Studies on Heterocyclic Compounds; III. Synthesis of Benzo[g]thieno[2,3-a]quinolizines

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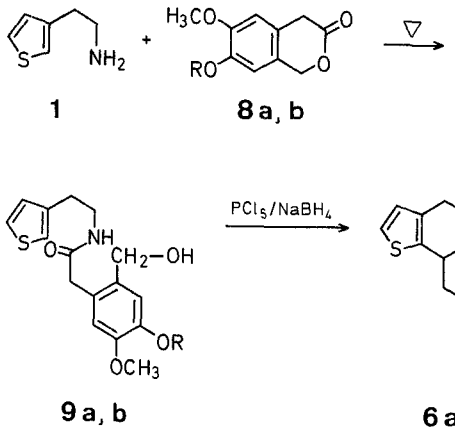
In continuation of our work on the synthesis of thiophene analogs of protoberberine alkaloids[1,2] with a view to study the influence of sulphur on the biological activities of these alkaloids, we report here a convenient synthesis of the hitherto unreported A-ring thiophene isosters of protoberberines, namely 9,10-dimethoxy-7*H*-4,5,12,12a-tetrahydrobenzo[g]thieno[2,3-*a*]quinolizine **(6a)** and the corresponding 9-benzyloxy compound.

2-(3-Thienyl)-ethylamine[3] **(1)** and 3,4-dimethoxyphenylacetic acid **(2a)** reacted on heating to give the amide **3a** in 62% yield. Cyclisation of the **3a** with phosphorus pentachloride in dry chloroform afforded the dihydroisoquinoline hydrochloride **4a** in 75% yield. Sodium borohydride reduction of **4a** in methanol furnished 7-(3,4-dimethoxybenzyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine **(5a)** in 80% yield. Finally, Mannich reaction[4] of **5a** with formalin and glacial acetic acid yielded compound **6a** in 81% yield (Scheme **A**).

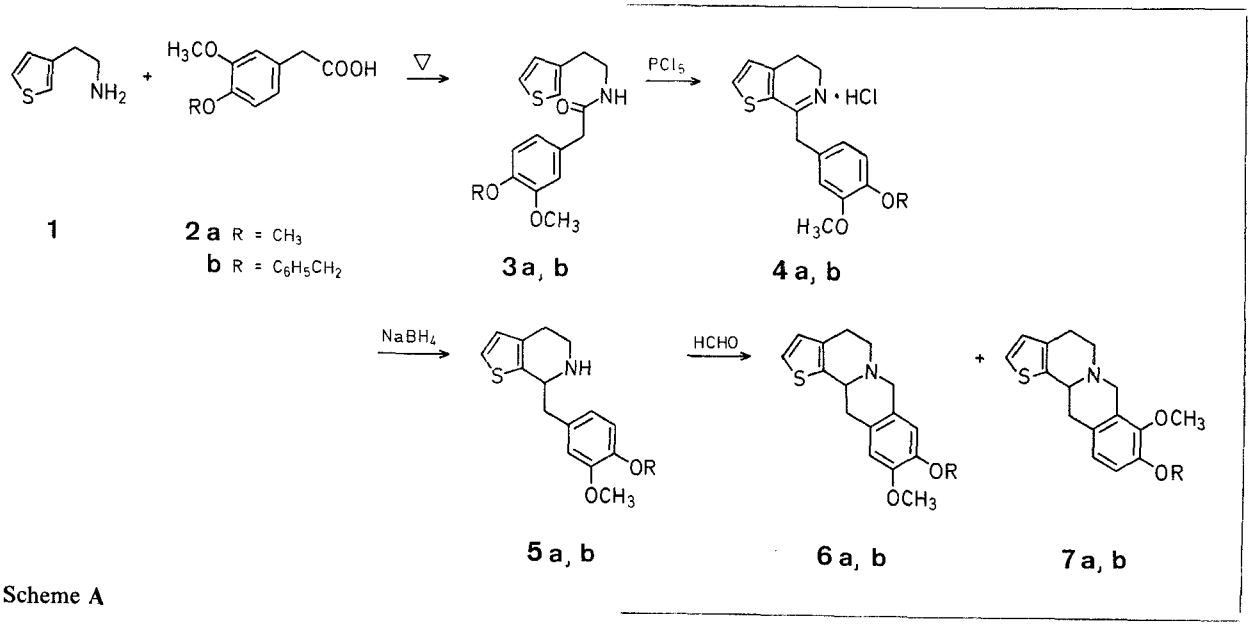
The Mannich reaction of the base **5a**, however, could take place either at the 6′- or the 2′-position of the benzene ring to give **6a** and/or **7a**. T.L.C. analysis of the reaction product showed only one spot, confirming that either **6a** or **7a** is formed. The ^{1}H-N.M.R. spectrum of the product shows two singlets at $\delta = 6.6$ ppm (1 H) and $\delta = 6.7$ ppm (1 H) due to the two benzenoid protons (H-C-8 and H-C-10). Two doublets at $\delta = 6.85$ ppm (1 H, $J = 5$ Hz) and $\delta = 7.2$ ppm (1 H, $J = 5$ Hz) (AB pattern due to thiophene protons) werde also observed. This confirms that the cyclisation had taken place exclusively at 6′-position to give the product **6a** and not the other isomer **7a**.

Further chemical evidence for the formation of **6a** is given in Scheme **B**. 3-Thienylethylamine **(1)** and the 3-isochromanone[5] **8a** were heated together to afford the hydroxymethylphenylacetamide **9a** in 77% yield. This compound was cyclized with phosphorus pentachloride followed by sodium borohydride reduction to afford a product which is identical with the compound **6a** (mixture m.p., mixture T.L.C., superimposable I.R. spectra).



Scheme **B**

The corresponding 9-benzyloxy compound **6b** was also synthesised analogously. All the compounds were characterised by ^{1}H-N.M.R., I.R., Mass spectra, and microanalysis. These data are listed in the Table.



Scheme **A**

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Table. Compounds **3**, **4**, **5**, **6**, and **9** prepared

Product	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. ($CHCl_3$) ν [cm^{-1}]	^1H-N.M.R. ($CDCl_3$) δ [ppm]
3a	62	107–108°	$C_{16}H_{19}NO_3S$ (305.2)	3380; 1650	2.7 (t, 2H, J=7 Hz, thiophene-CH_2); 3.3–3.6 (m, 4H, NH—CH_2 and CO—CH_2); 3.8–3.9 (2s, 6H, 2 OCH_3); 5.7 (br s, 1H, NH); 6.6–7.2 (m, 6 H_{arom})
3b	66	97–98°	$C_{22}H_{23}NO_3S$ (381.4)	3380; 1650	2.7 (t, 2H, J=7 Hz, thiophene-CH_2); 3.3–3.5 (m, 4H, NH—CH_2 and CO—CH_2); 3.8 (s, 3H, OCH_3); 5.1 (s, 2H, OCH_2—Ar); 5.6 (br s, 1H, NH); 6.6–7.4 (m, 11 H_{arom})
4a	75	—[b]	$C_{16}H_{18}ClNO_2S$ (323.8)	1620	3.1 (t, 2H, J=8 Hz, 4-C—CH_2); 3.7–4.1 (m, 10H, 2 OCH_3, C=N—CH_2, and N—C—CH_2); 6.9 (m, 3 H_{arom}); 7.1 (d, 1H, H—C-3); 8.0 (d, 1H, J=5 Hz, H—C-2)[c]
4b	70	—[b]	$C_{22}H_{22}ClNO_2S$ (399.9)	1625	3.1 (t, 2H, J=8 Hz, 4-C—CH_2); 3.5–4.0 (m, 5H, OCH_3 and C=N—CH_2); 4.2 (s, 2H, N=C—CH_2); 5.0 (s, 2H, OCH_2—Ar); 6.7–7.4 (m, 9 H_{arom}); 8.05 (d, 1H, J=5 Hz, H—C-2)[d]
5a·HCl	80	241° (dec.)	$C_{16}H_{20}ClNO_2S$ (325.9)	—[e]	2.8–3.5 (m, 7H, 1H exchangeable with D_2O); 3.8–3.9 (2s, 6H, 2 OCH_3); 4.3 (t, 1H, J=8 Hz, H—C-1); 6.8–7.0 (m, 4 H_{arom}); 7.2 (d, 1H, J=5 Hz, H—C-2)
5b·HCl	85	250° (dec.)	$C_{22}H_{24}ClNO_2S$ (402.0)	—[e]	2.9–3.7 (m, 7H, 1H exchangeable with D_2O); 3.9 (s, 3H, OCH_3); 4.25 (t, 1H, J=8 Hz, H—C-1); 5.1 (s, 2H, OCH_2—Ar); 6.8–7.5 (m, 10 H_{arom})[f]
6a·HCl	81	210°	$C_{17}H_{20}ClNO_2S$ (337.9)	2790; 2730	2.6–4.1 (m, 15H, including 2s, 6H, 2 OCH_3); 6.6 (s, 1H); 6.7 (s, 1H); 6.8 (d, 1H, J=5 Hz, H—C-10); 7.2 (d, 1H, J=5 Hz, H—C-9)[f]
6b·HCl	90	215°	$C_{23}H_{24}ClNO_2S$ (413.8)	2790; 2740	2.5–4.1 (m, 12H, including 1s, 3H, OCH_3); 5.1 (s, 2H, OCH_2—Ar); 6.55 (s, 1H); 6.65 (s, 1H); 6.75 (d, 1H, J=5 Hz, H—C-10); 7.15 (d, 1H, J=5 Hz, H—C-9); 7.2–7.5 (m, 5 H_{arom})[f]
9a	77	gum	$C_{17}H_{21}NO_4S$ (335.5)	3400; 3280; 1645	2.8 (t, 2H, J=7 Hz, thiophene-CH_2); 3.4 (t, 2H, J=7 Hz, NH—CH_2); 3.55 (s, 2H, CO—CH_2); 3.8–3.9 (2s, 6H, 2 OCH_3); 4.2 (br s, 2H, NH and OH); 4.5 (s, 2H, CH_2OH); 6.7–7.2 (m, 5 H_{arom})
9b	80	120–121°	$C_{23}H_{25}NO_4S$ (411.7)	3400; 3290; 1645	3.35 (t, 2H, J=7 Hz, NH—CH_2); 3.5 (s, 2H, CO—CH_2); 3.8 (s, 3H, OCH_3); 4.3–4.6 (s and br s, 4H, CH_2OH and NH); 5.1 (s, 2H, OCH_2—Ar); 6.6–7.4 (m, 10 H_{arom})

[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.31, H ±0.34, N ±0.30).
[b] Hygroscopic, unstable compound which was not analysed.
[c] D_2O solution.
[d] DMSO-d_6 solution.
[e] NH absorption of the free base was not seen clearly but the C=N absorption of the starting material disappeared completely.
[f] Spectrum of free base.

***N*-(3-Thienyl-β-ethyl)-3,4-dimethoxyphenylacetamide (3a):**
A mixture of 3-thienylethylamine (**1**; 1.27 g, 0.01 mol) and 3,4-dimethoxyphenylacetic acid (**2a**; 1.96 g, 0.01 mol) is heated in an oil bath at 150–160 °C (bath temp.) for 2 h, then cooled, and dissolved in chloroform (30 ml). The chloroform solution is washed with dilute hydrochloric acid (2 × 10 ml), dilute ammonia solution (2 × 10 ml), water (1 × 15 ml), and then dried with sodium sulphate. The solvent is distilled and the crude amide is recrystallised from benzene/hexane; yield: 1.9 g (62%).

7-(3,4-Dimethoxybenzyl)-4,5-dihydrothieno[2,3-*c*]pyridine Hydrochloride (4a):
A solution of the amide **3a** (1.5 g, 0.005 mol) in dry chloroform (5 ml) is cooled in ice and phosphorus pentachloride (1.2 g, 0.006 mol) is added. The mixture is allowed to stand at room temperature for 4 h and is then poured into dry ether (30 ml). The yellow solid, which is highly hygroscopic and becomes dark on exposure to atmosphere, obtained is washed with dry ether (3 × 10 ml) and used as such for the next stage; yield: 1.39 g (75%).

7-(3,4-Dimethoxybenzyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (5a):
Sodium borohydride (150 mg) is added in portions with stirring to a solution of the dihydropyridine hydrochloride **4a** (1.3 g, 0.004 mol) in methanol (15 ml) and the mixture is allowed to stand overnight. Methanol is distilled off, water (15 ml) is added, and the mixture is extracted with chloroform (2 × 20 ml). The extract is washed with water, dried, and the solvent is evaporated to give an almost colourless oil. The hydrochloride is prepared by passing dry hydrogen chloride gas into a solution of the base in dry benzene (3 ml); yield: 1.1 g (80%).

9,10-Dimethoxy-7*H*-4,5,12,12a-tetrahydrobenzo[*g*]thieno[2,3-*a*]quinolizine (6a):
A solution of the compound **5a** (500 mg, 1.7 mmol) in formalin (37%, 3 ml) and glacial acetic acid (3 ml) is heated under reflux for 1 h. The reaction mixture is diluted with water (20 ml) basified with ammonia solution (~15 ml) and then extracted with chloroform (2 × 25 ml). The extract is washed with water, dried with sodium sulphate, and evaporated to afford the title compound. The hydrochloride is prepared in the usual manner; yield: 420 mg (81%).

***N*-(3-Thienyl-β-ethyl)-4,5-dimethoxy-2-hydroxymethylphenylacetamide (9a):**
A mixture of 3-thienylethylamine (**1**; 0.6 g, 4.7 mmol) and 6,7-dimethoxy-3-isochromanone (**8a**; 1 g, 4.8 mmol) is heated for 2 h at 140 °C, then dissolved in chloroform (15 ml), washed with dilute sodium hydroxide solution, dilute hydrochloric acid, water, and dried with sodium sulphate. The compound is obtained as a gum which did not crystallise; yield: 1.3 g (77%).

Cyclisation of 9a to Quinolizine 6a:
Phosphorus pentachloride (200 mg) is added to an ice-cold solution of the amide **9a** (500 mg, 1.5 mmol) in dry chloroform (5 ml) and kept for 3 h. The reaction mixture is poured into dry ether (20 ml) and the resulting yellow solid is dissolved in methanol. Sodium borohydride (100 mg) is added and the mixture worked up as de-

scribed above; yield: 180 mg (75%). The product is identical with the quinolizine **6a** obtained as described above.

Received: January 16, 1980

[1] S. Jeganathan, M. Srinivasan, *Synthesis* **1979**, 195.
[2] S. Jeganathan, M. Srinivasan, *Ind. J. Chem.* [B] 1979 (in press).
[3] E. Campaigne, W. C. McCarthy, *J. Am. Chem. Soc.* **76**, 4466 (1954).
[4] T. Kametani, M. Ihra, *J. Chem. Soc.* [C] **1967**, 530.
[5] R. J. Spangler, *J. Org. Chem.* **42**, 2899 (1977).

0039-7881/80/0632-0471 $ 03.00