Studies on Heterocyclic Compounds; I. Synthesis of Thiophene Derivatives of Protoberberine Alkaloids

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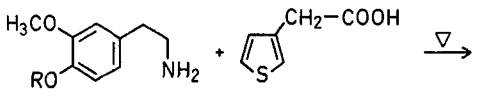
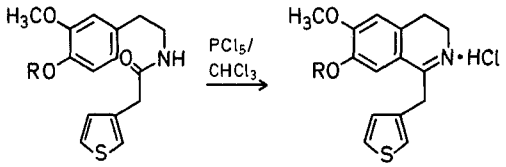
In continuation of our work on thiophene-condensed nitrogen heterocycles, we were interested in synthesising thiophene derivatives of aphorphine and protoberberine alkaloids. As the berbines and other isoquinoline derivatives have not been very successful as biologically active compounds, these investigations were taken up to study the influence of the sulphur heteroatom on the physiological activity. During our attempts to synthesise the D-ring thiophene derivatives of aphorphine alkaloids, we were able to synthesise the hitherto unreported 8*H*-5,6,12,12a-tetrahydrobenzo[*a*]thieno[2,3-*g*]quinolizines (**6a** and **6b**).

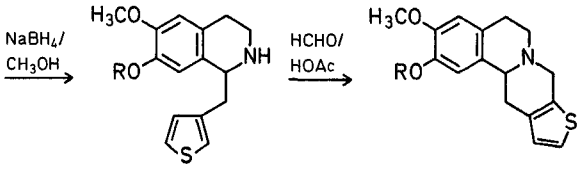
Thienylacetic acid[1] (**2**) reacted with the 2-phenylethylamine[2] **1** in the absence of solvent at 160° (bath temp.) to give the amide **3a** in excellent yield. Cyclisation of amide **3a** with phosphorus pentachloride[3] in dry chloroform afforded the dihydroisoquinoline hydrochloride **4a** (m.p. 164–165°) in 71 % yield. Reduction of the resulting dihydroisoquinoline hydrochloride **4a** with sodium borohydride in methanol gave the tetrahydroisoquinoline **5a** in 79 % yield. Compound **5a**, by a Mannich-type reaction[4] with formaldehyde and acetic acid yielded 2,3-dimethoxy-8*H*-5,6,12,12a-tetrahydrobenzo[*a*]thieno[2,3-*g*]quinolizine (**6a**).



1 **2**



3a, b **4a, b**



5a, b

6a R = H_3C

b R = $C_6H_5-CH_2-$

The latter cyclisation, however, though could take place either at the 2- or the 4-position of the thiophene ring; the reaction proceeded to give exclusively the 2-cyclised product only. T.L.C. analysis of the reaction product showed a single spot, confirming that the reaction product is homogeneous. The ^{1}H-N.M.R. spectrum of the pure compound is not very much different from that of the crude reaction product, which shows doublets at $\delta = 6.9$ ppm ($J = 5$ Hz) and

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Table. Characterisation of Products **3–6**

Product	R	Yield [%]	m.p.	Molecular formula[a]	I.R. ($CHCl_3$) ν_{max} [cm^{-1}]	^{1}H-N.M.R. (Solvent) δ [ppm]
3a	CH_3	92	94–95°	$C_{16}H_{19}NO_3S$ (305.2)	3390, 1650	$CDCl_3$: 2.7 (t, 2H, J=7 Hz, Ar—CH_2); 3.3–3.6 (m, 4H, CO—CH_2 and NH—CH_2); 3.8–3.9 (2s, 6H, $2OCH_3$); 6.5 (bs, 1H, NH); 6.7–7.4 (m, $6H_{arom}$)
3b	$CH_2C_6H_5$	74	82–83°	$C_{22}H_{23}NO_3S$ (381.4)	3370, 1650	$CDCl_3$: 2.6 (t, 2H, J=7 Hz, Ar—CH_2); 3.3 (t, 2H, J=7 Hz, N—CH_2); 3.4 (s, 2H, CO—CH_2); 3.8 (s, 3H, OCH_3); 5.1 (s, 2H, Ar—CH_2—O); 5.9 (bs, 1H, NH); 6.4–7.5 (m, $11H_{arom}$)
4a	CH_3	71	164–165°	$C_{16}H_{18}ClNO_2S$ (323.8)	1645	D_2O: 2.95 (t, 2H, J=8 Hz, Ar—CH_2); 3.65–4.0 (m, 8H, $2OCH_3$ and N—CH_2); 4.4 (s, 2H, N=C—CH_2); 6.8–7.5 (m, $5H_{arom}$)
4b	$CH_2C_6H_5$	85	208–210°	$C_{22}H_{22}ClNO_2S$ (399.9)	1640	$CDCl_3/CF_3COOH$: 3.1 (t, 2H, J=8 Hz, Ar—CH_2); 3.8–4.3 (m, 7H, OCH_3, C=N—CH_2, N=C—CH_2); 5.5 (s, 2H, Ar—CH_2—O); 6.6–7.4 (m, $10H_{arom}$)
5a·HCl	CH_3	79	184–185°	$C_{16}H_{20}ClNO_2S$ (325.9)	3300[b]	$(CD_3)_2CO/CCl_4$[b]: 2.5–3.2 (m, 7H, including 1H exchangeable with D_2O); 3.6–3.7 (2s, 6H, $2OCH_3$); 4.1 (m, 1H, H-1); 6.5 (s, 1H, H-5); 6.6 (s, 1H, H-8); 6.9–7.3 (m, 3H, thiophene ring)
5b·HCl	$CH_2C_6H_5$	83	191–192°	$C_{22}H_{24}ClNO_2S$ (402.0)	3310[b]	$(CD_3)_2CO/CCl_4$[b]: 2.6–3.3 (m, 7H, including 1H exchangeable with D_2O); 3.75 (s, 3H, OCH_3); 4.05 (m, 1H, H-1); 5.0 (s, 2H, Ar—CH_2—O); 6.6 (s, 1H, H-5); 6.75 (s, 1H, H-8); 6.9–7.6 (m, $8H_{arom}$)
6a·HCl	CH_3	95	238° (dec.)	$C_{17}H_{20}ClNO_2S$ (337.9)	2780[b], 2740	$CDCl_3$[b]: 2.4–4.1 (m, 15H, including 2s, 6H, $2OCH_3$ at 3.8–3.9); 6.55 (s, 1H, H-4); 6.65 (s, 1H, H-1); 6.9 (d, 1H, J=5 Hz, H-11); 7.3 (s, 1H, J=5 Hz, H-10)
6b·HCl	$CH_2C_6H_4$	90	231° (dec.)	$C_{23}H_{24}ClNO_2S$ (414.0)	2775[b], 2735	CD_3COOD[b]: 2.8–4.8 (m, 12H, including 1s, 3H, OCH_3 at 3.9); 5.15 (s, 2H, O—CH_2—Ar); 6.8–7.6 (m, $9H_{arom}$)

[a] All products gave satisfactory microanalyses (C ±0.37, H ±0.47, N ±0.42).
[b] Spectrum of free base

δ=7.3 ppm (J=5 Hz) (AB pattern due to thiophene ring) and no singlet due to 4-cyclised product. This is to be anticipated as the 2-position is far more reactive than 4-position in the thiophene ring. Compound **6a** was obtained by an independent approach[5] using the tetrahydroisoquinoline hydrochloride **5a**·HCl directly in aqueous medium with formalin. Compound **6b** was also synthesised thus in 83% yield. Debenzylation of **6b**, however, has not been achieved.

All compounds were characterised by ^{1}H-N.M.R., I.R., Mass spectra, and microanalysis. These data are listed in the Table for the dimethoxy and the benzyloxymethoxy derivatives. Further work is in progress towards the phenolic compound (R=H) and other substituted derivatives.

***N*-(3,4-Dimethoxy-β-phenethyl)-3-thienylacetamide (3a):**
A mixture of 2-(3,4-dimethoxyphenyl)-ethylamine (**1a**; 1.8 g, 10 mmol) and thienylacetic acid (**2**; 1.4 g, 10 mmol) is heated on an oil bath at 150–160° for 2.5 h, cooled, and dissolved in chloroform. The chloroform solution is washed with dilute hydrochloric acid, dilute ammonia solution, and water, then dried with sodium sulphate. The solvent is distilled and the crude amide is recrystallised from benzene/hexane; yield: 2.8 g (92%); m.p. 94–95°.

1-(3-Thenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline Hydrochloride (4a):
A solution of amide **3a** (2 g, 6.5 mmol) in dry chloroform (15 ml) is cooled in ice and phosphorus pentachloride (1.8 g) is added. The mixture is allowed to stand at room temperature for 24 h and is then poured into anhydrous ether (100 ml). The solid is filtered, washed with ether, and dissolved in absolute methanol. The hydrochloride is crystallised from this methanolic solution by adding anhydrous ether; yield: 1.5 g (71%); m.p. 164–165°.

1-(3-Thenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5a):
Sodium borohydride (120 mg) is added in portions with stirring to a solution of **4a** (1 g, 3 mmol) in methanol (15 ml) and kept over night. To the solution, water (40 ml) is added and then the mixture is extraced with chloroform. The extract is washed with water, dried with sodium sulphate, 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; yield: 800 mg (79%); m.p. 184–185°.

2,3-Dimethoxy-8*H*-5,6,12,12a-tetrahydrobenzo[*a*]thieno[2,3-*g*]-quinolizine (6a):
A mixture of hydrochloride **5a** (300 mg), 37% formalin (9 ml), and glacial acetic acid (9 ml) is heated under reflux for 45 min. The reaction mixture is diluted with water, basified with ammonia solution, and then extracted with chloroform. The extract is washed with water, dried with sodium sulphate, and evaporated to afford a gum which is T.L.C. pure. The hydrochloride is prepared by passing dry hydrogen chloride gas into a solution of the base in dry benzene; yield: 290 mg (95%); m.p. 238° (dec).

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