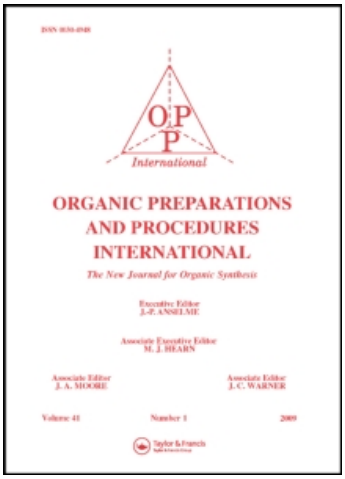

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THIOPHENE ANALOGUES OF SENDAVERINE

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THIOPHENE ANALOGUES OF SENDAVERINE

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(2/13/81)

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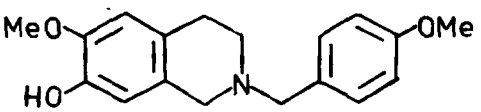
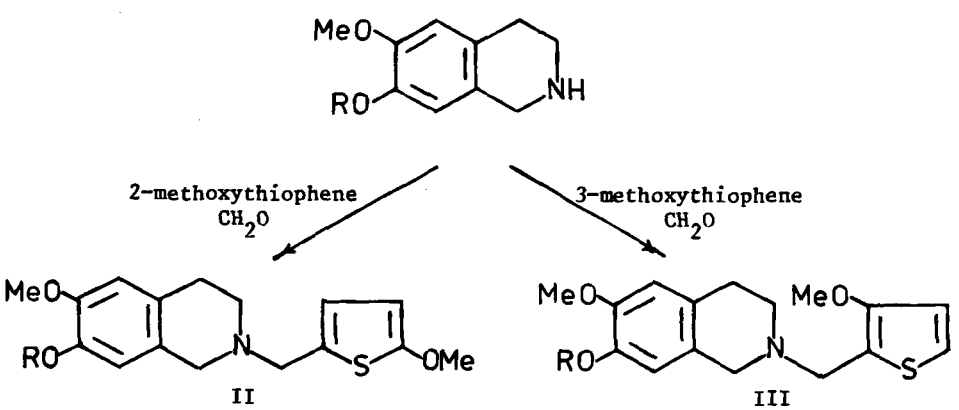
The alkaloid sendaverine (I), first isolated by Manske,[1] has previously been synthesised[2] by a route involving an alkylation with 4-meth-



I

oxybenzyl chloride. We now report the synthesis of the analogues IIa and IIIa of sendaverine, in which the benzyl group is replaced by 2-thenyl.



a) R = H b) R = Me

In addition we have prepared the related 7-methoxy compounds IIb and IIIb; it is of interest that comparable substances in the sendaverine series

showed sympathicolytic activity.[3] The compounds described in the present work were obtained by a Mannich-type reaction[4] of the methoxythiophene, formaldehyde and the appropriate tetrahydroisoquinoline, in aqueous acetic acid. The method of synthesis employed for the natural product[2] is inapplicable to II and III, since the methoxythenyl halides are very unstable.

EXPERIMENTAL

7-Hydroxy-6-methoxy-2-(5'-methoxy-2'-thenyl)-1,2,3,4-tetrahydroisoquinoline (IIa). - A mixture of 7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (1.5 g, 0.007 mole), anhydrous sodium acetate (0.8 g, 0.01 mole), water (2 ml), glacial acetic acid (4 ml) and formaldehyde (40% aqueous solution, 1 ml, 0.013 mole) was set aside at room temperature for one hour. 2-Methoxythiophene (1 g, 0.009 mole) was added and the mixture was shaken vigorously; a clear solution was produced and a rise in temperature was noted. After one hour, the solution was heated briefly on the steam bath, cooled, poured into water and basified (ammonium hydroxide, d = 0.88) and extracted several times with small portions of dichloromethane. The organic solution was washed firstly with water, then with brine, dried ($MgSO_4$) and evaporated to yield the crude product as a solid (1.9 g), which was crystallised from ethanol (twice) to give the sendaverine analogue IIa (0.93 g, 44%) as very pale yellow needles, mp. 159-160°.

NMR ($CDCl_3$): δ 6.59 (s, 2H, H-5 and H-8), 6.59 (d, 1H, J = 3.8 Hz, H-3'), 6.05 (d, 1H, J = 3.8 Hz, H-4'), 3.89 (s, 6H, 2 x OCH_3), 3.75 (s, 2H, H-1), 3.58 (s, 2H, thenyl CH_2), 2.59 (s, 4H, H-3 and H-4).

Anal. Calcd. for $C_{16}H_{19}NO_3S$: C, 62.95; H, 6.23; N, 4.59%

Found : C, 62.54; H, 6.68; N, 4.36%

7-Hydroxy-6-methoxy-2-(3'-methoxy-2'-thenyl)-1,2,3,4-tetrahydroisoquinoline (IIIa).- Reaction of 7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (1 g, 0.0046 mole), sodium acetate (0.6 g, 0.007 mole), glacial acetic acid (4 ml), formaldehyde (40% aqueous solution, 0.75 ml, 0.01 mole) and water (2 ml) with 3-methoxythiophene (0.6 g, 0.005 mole) in exactly the same manner as described above led to compound IIIa (0.77 g, 54%) mp. 142-144° (yellow blades from ethanol).

NMR ($CDCl_3$): δ 7.05 (d, 1H, J = 6 Hz, H-5') 6.75 (d, 1H, J = 6 Hz, H-4'), 6.48 (s, 2H, H-5 and H-8), 3.75 (s, 8H, 2 x OCH_3 and H-1), 3.52 (s, 2H, thenyl CH_2), 2.70 (s, 4H, H-3 and H-4).

Anal. Calcd. for $C_{16}H_{19}NO_3S$: C, 62.95; H, 6.23; N, 4.59%

Found: C, 62.65; H, 6.46; N, 4.48%

6,7-Dimethoxy-2-(5'-methoxy-2'-thenyl)-1,2,3,4-tetrahydroisoquinoline (IIb)

To a mixture of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (2.7 g, 0.14 mole), glacial acetic acid (2 ml), water (1 ml) and formaldehyde (40% aqueous solution, 1.1 ml, 0.015 mole) was added 2-methoxythiophene (1.7 g, 0.015 mole) and the whole was shaken until a clear solution was obtained. The mixture was set aside at room temperature for one hour, made basic (6M sodium hydroxide), then extracted with dichloromethane several times. Evaporation of the washed (water) and dried ($MgSO_4$) extracts afforded an oil which, on trituration with cold ether, gave a solid. This was crystallised from ethanol to yield compound IIb (2.7 g, 61%) as a pale-yellow solid, mp. 98-100°.

NMR ($CDCl_3$): δ 6.56 (s, 2H H-5 and H-8), 6.49 (d, 1H, J = 3.8 Hz, H-3'), 5.97 (d, 1H, J = 3.8 Hz, H-4'), 3.82 (s, 9H, 3 x OCH_3), 3.72 (s, 2H, H-1), 3.58 (s, 2H, thenyl CH_2), 2.76 (s, 4H, H-3 and H-4).

Anal. Calcd. for $C_{17}H_{21}NO_3S$: C, 63.93; H, 6.63; N, 4.39%
Found : C, 63.82; H, 6.84; N, 4.18%

6,7-Dimethoxy-2-(3'methoxy-2-thenyl)-1,2,3,4-tetrahydroisoquinoline (IIIb). A reaction was carried out as for the preparation of IIb above with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (2.2 g, 0.011 mole), glacial acetic acid (2 ml), water (1 ml), 40% aqueous formaldehyde (1.1 ml, 0.015 mole) and 3-methoxythiophene (1.3 g, 0.011 mole). The solid obtained from the dichloromethane extracts was rather impure; it was dissolved in benzene and passed through a short column of alumina before being crystallised from ethanol (twice). Thus the title isoquinoline IIIb (1.25 g, 34%) was obtained as a pale-yellow solid, mp. 119-121°.
NMR ($CDCl_3$) : δ 6.99 (d, 1H, J = 6 Hz, H-5'), 6.65 (d, 1H, J = 6 Hz, H-4') 6.45 and 6.35 (both s, H-5/H-8), 3.73 (s, 11H, H-1 and 3 x OCH_3), 3.51 (s, 2H, thenyl CH_2), 2.72 (s, 4H, H-3 and H-4).
Anal. Calcd. for $C_{17}H_{21}NO_3S$: C, 63.93; H, 6.63; N, 4.39%
Found : C, 63.73; H, 7.02; N, 4.13%

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