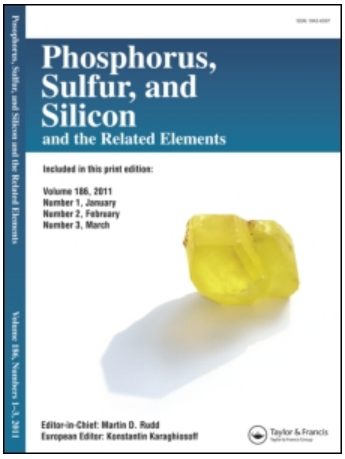

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STUDIES ON HETEROCYCLIC COMPOUNDS VI: Synthesis of Thiophene Isosters of Protoberberine Alkaloids[1]

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STUDIES ON HETEROCYCLIC COMPOUNDS VI
Synthesis of Thiophene Isosters of Protoberberine Alkaloids[1]

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Synthesis of thiophene isosters of protoberberine alkaloids (6, 12, 19) is described. The Mannich type reaction of the tetrahydroisoquinolines (5, 11) and the thienopyridine (18) with formaldehyde in glacial acetic acid afforded the title compounds. Cyclization of the tetrahydroisoquinoline derivative (23) failed to furnish the D-ring protoberberine isoster (25), but gave an unexpected product, the oxazepinoisoquinoline derivative (24). The conversion of the compound (24) to the 2-substituted isoquinoline (27) is also described.

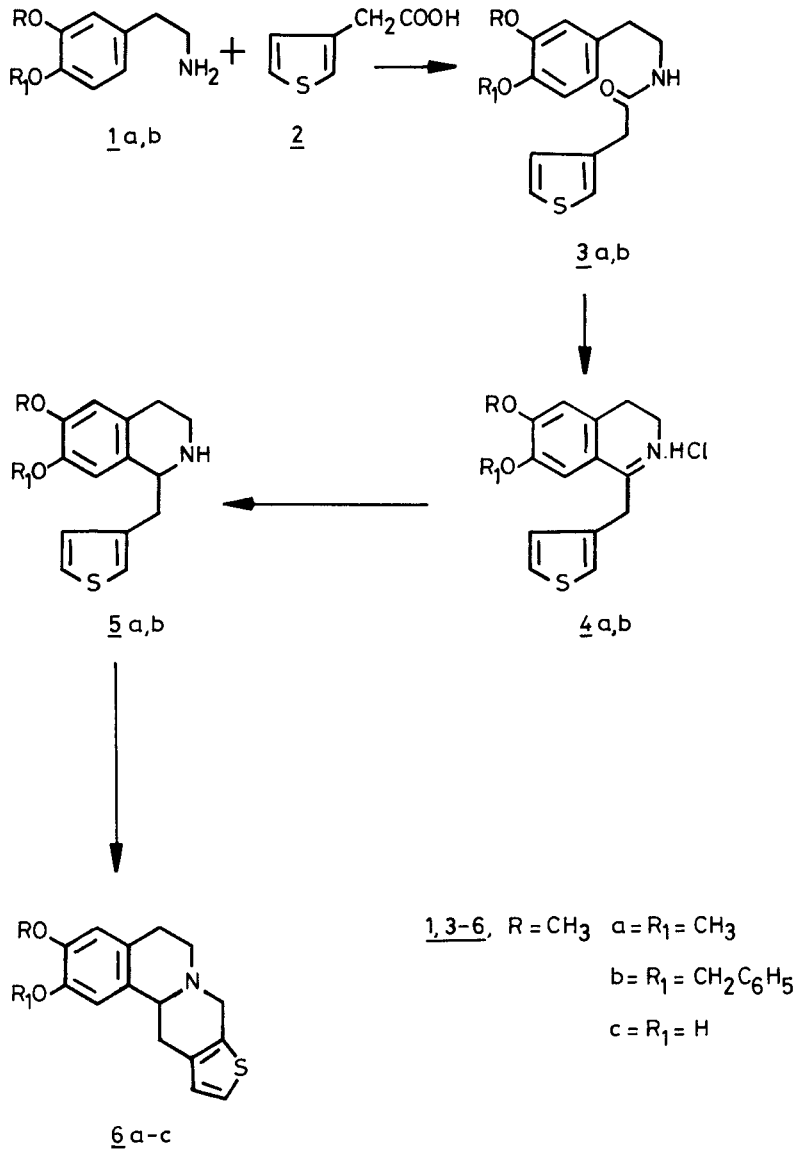
INTRODUCTION

There are many reports in literature on the isolation, synthesis and biological activities of protoberberine alkaloids. The tetrahydroprotoberberine alkaloids have not been successful as biologically active compounds, except they exhibited CNS depressant action.[2] No heterocyclic isoster of protoberberine alkaloids has been synthesized so far. This prompted us to undertake the synthesis of a new class of compounds viz. the thiophene isosters of protoberberine alkaloids with a view to study the effect of an extra heteroatom, sulphur, on the biological activities of these compounds. We report here our results on the synthesis of D-ring. A-ring and A/D-ring thiophene isosters of protoberberines as well as our attempts to synthesize a new type of D-ring isoster (25).

RESULTS AND DISCUSSION

3-Thienylacetic acid[3] (2) reacted with 3,4-dimethoxyphenethylamine[4] (1a) in the absence of any solvent at 160°C (bath temp.) to give the amide (3a) in 92% yield. Cyclization of the amide (3a) with phosphorus pentachloride in dry chloroform afforded the dihydroisoquinoline hydrochloride (4a) in 71% yield. Reduction of the hydrochloride (4a) with sodium borohydride gave the tetrahydroisoquinoline (5a) in 79% yield. The Mannich reaction of the compound (5a) with formaldehyde and acetic acid yielded 2,3-dimethoxy-8H-5,6,12,12a-tetrahydrobenzo[a]thieno[2,3-g]-quinolizine (6a) (Scheme 1), which is a D-ring thiophene isoster of protoberberines.

The cyclization of the compound (5a), though could take place either at the 2- or the 4- position of the thiophene ring, proceeded to give the 2-cyclized product (6a). T.L.C. analysis of the reaction product showed a single spot, confirming that the reaction product is homogeneous. The ^{1}H-NMR spectrum of the pure compound is not very much different from that of the reaction product, which shows two doublets at 6.9 (J = 5Hz, 1H) and 7.3 (J = 5Hz, 1H) (AB pattern due to thiophene protons), confirming that the cyclization had taken place at the 2-position of the thiophene ring. Compound (6b) was also synthesized in 83% yield. Debenzylation of



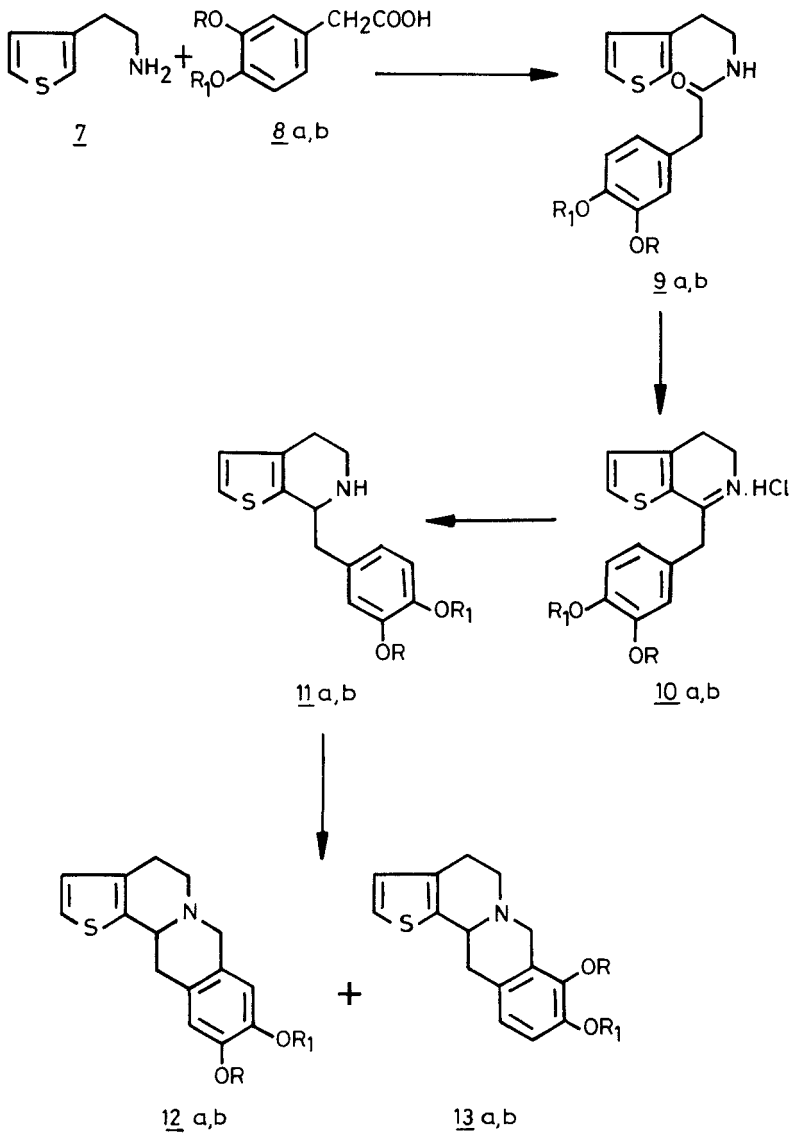
SCHEME 1

(6b) with hydrobromic acid (48/) in methanol afforded the corresponding hydroxy compound (6c) in 91% yield.

The IR spectrum of the compound (6a) showed Bohlmann bands[5] in the region 2800–2700 cm^{-1}, confirming that the quinolizidine nucleus is in *trans*-conformation. The appearance of the C_{12a}-proton at 3.7 (q) lends further support for the observation that the quinolizidine is in *trans*-conformation. The position of C_{12a}-proton is in accordance with that of the C_{13a}-proton of protoberberines.[6]

3-Thienyl-β-ethylamine[7] (7) and 3,4-dimethoxyphenylacetic acid (8a) reacted on heating to give the amid (9a) in 62% yield. Cyclization of the amide (9a) with phos-

phorus pentachloride afforded the dihydrothieno[2,3-c]pyridine hydrochloride (10a) in 75% yield. Sodium borohydride reduction of the compound (10a) furnished the tetrahydrothieno[2,3-c]pyridine (11a) in 80% yield. Finally, Mannich reaction of the compound (11a) with formalin and acetic acid yielded 9.10-dimethoxy-7H-4,5,12,12a-tetrahydrobenzo[g]thieno[2,3-a]quinolizine (12a) in 81% yield, which is an A-ring thiophene isoster of protoberberines (Scheme 2).



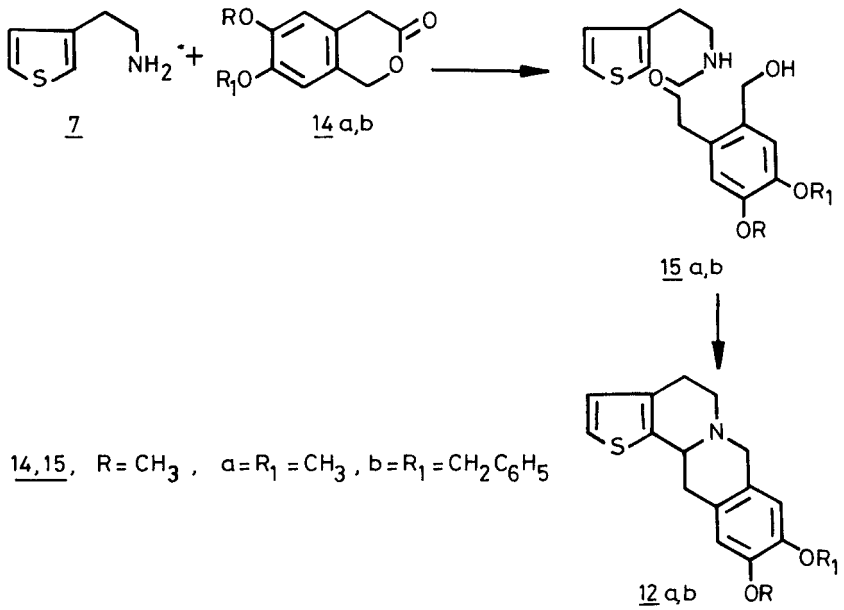
SCHEME 2

Here again, the Mannich reaction of the base (11a) could take place either at the 6′- or the 2′-position of the benzene ring to give (12a) and/or (13a). T.L.C. analysis of the reaction product showed only one spot, confirming that either (12a) or (13a) is formed. The ^{1}H-NMR spectrum of the product shows two singlets at δ6.6 (1H) and δ6.7 (1H) due to the two benzenoid protons (H—C_8 and H—C_{11}). Two doublets at δ6.85 (J = 5Hz,1H) and δ7.2 (J = 5Hz,1H) (AB pattern due to thiophene protons) were also observed. This confirms that the cyclization had taken place exclusively at 6′-position to give the product (12a) and not the other isomer (13a).

Further chemical evidence, for the formation of the compound (12a) is given in Scheme 3. 3-Thienylethylamine (7) and the isochromanone[8] (14a) were heated together to afford the hydroxymethylphenylacetamide (15a) in 77% yield. This compound was cyclized with phosphorus pentachloride followed by sodium borohydride reduction to afford a product which was identical with the compound (12a) (mixed m.p., mixed T.L.C., superimposable IR spectra). The corresponding 9-benzyloxy compound (12b) was also synthesized analogously.

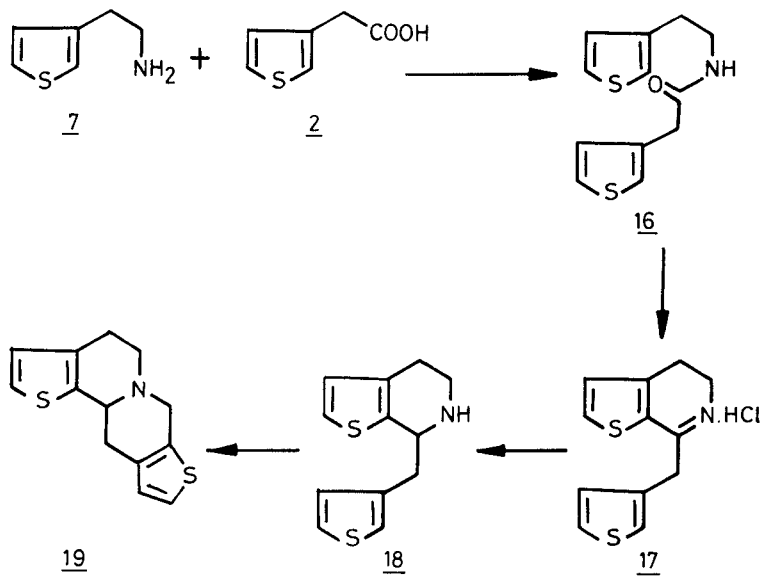
As in the previous case, the compounds (12a and 12b) showed the presence of Bohlmann bands in their IR spectrum as well as the quartet for C_{12a}-proton at δ3.7. This indicates that the quinolizidine ring is in *trans*-conformation.

Simultaneously, the synthesis of A/D-rings thiophene isoster was also carried out (Scheme 4). 3-Thienylethylamine (7) and 3-thienylacetic acid (2) were heated together to furnish the amide (16) in 85% yield, and then the amide (16) was cyclized with phosphorus pentachloride to give the compound (17) in 70% yield. Sodium borohydride reduction of (17) afforded the tetrahydrothieno 2,3-c pyridine derivative (18) in 90% yield. This compound was then subjected to Mannich reaction to afford the 7H-4,5,11,11a-tetrahydrodithieno[2,3-a, 2,3-g]quinolizine (19) in 87% yield. Its ^{1}H-NMR spectrum showed two doublets at δ6.8 (2H, J = 5Hz) and 7.15



14,15, R = CH_3 , a = R_1 = CH_3 , b = R_1 = $CH_2C_6H_5$

SCHEME 3



7 2 16 17 18 19

SCHEME 4

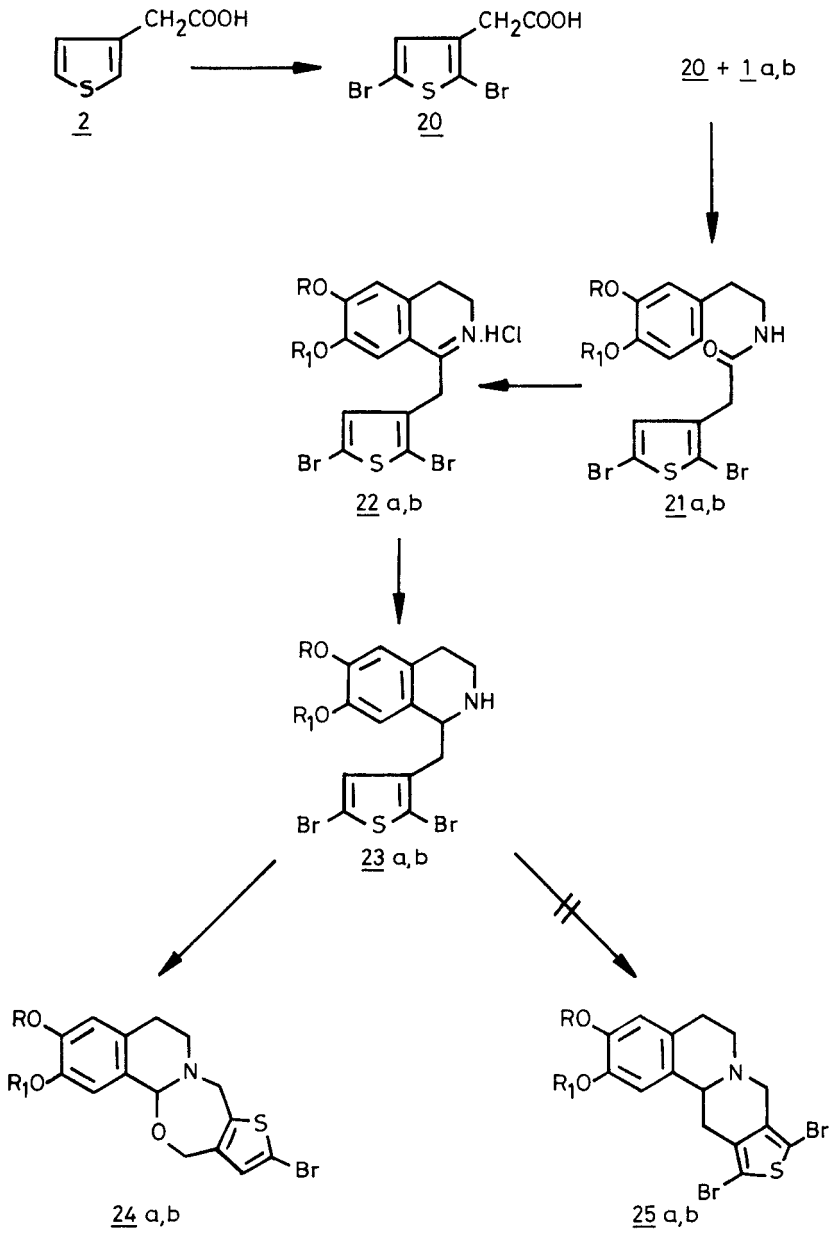
(2H, J = 5Hz). The doublet at δ6.8 was assigned to C_3 and C_{10}-protons while the doublet at 7.15 was due to C_2 and C_9-protons. These two sets of protons are more or less in the identical environments and hence appear as a AB quartet, thus indicating that the cyclization had taken place exclusively, as anticipated, at the 2-position of the thiophene ring. The presence of Bohlmann bands and the appearance of the C_{11a}-proton at 3.6–3.7 confirms that the quinolizidine nucleus is in *transoid*-conformation.

As an extension of this work, it was felt worthwhile to synthesize a D-ring thiophene isoster of the type (25), where the cyclization will take place at the 3-position of the thiophene ring. To achieve this it is necessary to block the active 2-position of the thiophene ring so that the cyclization can be forced to take place at the 3-position.

In an attempt to prepare the 2-bromo-3-thienylacetic acid, 3-thienylacetic acid (2) was brominated in acetic acid medium, but it was observed that when the acid (2) was treated with either one or excess of bromine it afforded only the 2,5-dibromo-3-thienylacetic acid (20). The synthesis of the compound (25) was carried out with the dibromo acid (20) as shown in Scheme 5.

The dibromo acid (20) was condensed with the phenethylamine (1a) to give the amide (21a) in 70% yield. Cyclization of the amide afforded the dihydroisoquinoline hydrochloride (22a) in 88% yield. Reduction of the compound (22a) with sodium borohydride furnished the tetrahydroisoquinoline derivative (23a) in 95% yield. The Mannich reaction of the base (23a) with formalin and glacial acetic acid afforded a product, m.p. 144–146 C, in 91% yield.

Its IR spectrum did not show the NH absorption, and the mass spectrum showed the molecular ion at m/z 395,397(1:1), which indicates that a bromine atom from (23a) is eliminated and one carbon, hydrogen and oxygen atoms each have been incorporated. Its ^{1}H-NMR spectrum showed a multiplet at δ2.5–3.2(4H) two singlets at 3.8–3.9(6H), a doublet at 4.0(1H), a doublet at 4.55(1H), a singlet at 4.8(2H), a singlet at 5.4(1H,H—C_{13a}) and three singlets at 6.6, 6.8 and 6.85(1H each). Based on

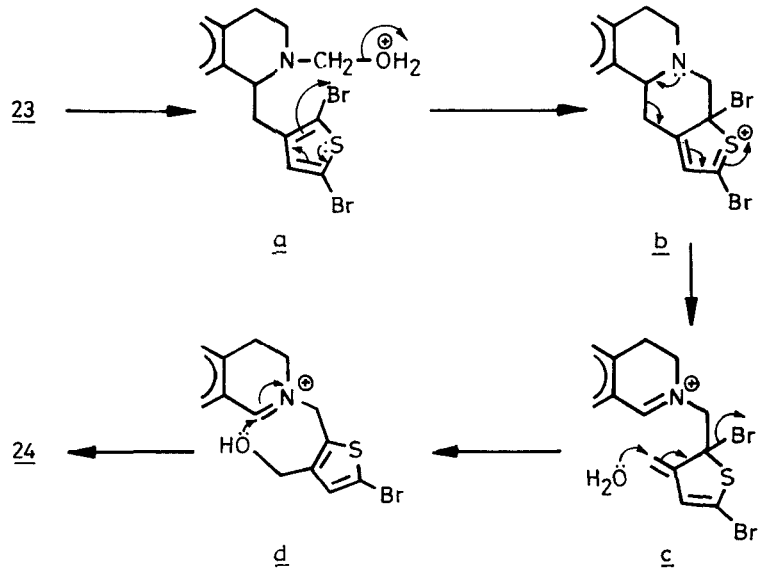


1, 21-25, R = CH_3 , a=R_1=CH_3 , b = R_1 = $CH_2C_6H_5$

SCHEME 5

the above mentioned spectral data the structure (24a) was assigned to the product, viz. 2-bromo-7,8-dimethoxy-4,5,10,11-tetrahydro-13*H*-thieno[2',3':5,6][1,3]oxazepino[2,3-*a*]isoquinoline.

A probable mechanistic pathway for the formation of the compounds (24) is outlined in Scheme 6. The tetrahydroisoquinoline (23) first forms the intermediate **a**

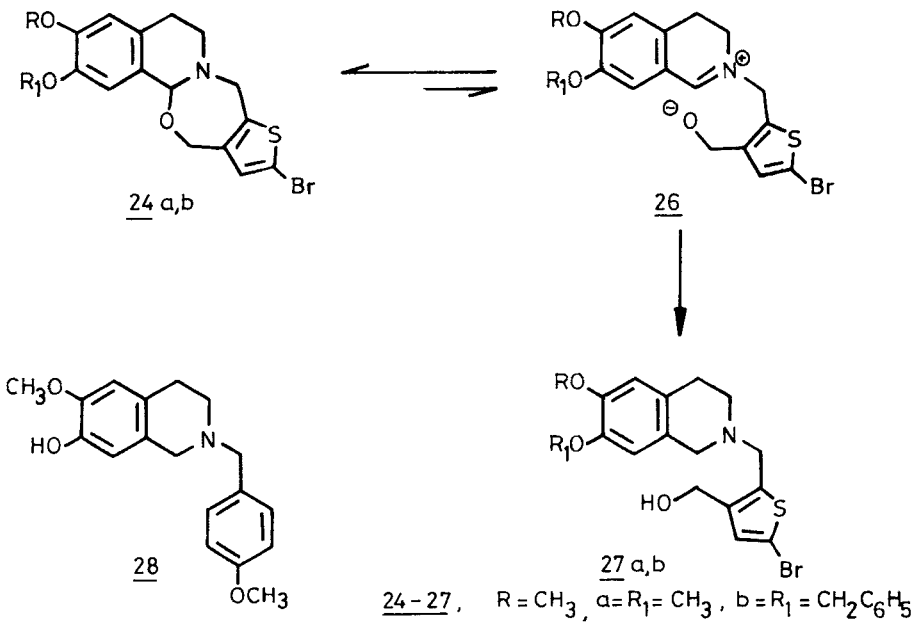


SCHEME 6

from which a molecule of water is eliminated to give **b**. Subsequently the bond β- to nitrogen cleaved to give **c** and a water molecule attacks the exocyclic double bond, thereby eliminating the bromine atom to give **d** where the aromaticity of the thiophene ring is regained. The hydroxyl group of **d** then undergoes a Michael type addition across the C=N bond to give the oxazepinoisoquinoline derivative (24).

The UV spectrum of the compound (24a) in methanol showed λmax at 240 (log 2.52), 310 (log 2.37) and 368 (log 2.34), which is characteristic of the dihydroisoquinolinium chromophore. So it was thought this compound (24a) exists in equilibrium with (26a). However, the ^{1}H-NMR of (24a) did not show any signals corresponding to (26a). So even if there is any equilibrium in polar solvents it must be to a small extent that it cannot be observed in ^{1}H-NMR. The reduction of (24a) with sodium borohydride was attempted, in order to reduce (26a) if present, since such an approach might shift the quilibrium to (26a) and then it could be converted to (27a). Sodium borohydride reduction of (24a) indeed a afforded the 2-(5-bromo-3-hydroxymethyl-2-thenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (27a) in 76% yield.

The IR spectrum of the compound (27a) showed a broad band at 3350–3100 cm^{-1} for the OH group. Its ^{1}H-NMR spectrum showed the following signals. A singlet at 2.8(4H), a singlet at 3.6(2H), a singlet at 3.75(2H), two singlets at 3.8–3.9(6H), a singlet at 4.6(3H), a braod singlet at 4.8(OH, exchangeable with D_2O) and three singlets at 6.5, 6.6 and 6.9(1H each). The singlet for the two C_3 and C_4-methylenes at 2.8 is rather unusual. The naturally occurring 2-benzyl tetrahydriisoquionoline alkaloid Sendaverine[9] (28) exhibits a similar ^{1}H-NMR spectrum. It also showed a singlet at 2.7(4H) for the C_3 and C_4 methylene groups. Similarly the corresponding benzyloxy compound (27b) was also synthesized.



SCHEME 7

SUMMARY

The tetrahydroisoquinolines (5,11) and the thienopyridine derivatives (18) reacted smoothly with formaldehyde in glacial acetic acid to afford the corresponding thiophene isoster of protoberberine alkaloids (6,12,19). In all these compounds the quinolizidine ring was found tobe in *trans*-conformation. The Mannich reaction of the bromothenylisoquinoline (23) afforded the oxazepinoisoquinoline derivative (24) instead of the expected quinolizidine compound (25). A reasonable mechanism is also proposed for this rearrangement and the product (25) was converted into N-substituted isoquinoline derivative (27). The biological testing of these compounds for antiinflammatery as well as CNS depressant action will be published elsewhere.

EXPERIMENTAL

Melting points were recorded with a Toshnival melting point apparatus and are uncorrected. Infrared aspectra were recorded in chloroform (unless otherwise stated) with a Perkin-Elmer model 257 spectrophotometer. NMR spectra were run on a Varian XL-100 instrument (TMS as internal standard) in $CDCl_3$ unless otherwise specified.

2,5-Dibromo-3-thienylacetic acid (20)

Bromine (3.2 g, 20 mmoles) in 10 ml of glacial acetic acid was added dropwise to a solution of 3-thienylacetic acid (2.1 g, 10 mmoles) in 10 ml of glacialacetic acid at 5–10° and stirred for 2 hours at room temp. The reaction mixture was poured into water and the product was filtered, dried and recrystallized from benzene. m.p. 116–118°.
Yield: 2.4 g (80%). IR: 3200–2900 cm^{-1}.
^{1}H-NMR: 3.6 (s, 2H), 7.0 (s, 1H), 7.7 (bs, COOH).
Anal: calcd. for $C_6H_4Br_2O_2S$: C, 24.00; H, 1.33. Found: C, 24.31; H, 1.51%.

General preparation of the amids (3, 9, 16, 21)

A mixture of the amine (10 mmoles) and the acid (10 mmoles) was heated on an oil bath at 150–160° for two hours, cooled and dissolved in chloroform. The chloroform solution was washed with dilute HCl, dilute ammonia solution and water, then dried with sodium sulphate. The solvent was evaporated and recrystallized from benzene/hexane.

N-(3,4-Dimethoxy-β-phenethyl)-3-thienylacetamide (3a) This compound had m.p. 94–95°. Yield: 92%. IR: 3390 (NH), 1650 (CO)cm^{-1}; ^{1}H-NMR: δ 2.7 (t, 2H, J = 7 Hz), 3.45 (t, 2H, J = 7 Hz), 3.55 (s, sH), 3.8–3.9(2, 6H) 5.9 (bs, NH) and 6.5–7.3 (m, 6H).
Anal. calcd. for $C_{16}H_{19}NO_3S$: C, 62.96; H, 6.23; N, 4.95
Found: C, 62.85; H, 6.37; N, 4.59%.

N-(4-Benzyloxy-3-methoxy-β-phenethyl)-3-thienylacetamide (3b) This compound had m.p. 82–83°. Yield: 74%. IR: 3370, 1650 cm^{-1}. ^{1}H-NMR: δ 2.6 (t, 2H, J = 7 Hz), 3.3 (t, 2H, J = 7 Hz), 3.4 (s, 2H), 3.8 (s, 3H), 3.8 (s, 3H), 5.1 (s, 2H), 5.9 (bs, NH), 6.7–7.5 (m, 11H).
Anal. calcd. for $C_{22}H_{23}NO_3S$: C, 69.29; H, 6.03. Found: C, 69.51; H, 6.34%.

N-(3-Thienyl-β-ethyl)-3,4-dimethoxyphenylacetamide (9a) This compound had m.p. 107–108°. Yield: 62%. IR: 3380, 1650 cm^{-1}. ^{1}H-NMR: δ 2.7 (t, 2H, J = 7 Hz), 3.3–3.6 (m, 4H), 3.8–3.9 (2s, 6H), 5.7 (bs, NH), 6.7–7.2 (m, 6H).
Anal. calcd. for $C_{16}H_{19}NO_3S$: C, 62.96; H, 6.23; N, 4.59,
Found: C, 62.78; H, 6.28; N, 4.52%.

N-(3-Thienyl-β-ethyl)-4-benzyloxy-3-methoxyphenylacetamide (9b) This compound had m.p. 97°. Yield: 66%. IR: 3380, 1650 cm^{-1}. ^{1}H-NMR: δ 2.7 (t, 2H, J = 7 Hz), 3.3–3.6 (m, 4H), 3.8 (s, 3H), 5.1 (s, 2H), 5.6 (bs, NH), 6.6–7.4 (m, 11H).
Anal. calcd. for $C_{22}H_{23}NO_3S$: C, 69.29; H, 6.03, Found: C, 69.60; H, 6.33%.

N-(3-Thienyl-β-ethyl)-3-thienylacetamide (16) This compound had m.p. 52–53°. Yield: 72%. IR: 3400, 1650 cm^{-1}. ^{1}H-NMR: δ 2.8 (t, 2H, J = 7 Hz), 3.4 (t, 2H, J = 7 Hz), 3.55 (s, 2H), 6.1 (bs, NH) 6.8–6.9 (m, 6H).
Anal. calcd. for $C_{12}H_{13}NOS_2$: C, 57.37; H, 5.17; Found: C, 57.51; H, 4.95%.

N-(3,4-Dimethoxy-β-phenethyl)-2,5-dibromo-3-thienylacetamide (21a) This compound had m.p. 124°. Yield: 70%. IR: 3380, 1650 cm^{-1}. ^{1}H-NMR: 2.7 (t, 2H, J = 7 Hz), 3.3–3.5 (m, 4H), 3.85 (s, 6H), 5.85 (bs, NH), 6.6–6.9 (m, 4H).
Anal. calcd. for $C_{16}H_{17}Br_2NO_3S$: C, 41.46; H, 3.67; N, 3.02.
Found: C, 41.21; H, 3.92; N, 2.90%.

N-(4-Benzyloxy-3-methoxy-β-phenethyl)-2,5dibromo-3-thienylacetamide (21b) This compound had m.p. 115–116°. Yield: 65%. IR: 3390, 1650 cm^{-1}. ^{1}H-NMR: δ 2.7 (t, 2H, J = 7 Hz), 3.3–3.6 (m, 4H), 3.8 (s, 3H), 5.1 (s, 2H), 5.6 (bs, NH), 6.5–6.8 (m, 3H).
Anal. calcd. for $C_{22}H_{21}Br_2NO_2S$: C, 48.97; H, 3.89; N, 2.95.
Found: C, 48.77; H, 3.61; N, 2.48%.

General preparation of the hydrochlorides (4, 10, 17, 22)

A solution of the amide (10 mmoles) in dry chloroform (15 ml) was cooled in ice and phosphorus pentachloride (15 mmoles) was added. The mixture was allowed to stand at room temperature for 10 hours and was then poured into dry ether. The yellow solid was filtered and recrystallized from dry methanol and dry ether.

1-(3-Thenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (4a) This compound had m.p. 164–165°. Yield: 77%. IR: 1645 cm^{-1} (C=N). ^{1}H-NMR: (D_2O) δ 2.95 (t, 2H, J = 8 Hz), 3.6–4.0 (m, 8H), 4.4 (s, 2H), 6.85 (s, 1H), 7.0 (d, 1H, J = 5 Hz), 7.3 (s, 1H), 7.4 (m, 2H).
Anal. calcd. for $C_{18}H_{18}ClNO_2S$: C, 59.44; H, 5.57; N, 4.33.
Found: C, 59.33; H, 5.63; N, 4.65%.

1-(3-Thenyl)-7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline hydrochloride (4b) This compound had m.p.

208–210°. Yield: 85%. IR: 1640 cm^{-1}. ^{1}H-NMR: (DMSO-d_6) δ 3.1 (t, 2H, J = 8 Hz); 3.8–4.1 (m, 5H), 4.3 (s, 2H), 5.1 (s, 2H), 6.9–7.5 (m, 10H).
Anal calcd. for $C_{22}H_{22}ClNO_2S$: C, 66.16; H, 5.51.
Found: C, 66.02; H, 5.81%.

7-(3'-4'-Dimethoxybenzyl)-4,5-dihydrothieno[2,3-c]pyridine hydrochloride (10a) This compound was highly hygroscopic and became black on exposure to atmosphere. It was washed several times with dry ether and used as such for next reaction. IR: 1620 cm^{-1}; ^{1}H-NMR(D_2O): δ 3.1 (t, 2H, J = 8 Hz), 3.7–4.1 (m, 10H), 6.9 (m, 3H), 7.1 (d, 1H, J = 5 Hz), 8.0 (d, 1H, J = 5 Hz).

7-(4'-Benzyloxy-3'-methoxybenzyl)-4,5-dihydrothieno[2,3-c]pyridine hydrochloride (10b) This compound was also hygroscopic and became dark on exposure to atmosphere. IR: 1625 cm^{-1}; ^{1}H-NMR(DMSO-d_6): δ 3.1 (t, 2H, J = 8 Hz), 3.5–4.0 (m, 5 Hz), 4.2 (s, 2H), 5.0 (s, 2H), 6.7–7.4 (m, 9H), 8.05 (d, 1H, J = 5 Hz).

7-(3-Thenyl)-4,5-dihydrothieno[2,3-c]pyridine hydrochloride (17) This compound had m.p. 223° (dec.). Yield: 70%. IR: 1640 cm^{-1}, ^{1}H-NMR (D_2O): δ 3.1 (t, 2H, J = 8 Hz), 3.9 (t, 2H, J = 8 Hz), 4.85 (s, 2H), 7.0–7.4 (m, 4H), 8.1 (d, 1H, J = 5 Hz).
Anal. calcd. for $C_{12}H_{12}NS_2Cl$: C, 53.33; H, 4.46.
Found: C, 53.58; H, 4.70%.

1-(2,5-Dibromo-3-thenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (22a) This compound had m.p. 185° (dec.) Yield: 88%. IR: 1640 cm^{-1}; ^{1}H-NMR(DMSO-d_6): δ 3.1 (t, 2H, J = 8 Hz), 3.7–4.0 (m, 8H), 4.5 (s, 2H), 7.15 (s, 1H), 7.3 (s, 1H), 7.4 (s, 1H).
Anal. calcd. for $C_{16}H_{16}Br_2NO_2S$: C, 39.90; H, 3.32.
Found: C, 39.56; H, 3.51%.

1-(2,5-Dibromo-3-thenyl)-7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline hydrochloride (22b) This compound had m.p. 210° (dec.). Yield: 87%. IR: 1640 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 3.1 (t, 2H, J = 8 Hz), 3.9 (t, 2H, J = 8 Hz), 4.0 (s, 3H), 4.2 (s, 2H), 5.2 (s, 2H), 7.1 (s, 1H), 7.2 (s, 1H), 7.4 (s, 5H), 7.5 (s, 1H).
Anal. calcd. for $C_{22}H_{20}Br_2NO_2S$: C, 47.39; H, 3.59.
Found: C, 47.42; H, 3.38%.

General preparation of the tetrahydroisoquinolines (5, 11, 18, 23).

Sodium borohydride (3 mmoles) was added in portions with stirring to a solution of the dihydroisoquinoline (5 mmoles) in methanol (15 ml) and kept overnight. Methanol was evaporated water (20 ml) was added and extracted with chloroform. The extract was washed with water, dried with sodium sulphate and the solvent was evaporated to a colorless oil. The hydrochloride was prepared by passing dry hydrogen chloride gas into a solution of the base in dry benzene.

1-(3-Thenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5a) M.p. of the hydrochloride was 184–185°. Yield: 79%. IR: 3300 cm^{-1}; ^{1}H-NMR: δ 2.5–3.2 (m, 7H, including NH), 3.7–3.8 (2s, 6H), 4.1 (q, 1H, H—C_1), 6.5 (s, 1H), 6.6 (s, 1H), 6.9–7.3 (m, 3H).
Anal. calcd. for $C_{16}H_{20}ClNO_2S$: C, 59.08; H, 6.15.
Found: C, 59.38; H, 6.18%.

1-(3-Thenyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (5b) M.p. of the hydrochloride was 191–192°. Yield: 87%. IR: 3300 cm^{-1}; ^{1}H-NMR: δ 2.5–3.3 (m, 7H, including NH), 3.85 (s, 3H), 4.1 (q, 1H), 5.0 (s, 2H), 6.55 (s, 1H), 6.6 (s, 1H), 6.9–7.4 (m, 9H).
Anal. calcd. for $C_{22}H_{24}ClNO_2S$: C, 65.83; H, 5.98.
Found: C, 65.67; H, 5.95%.

7-(3',4'-Dimethoxybenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine (11a) M.p. of the hydrochloride was 241°. Yield: 80%. IR: NH absorption was not seen clearly but the C=N absorption of the starting material disappeared completely. ^{1}H-NMR: δ 2.8–3.5 (m, 7H, including NH), 3.8–3.9 (2s, 6H), 4.3 (t, 1H), 6.8–7.0 (m, 4H), 7.2 (d, 1H, J = 5 Hz).
Anal. calcd. for $C_{16}H_{20}ClNO_2S$: C, 59.08; N, 6.15; H, 4.31.
Found: C, 58.85; H, 6.14; N, 4.28%.

7-(4'-Benzyloxy-3'-methoxybenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine (11b) M.p. of the hydrochlo-

ride was 240° (dec.). Yield: 87%. IR: NH absorption was not seen clearly. ^{1}H-NMR: δ 2.9–3.7 (m, 7H, including NH), 3.9 (s, 3H), 4.25 (t, 1H, J = 8 Hz), 5.1 (s, 2H), 6.8–7.00 (m, 4H), 7.1 (d, 1H, J = 5 Hz), 7.3–7.5 (m, 5H).
Anal. calcd. for $C_{22}H_{24}ClNO_2S$: C, 65.83; H, 5.98; N, 3.49.
Found: C, 65.52; H, 6.03; N, 3.55%.

7-(3-Thenyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine (18). M.p. of the hydrochloride was 216–217°. Yield: 90%. IR: NH absorption was not seen clearly. ^{1}H-NMR: δ 2.0 (s, NH), 2.5–3.3 (m, 6H), 4.3 (t, 1H, J = 7 Hz); 6.8–7.4 (m, 5H).
Anal. calcd. for $C_{12}H_{14}ClNS_2$: C, 53.13; H, 5.16.
Found: C, 53.41; H, 5.42%.

was 232–233°. Yield: 95%. IR: 3400–3200 cm^{-1}; ^{1}H-NMR: δ 2.0 (s, NH), 2.6–3.4 (m, 6H), 3.8–3.9 (2s, 6H), 4.2 (t, 1H, J = 8 Hz), 6.6 (s, 2H), 6.9 (s, 1H).
Anal. calcd. for $C_{16}H_{18}Br_2ClNO_2S$: C, 39.75; H, 3.72; N, 2.89.
Found: C, 39.81; H, 3.79; N, 3.24%.

drochloride was 220–221°. Yield: 93%. IR: 3400–3250 cm^{-1}; ^{1}H-NMR: δ 2.6–3.3 (m, 7H), 3.8 (s, 3H), 4.1 (t, 1H, J = 8 Hz), 5.1 (s, 2H), 6.5 (s, 1H), 6.6 (s, 1H), 6.8 (s, 1H), 7.2–7.5 (m, 5H).
Anal. calcd. for $C_{22}H_{22}Br_2ClNO_2S$: C, 47.22; H, 3.93; N, 2.50.
Found: C, 47.43; H, 4.12; N, 2.71%.

General preparation of the quinolizines (6, 12, 19)

A mixture of the tetrahydroisoquine (2 mmoles), 37% formalin (9 ml) and glacial acetic acid (9 ml) was heated under reflux for 1 hr. The reaction mixture was diluted with water, basified with ammonia solution and then extracted with chloroform. The extract was washed with water, dried with sodium sulphate and evaporated to give the required compounds.

2,3-Dimethoxy-8H,5,6,12,12a-tetrahydrobenzo[a]thieno[2,3-g]quinolizine (6a) M.p. of the hydrochloride was 238° (dec.). Yield: 95%.IR: 2810, 2790, 2740 cm^{-1} (Bohlmann bands); ^{1}H-NMR: δ 2.5–3.4 (m, 6H), 3.7 (q, 1H), 3.8 (d, 1H), 3.85–3.95 (2s, 6H), 4.1 (d, 1H), J = 15 Hz), 6.6 (s, 1H), 6.7 (s, 1H), 6.8 (d, 1H, J = 5 Hz), 7.15 (d, 1H, J = 5 Hz).
Anal. calcd. for $C_{17}H_{20}ClNO_2S$: C, 60.53; H, 5.93; N, 4.15.
Found: C, 60.72; H, 6.08; N, 4.44%.

2-Benzyloxy-3-methoxy-8H-5,6,12,12a-tetrahydrobenzo[a]thieno[2,3-g]quinolizine (6b) M.p. of the hydrochloride was 231° (dec.). Yield: 91%. IR: 2800–2700 cm^{-1}; ^{1}H-NMR: δ 2.5–3.3 (m, 6H), 3.65 (q, 1H), 3.75 (d, 1H), 3.9 (s, 3H), 4.1 (d, 1H, J = 15 Hz), 5.1 (s, 2H), 6.6 (s, 1H), 6.7 (s, 1H), 6.8 (d, 1H, J = 5 Hz), 7.1 (d, 1H, J = 5 Hz), 7.2–7.5 (m, 5H).
Anal. calcd. for $C_{23}H_{24}ClNO_2S$: C, 66.82; H, 5.81; N, 3.38.
Found: C, 66.64; H, 5.97; N, 3.32%.

9,10-Dimethoxy-7H-4,5,12,12a-tetrahydrobenzo[g]thieno[2,3-a]quinolizine (12a) This compound had the m.p. 132–133°. Yield: 81%. IR: 2800–2700 cm^{-1}; ^{1}H-NMR: δ 2.6–3.3 (m, 6H), 3.65–3.8 (m, 2H), 3.8 (2s, 6H), 4.05 (d, J = 15 Hz, 1H), 6.6 (s, 1H), 6.7 (s, 1H), 6.8 (d, 1H), J = 5 Hz); 7.2 (d, 1H, J = 5 Hz).
Anal. calcd. for $C_{17}H_{20}ClNO_2S$: C, 60.53; H, 5.93; N, 4.15.
Found: C, 60.46; H, 6.12; N, 3.85%.

9-Benzyloxy-10-methoxy-7H-4,5,12,12a-tetrahydrobenzo[g]thieno[2,3-a]quinolizine (12b) M.p. of the hydrochloride was 215°C. Yield: 83%. IR: 2800–2700 cm^{-1}. ^{1}H-NMR: δ 2.5–3.2 (m, 6H), 3.5–3.7 (m, 2H), 3.8–4 (s and d, 4H), 5.1 (s, 2H), 6.5 (s, 1H), 6.6 (s, 1H), 6.7 (d, 1H), 7.1 (d, 1H), 7.2–7.5 (m, 5H).
Anal. calcd. for $C_{23}H_{24}ClNO_2S$: C, 66.82; H, 5.81; N, 3.38.
Found: C, 66.61; H, 5.77; N, 2.96%.

7H-4,5,11,11a-tetrahydrodithieno[2,3-a,2,3-g]quinolizine (19) M.p. of the hydrochloride 201–202°. Yield: 77%. IR: 2800–2700 cm^{-1}; ^{1}H-NMR: δ 2.6–3.4 (m, 6H), 3.6–3.7 (m, 2H), 4.2 (d, 1H, J = 16 Hz), 6.8 (d, 2H, J = 5 Hz), 7.1 (d, 2H, J = 5 Hz).
Anal. calcd. for $C_{13}H_{14}ClNS_2$: C, 55.12; H, 4.94.
Found: C, 54.95; H, 4.94%.

2-Hydroxy-3-methoxy-8H-5,6,12,12a-tetrahydrobenzo[a]thieno[2,3-g]quinolizine (6c) This compound had m.p. 156°. Yield: 85%. IR: 3360, 2800–2700 cm^{-1}; ^{1}H-NMR: δ 1.7 (bs, OH), 2.6–3.4 (m, 6H), 3.65 (q, 1H), 3.8 (d, 1H, J = 15 Hz), 3.9 (s, 3H), 4.1 (d, J = 15 Hz, 1H), 6.6 (s, 1H), 6.8 (s, 1H), 6.85 (d, 1H, J = 5 Hz), 7.15 (d, 1H, J = 5 Hz).
Anal. calcd. for $C_{16}H_{17}NO_2S$: C, 66.89; H, 5.92; N, 4.87.
Found: C, 67.02; H, 5.65; N, 4.52%.

General preparation of the hydroxymethyl amides (15a,b)

A mixture of 3-thienylethylamine (7,5 mmoles) and the isochromanone (14,5.1 mmoles) was heated for 2 hr at 140° and then worked up according to the procedure described for the amide (3).

N-(3-Thienyl-β-ethyl)-4,5-dimethoxy-2-hydroxymethylphenylacetamide (15a) This compound was a gum. Yield: 77%. IR: 3400, 3280, 1645 cm^{-1}; ^{1}H-NMR: δ 2.8 (t, 2H, J = 7 Hz), 3.4 (t, 2H, J = 7 Hz), 3.5 (s, 2H), 3.8–3.9 (2s, 6H), 4.2 (bs, OH, NH), 4.5 (s, 2H), 6.7–7.2 (m, 5H).
Anal. calcd. for $C_{17}H_{21}NO_4S$: C, 60.89; N, 6.26.
Found: C, 60.97; H, 5.92%.

N-(3-Thienyl-β-ethyl)-4-benzyloxy-5-methoxy-2-hydroxymethylphenylacetamide (15b) This compound had m.p. 120°. Yield: 80%. IR: 3400, 3290, 1645 cm^{-1}; ^{1}H-NMR: δ 2.7 (t, 2H, J = 7 Hz), 3.3 (t, 2H, J = 7 Hz), 3.5 (s, 2H), 3.8 (s, 3H), 4.3–4.6 (s and bs, 4H), 5.1 (s, 2H), 6.6–7.4 (m, 10H).
Anal. calcd. for $C_{23}H_{25}NO_4S$: C, 67.15; H, 6.08.
Found: C, 67.43; H, 5.82%.

Preparation of oxazepinoisoquinolines (24a and 24b)

A mixture of the tetrahydroisoquinoline (23, 2 mmoles) and formalin (37% 6 ml) in glacial acetic acid (10 ml) was refluxed for 1 hr. and worked up according to the procedure described for the compounds (6).

2,3-Dimethoxy-13aH-5,6,8,12-tetrahydrothieno[2',3'-5,6]oxazepino[2,3-a]isoquinoline (24a) This compound had m.p. 144–146°. Yield: 91%. IR: 3000, 1600 cm^{-1}; ^{1}H-NMR: δ 2.5–3.2 (m, 4H), 3.8–3.9 (2s, 6H), 4.0 (d, 1H, J = 15 Hz), 4.5 (d, 1H, J = 15 Hz), 4.8 (s, 2H), 5.4 (s, 1H), 6.6 (s, 1H), 6.8 (s, 1H), 6.8 (s, 1H).
Anal. calcd. for $C_{17}H_{18}BrNO_3S$: C, 51.51; H, 4.54; N, 3.53.
Found: C, 51.38; H, 4.71; N, 3.47%.

2-Benzyloxy-3-methoxy-13aH-5,6,8,12-tetrahydrothieno[2',3'-5,6]oxazepino[2,3-a]isoquinoline (24b) This compound had m.p. 138–140°. Yield: 80%. IR: 3000, 1600 cm^{-1}; ^{1}H-NMR: δ 2.5–3.4 (m, 4H), 3.85 (s, 3H), 4.0 (d, 1H, J = 15 Hz), 4.6 (d, 1H, J = 15 Hz), 4.8 (s, 2H), 5.1 (s, 2H), 5.45 (s, 1H), 6.6 (s, 1H), 6.75 (s, 1H), 7.2–7.5 (m, 5H).
Anal. calcd. for $C_{23}H_{22}BrNO_3S$: C, 58.47; H, 4.66; N, 2.96.
Found: C, 58.61; H, 4.38; N, 2.89%.

General Preparation of the 2-Thenyl isoquinolines (27a,b)

Sodium borohydride (1 mmole) was added in portions to a solution of the oxazepinoisoquinoline (24, 2 mmoles) in methanol at 10–20°, kept overnight and worked up in the usual manner.

2-(5-Bromo-3-hydroxymethyl-2-thenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (27a) This compound had m.p. 132–133°. Yield: 76%. IR: 3350–3100 cm^{-1}; ^{1}H-NMR: δ 2.8 (s, 4H), 3.6 (s, 2H), 3.75 (s, 2H), 3.8–3.9 (2s, 6H), 4.5 (s, 2H), 4.8 (bs, OH), 6.5 (s, 1H), 6.6 (s, 1H), 6.9 (s, 1H).
Anal. calcd. for $C_{18}H_{20}BrNO_3S$: C, 51.25; H, 5.02; N, 3.53.
Found: C, 51.05; H, 5.38; N, 3.38%.

2-(5-Bromo-3-hydroxymethyl-2-thenyl)-7-benzyloxy-3-methoxy-1,2,3,4-tetrahydroisoquinoline (27b) This compound had m.p. 121–12°. Yield: 60%. IR: 3400–3200 cm^{-1}; ^{1}H-NMR: δ 2.8 (s, 4H), 3.5 (s, 2H), 3.7 (s, 2H), 3.8 (s, 3H), 4.3 (bs, OH), 4.55 (s, 2H), 5.1 (s, 2H), 6.5 (s, 1H), 6.6 (s, 1H), 6.9 (s, 1H), 7.2–7.5 (m, 5H).

Anal. calcd. for $C_{23}H_{24}BrNO_3S$: C, 58.22; H, 5.06; N, 2.95.
Found: C, 58.42; H, 4.91; N, 2.89%.

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