloride in the presence of potassium hydroxide afforded 8-amino-7-nitroquinoline (**10**). The nitro-amine on treatment with 98% hydrazine hydrate in the presence of Raney-nickel, underwent smooth reduction to give crude 7,8-diaminoquinoline (**11**) which was directly reacted with thionyl chloride in dry benzene to afford 1,2,5-thiadiazolo[3,4-*b*]quinoline (**12**; 28% yield). 7,8-Diaminoquinoline (**11**) was also treated with selenium dioxide in dioxan to give 1,2,5-selenadiazolo[3,4-*b*]quinoline (**13**) in 18% yield (Scheme B).



Scheme B

The melting points are not corrected. I.R. and $^1\text{H-N.M.R.}$ spectra were recorded on Beckman IR-20 and Perkin Elmer R-32 90 MHz spectrometers. Thionyl chloride was purified by distillation from quinoline followed by a second distillation from linseed oil.

Quinoline *N*-Oxide:

Quinoline **1** (12.9 g, 0.1 mol) is oxidised by hydrogen peroxide/acetic acid according to Ref.⁵; yield: 9.2 g (63%); m.p. 60°C (Lit.⁶, m.p. 62°C).

3-Nitroquinoline *N*-Oxide (**2**):

Benzoyl chloride (7.0 g, 0.05 mol) in dry dichloromethane (30 ml) is gradually added to a vigorously stirred solution of silver nitrate (17.1 g, 0.1 mol) in dry dichloromethane (30 ml). The reaction mixture is quickly filtered and transferred to a separatory funnel and gradually added to a

stirred ice-cold solution of quinoline *N*-oxide (7.2 g, 0.05 mol) in dry dichloromethane (25 ml) at such a rate as to maintain the temperature below 0°C and stirred for 30 min. The reaction mixture is heated on a water bath for 2 h. After being cooled, dry ammonia is passed until the solution is alkaline and the solution is then filtered. The solvent is distilled off and the residue is passed through a column of silica gel and eluted with 9/1 benzene/acetone to give a yellow solid; yield: 3.0 g (33%); m.p. $187\text{--}188^\circ\text{C}$.

$\text{C}_9\text{H}_6\text{N}_2\text{O}_3$	calc.	C 56.84	H 3.18	N 14.73
(190.2)	found	56.8	3.2	14.7

I.R. (KBr): $\nu = 1510, 1370$ (NO_2); 1240 cm^{-1} ($\text{N}\rightarrow\text{O}$).

2-Chloro-3-nitroquinoline (**3**):

3-Nitroquinoline *N*-oxide (**2**; 1.9 g, 0.01 mol) is taken up in excess phosphoryl chloride (10 ml). The mixture is refluxed for 4 h, cooled, poured into cold water (50 ml), basified with 10% aqueous ammonia solution (~ 20 ml), and extracted with chloroform (2×50 ml). Evaporation of the solvent and column chromatography on silica gel, eluting with 1:1 benzene/petroleum ether gives a light yellow solid; yield: 1.4 g (70%); m.p. $120\text{--}121^\circ\text{C}$.

$\text{C}_9\text{H}_5\text{ClN}_2\text{O}_2$	calc.	C 51.82	H 2.42	N 13.43	Cl 17.00
(208.6)	found	51.9	2.4	13.5	16.8

I.R. (KBr): $\nu = 1560, 1340\text{ cm}^{-1}$ (NO_2).

2-Amino-3-nitroquinoline (**4**):

2-Chloro-3-nitroquinoline (**3**; 1.0 g, 0.005 mol) is heated with excess 25% ammonia solution (10 ml) on a water bath for 8 h. The cold mixture is

extracted with chloroform (2×75 ml) and the extract is dried with magnesium sulphate. Stripping off the solvent followed by column chromatography on silica gel, eluting with benzene gives a yellow solid; yield: 0.7 g (75%); m.p. 260°C .

$\text{C}_9\text{H}_7\text{N}_3\text{O}_2$	calc.	C 57.14	H 3.73	N 22.21
(189.2)	found	57.1	3.7	22.2

I.R. (KBr): $\nu = 3460, 3180$ (NH_2); $1530, 1350\text{ cm}^{-1}$ (NO_2).

2,3-Diaminoquinoline (**5**):

Raney-nickel (0.5 g out of the total of 2.0 g) followed by 98% hydrazine hydrate (1.5 ml out of the total of 6.0 ml) is added to a warm solution of 2-amino-3-nitroquinoline (**4**; 0.47 g, 0.0025 mol) in ethanol (50 ml). When the vigorous reaction has subsided another portion of Raney-nickel (0.5 g) and hydrazine hydrate (1.5 ml) is added. This procedure is re-

peated until the additions are complete. Refluxing is continued until the yellow colour of the mixture disappears. The mixture is filtered hot and removal of the solvent from the filtrate provides the dark brown coloured diamine **5** which is used as such for conversion to **6** and **7**.

1,2,5-Thiadiazolo[3,4-*b*]quinoline (**6**):

The diamine **5** (0.74 g, ~0.0047 mol) is taken up in dry benzene (100 ml), purified thionyl chloride (3 ml) is added, and the mixture is refluxed for 8 h. Excess thionyl chloride and benzene are distilled off. Water (50 ml) is added to the residue and the mixture is extracted with chloroform (2 × 100 ml). The aqueous layer is washed with chloroform (2 × 50 ml), the combined chloroform extracts are washed with water (100 ml), and dried with sodium sulphate. Distillation of the solvent and column chromatography of the residue on silica gel, eluting with petroleum ether gives the colourless solid product; yield: 0.21 g (24%); m.p. 144–145 °C.

C ₉ H ₅ N ₃ S	calc.	C 57.76	H 2.69	N 22.45	S 17.10
(187.2)	found	57.1	2.7	22.5	17.1

¹H-N.M.R. (CDCl₃/CF₃COOH): δ=7.7–7.9 (m, 2H, H-6, H-7); 8.00 (dd, *J*_{7,8}=9 Hz, 1H, H-8); 8.28 (dd, *J*_{5,7}=2.5 Hz, *J*_{3,6}=9.0 Hz, 1H, H-5); 8.70 ppm (s, 1H, H-9).

1,2,5-Selenadiazolo[3,4-*b*]quinoline (**7**):

The diamine **5** (0.4 g, 0.0025 mol) is taken up in dioxan (10 ml), selenium dioxide (0.41 g, 0.0031 mol) is added, the mixture is heated under reflux for 8 h, cooled, and then poured in cold water (50 ml). The mixture is extracted with chloroform (3 × 75 ml), the extract is washed with water (100 ml) and dried with magnesium sulphate. Removal of the solvent and column chromatography of the residue on silica gel, eluting with benzene gives the light yellow product; yield: 0.12 g (20%); m.p. 240–241 °C.

C ₉ H ₅ N ₃ Se	calc.	C 46.17	H 2.15	N 17.95
(234.1)	found	46.9	2.2	17.4

¹H-N.M.R. (CDCl₃): δ=7.7–8.0 (m, 2H, H-6, H-7); 7.93 (dd, 1H, *J*_{7,8}=8.75 Hz, *J*_{6,7}=2.5 Hz); 8.05 (dd, 1H, *J*_{5,6}=8.75 Hz, *J*_{5,7}=2.5 Hz, H-5); 8.65 ppm (s, 1H, H-9).

7-Nitroquinoline (**9**):

Glycerol (184 g) is thoroughly mixed with an intimate mixture of finely powdered *m*-nitroaniline (**8**; 59 g, 0.5 mol) and arsenic pentoxide (86 g), and 80% sulphuric acid (120 ml) is added with stirring. The reaction mixture is placed in an oil bath and the temperature is raised; when a vigorous exothermic reaction begins at 195 °C, the flask is removed from the oil bath and cooled with water to moderate the vigour of reaction, whereupon the temperature is maintained at 170 °C for 8 h. After being cooled to room temperature, the reaction mixture is poured into ice/water (1000 ml), basified with 50% aqueous ammonium hydroxide solution (400 ml), and extracted with chloroform (4 × 100 ml). The combined chloroform extracts are washed with water (100 ml) and dried with magnesium sulphate. The solvent is stripped off and the blackish residue, thus obtained, shows two spots on T.L.C. plates. Column chromatography (silica gel/petroleum ether) provides the desired product; yield: 30.0 g (35%); m.p. 130–131 °C (Lit.⁷, m.p. 132–133 °C).

8-Amino-7-nitroquinoline (**10**):

To 7-nitroquinoline (**9**; 5.2 g, 0.003 mol) in ethanol (75 ml) is added hydroxylamine hydrochloride (6 g) dissolved in hot 96% ethanol (25 ml). The mixture is allowed to cool whilst being shaken so that the sparingly soluble nitroquinoline separates in very small crystals. Then 20% alcoholic potassium hydroxide (40 ml) is added in one portion at room temperature, potassium chloride separates out immediately and, after brief shaking, 7-nitroquinoline dissolves, imparting a yellow colouration to the solution. The amino-nitroquinoline starts to precipitate out of solution forming a crystalline mass. Luke-warm water (200 ml) is added and the yellow crystalline mass is filtered and drained well. The mother liquor is concentrated to give another crop of the product, the combined solid is recrystallised from ethanol; yield: 4.2 g (75%); m.p. 184–185 °C (Lit.⁸, m.p. 185–186 °C).

7,8-Diaminoquinoline (**11**):

7-Nitro-8-aminoquinoline (**10**; 3.1 g, 0.0016 mol) is smoothly reduced with Raney-nickel (2.5 g) and 98% hydrazine hydrate (7.5 ml) following the procedure described for the compound **5** to give the desired crude diamine **11** which is directly used for the next steps; yield: 2.0 g.

1,2,5-Thiadiazolo[3,4-*b*]quinoline (**12**):

7,8-Diaminoquinoline (**11**; 1.6 g, 0.01 mol) is taken in dry benzene (30 ml), purified thionyl chloride (5 ml) is added, and the mixture is refluxed

for 10 h. Work-up as described for the compound **6** and column chromatography over silica gel, eluting with petroleum ether gives the colourless product; yield: 0.5 g (26%); m.p. 139–140 °C (Lit.⁹, m.p. 141–142 °C).

¹H-N.M.R. (CDCl₃): δ=7.47 (q, 1H, *J*_{6,7}=8.5 Hz, *J*_{7,8}=4.0 Hz, H-7); 7.97 (d, 1H, H-4); 8.02 (d, 1H, H-5); 8.87 (dd, 1H, *J*_{6,7}=8.5 Hz, *J*_{6,8}=2.0 Hz, H-6); 9.00 ppm (dd, 1H, *J*_{7,8}=4.0 Hz, *J*_{6,8}=2.0 Hz, H-8).

1,2,5-Selenadiazolo[3,4-*b*]quinoline (**13**):

7,8-Diaminoquinoline (**11**; 1.6 g, 0.01 mol) is taken in dioxan (30 ml) and reacted with powdered selenium dioxide (1.65 g, 0.015 mol) as described for compound **7**. Work-up and column chromatography on silica gel, eluting with 4:1 benzene/petroleum ether gives colourless crystals; yield: 0.40 g (18%); m.p. 150–151 °C.

C ₉ H ₅ N ₃ Se	calc.	C 46.17	H 2.15	N 17.95
(234.1)	found	46.4	2.1	17.6

¹H-N.M.R. (CDCl₃): δ=7.58 (q, 1H, *J*_{6,7}=8.5 Hz, H-7); 8.03 (AB q, 2H, H-4, H-5); 8.95 (dd, 1H, *J*_{6,7}=8.5 Hz, *J*_{6,8}=2.0 Hz, H-6); 9.00 ppm (dd, 1H, *J*_{7,8}=4.0 Hz, *J*_{6,8}=2.0 Hz, H-8).

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