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Potential reserpine analogues. Derivatives of reduced isoquinolines and of meconine

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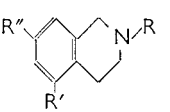
The syntheses of a series of eight 1,2,3,4-tetrahydro-2-methylisoquinolines substituted in positions 5 and 7 are described. In addition meconine-3-acetanilide and meconine-3-acetmorpholide have been prepared. None of the compounds caused any appreciable potentiation of barbiturate hypnosis in mice. Other tests for reserpine-like activity were not made.

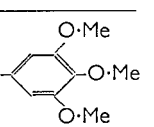
IN the belief that the pharmacological activity of reserpine may be connected with the presence of an isoquinoline fragment (rings D & E), 1,2,3,4-tetrahydro-5-methoxycarbonyl-2-methyl-7-(3,4,5-trimethoxybenzamido)isoquinoline [I; R = Me; R′ = COOMe; R″ = $NHCOC_6H_2(OMe)_3$] was prepared and subjected to pharmacological tests.

In addition, following the work of Chodnekar, Karim, Linnell & Sharp (1960, 1962) on substituted benzamides as potential reserpine analogues, meconine-3-acetanilide (II) and meconine-3-acetmorpholide (III) were also prepared, and tested.

None of the above compounds showed any appreciable potentiation of barbiturate hypnosis in mice and therefore other pharmacological tests, i.e., those for the depletion of the 5-hydroxytryptamine content of brain and spleen and for hypotensive action, were not made.



(I)

Compound	R	R′	R″
	Me	C·O·Me ‖ O	
IV	Me	CN	H
V	Me	CN	NO_2
VI(HCl)	Me	CO_2H	NO_2
VII	Me	CO·O·Me	NH_2
VIII	Me	CO·O·Me	OH
IX	Me	$CH_2·NH_2$	—
X	Me	$CO·NH·NH_2$	NO_2

The D and E rings of reserpine consist of a substituted decahydroisoquinoline; these isoquinoline derivatives should carry the same substituents at positions 5 and 7 as are present in reserpine at the corresponding positions 16 and 18. The methoxyl group at position 17 in reserpine is not important as it was shown that 17-desmethoxydeserpidine

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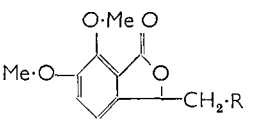
has hypotensive and sedative properties comparable with those of reserpine.

Onda, Kawanishi & Sasamoto (1956) prepared some tetrahydroisoquinolines with various substituents at positions 6 and 7. More recently Chodnekar, Sharp & Linnell (1962) have reported a series of benzamide derivatives; their work was based on the previous work of Karim & others (1960) with an attempt to combine the pharmacologically active trimethoxybenzanilide with other favoured fragments of reserpine. Their preparation of amides of 4-ethoxycarbonyloxy-3,5-dimethoxybenzoic acid followed the work of Lucas, Kudhne, Ceglowski, Dzieman & Macphillamy (1959) on syrosingopine.

The observation of Karim & others (1960) and the report by Borsy (1960) that the morpholide of 3,4,5-trimethoxybenzoic acid is neurosedative prompted the preparation and testing of the compounds II and III.



(II) R = CO·NHPh

(III) R = CO·N O

Experimental

5-*Cyano*-2-*methylisoquinolinium iodide*. 5-Cyanoisoquinoline (0·2 g) was dissolved in excess of methyl iodide (5 ml) by warming on a water-bath until a clear solution was obtained. It was kept at room temperature for 4 hr. Ether was added and the crystalline methiodide thus obtained was filtered off and washed with ether. Yield 0·29 g (50%), m.p. 275–76° (decomp.). Found: C, 44·6; H, 3·0; N, 9·7. $C_{11}H_9IN_2$ requires C, 44·6; H, 3·05; N, 9·5%.

5-*Cyano*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (IV). 5-Cyano-2-methylisoquinolinium iodide (0·9 g) in methanol (30 ml) was treated with potassium borohydride (1 g), added slowly with shaking and gentle warming on a water-bath. The reaction mixture was left overnight, the solvent removed at the water pump, and the residue taken up in little water. The solution was basified with 2% sodium hydroxide solution and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4 (anhydrous), filtered, and the solvent removed *in vacuo*. The residue on distillation yielded a liquid (b.p. 75°/0·1 mm) which solidified to a crystalline solid melting at 40–42°, 52° after crystallisation from ether. Found: C, 76·6; H, 7·15; N, 16·0. $C_{11}H_{12}N_2$ requires C, 76·7; H, 6·9; N, 16·3%.

5-*Cyano*-1,2,3,4-*tetrahydro*-2-*methyl*-7-*nitroisoquinoline* (V). To 5-cyano-1,2,3,4-tetrahydro-2-methylisoquinoline (0·9 g) dissolved in concentrated sulphuric acid (d = 1·84) (4 ml) was added dropwise with

continuous stirring a solution of sodium nitrate (0·9 g) in concentrated sulphuric acid (d = 1·84) (4 ml) at 0°. The reaction mixture was kept at room temperature for 2 hr, and then poured onto crushed ice. The solution obtained was basified with sodium hydrogen carbonate (solid) and extracted with chloroform. The chloroform solution was washed with water, dried over anhydrous sodium sulphate and filtered. Removal of the solvent at the water pump at low temperature yielded the nitro-compound, which crystallised from ethyl acetate and light petroleum (b.p. 40–60°), m.p. 111–12° to yield 0·9 g (70%). Found: C, 60·9; H, 5·1; N, 18·5. $C_{11}H_{11}N_3O_2$ requires C, 60·8; H, 5·1; N, 19·35%.

The location of the nitro-group at position 7 was established by nuclear magnetic resonance spectrum of the compound V as follows.

τ	Number of protons	Appearance	Assignment
7·44	3	Singlet	N – Me
7·13	2	Distorted triplet J = 5 c/s	Protons on position 3
6·83	2	Distorted triplet J = 5 c/s	Protons on position 4
6·26	2	Singlet	Protons on position 1
1·73	1	Singlet ⎫ meta splitting at top	Proton on position 6
1·53	1	Singlet ⎭ of peak J = 2·5 c/s	Proton on position 8

The spectrum was run in deuterochloroform with tetramethylsilane as an internal standard. The spectrum tabulated above has been totally assigned and firmly supports the suggested structure. The alternative structure with nitro-group on position 8 is thus ruled out.

1,2,3,4-*Tetrahydro-2-methyl-7-nitroisoquinoline-5-carboxylic acid hydrochloride* (VI). 5-Cyano-1,2,3,4-tetrahydro-2-methyl-7-nitroisoquinoline (0·55 g) and concentrated hydrochloric acid (6 ml) were heated in a sealed Carius tube in a muffle furnace at 150° for 8 hr. The tube was then left to cool to room temperature and the yellowish crystalline slurry transferred with the aid of the least amount of water to an evaporating dish and evaporated on a water-bath. The golden-yellow solution obtained by dissolving the residue in water and charcoaling, deposited crystals which melted at 239–42° (frothing and decomp.). These on recrystallisation from MeOH/ether yielded needles, having the same melting-point. Found: C, 48·1; H, 4·7; Cl, 13·2; N, 10·1. $C_{11}H_{13}ClN_2O_4$ requires C, 48·4; H, 4·8; Cl, 13·0; N, 10·3%.

7-*Amino*-1,2,3,4-*tetrahydro*-5-*methoxycarbonyl*-2-*methylisoquinoline* (VII). (*a*) 1,2,3,4-Tetrahydro-2-methyl-7-nitroisoquinolin-5-carboxylic acid hydrochloride (0·2 g) in thionyl chloride (2·0 ml) was heated on a water-bath until all the thionyl chloride had evaporated off. Absolute methanol, at the water-bath temperature, was carefully added until solution was obtained. After removal of the methanol, the residue was washed with ether and crystallised from methanol/ether yielding the hydrochloride of the required product melting at 195–198° (decomp. sealed tube), yield 0·15 g (71%).

(*b*) 1,2,3,4-Tetrahydro-5-methoxycarbonyl-2-methyl-7-nitroisoquinoline hydrochloride (0·07 g) was dissolved in the minimum quantity of water and ammonia solution was added until the solution was just alkaline.

This at once deposited a pale yellow precipitate, which after extracting with ethyl acetate, washing the ethyl acetate extract with water, drying over Na_2SO_4 (anhydrous) and removing the solvent, was crystallised from ethyl acetate/light petroleum (40–60°) yielding the free base m.p. 129–30°.

(*c*) 1,2,3,4-Tetrahydro-5-methoxycarbonyl-2-methyl-7-nitroisoquinoline (0·4 g) was hydrogenated in ethanol (50 ml) with palladium charcoal (30%, 0·9 g) for 2½ hr. After 1 hr the absorption of hydrogen seemed to be complete. The reaction mixture was filtered, and the solvent removed from the filtrate *in vacuo*. The residue, on crystallisation from Me OH/ether yielded the product (VII), m.p. 144–46°. Found: C, 65·3; H, 7·5; N, 12·8. $C_{12}H_{16}N_2O_2$ requires C, 65·45; H, 7·3; N, 12·7%.

The *base hydroiodide* melted at 219°. *Acetyl derivative:* m.p. 93–95°.

1,2,3,4-*Tetrahydro-5-methoxycarbonyl-2-methyl-7-(3,4,5-trimethoxybenzamido)isoquinoline* (I). 3,4,5-Trimethoxybenzoic acid (0·34 g) was dissolved in redistilled thionyl chloride (5 ml) and the solution evaporated on a water-bath. The residue was again treated similarly. Benzene (5 ml) was added and evaporated. To the 3,4,5-trimethoxybenzoyl chloride left behind, was added a solution of 7-amino-1,2,3,4-tetrahydro-5-methoxycarbonyl-2-methylisoquinoline (0·3 g) in dry pyridine (5 ml) whereupon a precipitate appeared at once. The mixture was evaporated to dryness on the water-bath. Water (least amount) was added to the residue and the solution was again evaporated. The residue was again dissolved in the least amount of water, the solution just made alkaline by addition of a dilute sodium hydrogen carbonate solution, then extracted with benzene, washed with water, dried over sodium sulphate (anhydrous) and the solvent removed. The residue (0·3 g) was crystallised from ethyl acetate, m.p. 170–71°. Found: C, 63·9; H, 6·3; N, 6·6. $C_{22}H_{26}N_2O_6$ requires C, 63·8; H, 6·3; N, 6·8%.

1,2,3,4-*Tetrahydro-7-hydroxy-methoxycarbonyl-2-methylisoquinoline* (VIII). A cooled solution of 7-amino-1,2,3,4-tetrahydro-5-methoxycarbonyl-2-isoquinoline (0·4 g) in dilute sulphuric acid (2 ml of concentrated acid in 6 ml water) was diazotised by the dropwise addition with continuous stirring of sodium nitrite solution (0·15 g in 4 ml water). The temperature of the mixture was kept at 0°. The diazotised solution was poured slowly into a boiling saturated copper sulphate solution (15–20 ml) whereupon brisk evolution of nitrogen occurred. Boiling was continued for 5 min. The solution was cooled, basified with concentrated ammonia solution, and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulphate (anhydrous) and filtered. The solvent was then removed from the filtrate. The residue was the crystalline phenolic compound (0·2 g 50%), m.p. 168–70°. 180–181° after crystallising from ethyl acetate. Found: C, 64·7; H, 6·9; N, 6·15. $C_{12}H_{15}NO_3$ requires C, 65·15; H, 6·8; N, 6·3%.

5-*Aminomethyl*-1,2,3,4-*tetrahydro*-2-*methylisoquinoline* (IX). 2-Cyano-1,2,3,4-tetrahydro-2-methylisoquinoline (1 g) was dissolved in sodium-dried ether (24 ml). Lithium aluminium hydride (1 g) was added carefully and the mixture refluxed for 6 hr. The cooled reaction mixture was

decomplexed carefully by addition of water. The base thus liberated was extracted with an additional amount of ether. The ether extract was washed with water, dried over sodium sulphate (anhydrous), filtered and the solvent removed from the filtrate. The residue failed to crystallise. This was therefore dissolved in the least amount of pyridine and an excess of acetic anhydride was added. The mixture was then evaporated in a crystallising dish on a water-bath. The excess of acetic anhydride was destroyed by the repeated addition of water followed by evaporation on a water-bath. The residue, 5-acetamidomethyl-1,2,3,4-tetrahydro-2-methyl isoquinoline, thus obtained was crystallised from ethyl acetate and light petroleum (b.p. 40–60), and melted at 126–126·5°. Found: C, 71·2; H, 8·4; N, 12·7. $C_{13}H_{18}N_2O$ requires C, 71·6; H, 8·3; N, 12·8%.

1,2,3,4-*Tetrahydro-2-methyl-7-nitroisoquinoline-5-carboxyhydrazide* (X). 1,2,3,4-Tetrahydro-5-methoxycarbonyl-2-methyl-7-nitroisoquinoline (0·1 g) was dissolved in methanol, a slight excess of hydrazine hydrate (0·4 g) was added, and the mixture left overnight, whereupon crystals appeared. These were recrystallised from water, m.p. 185°. Found: C, 52·5; H, 6·0; N, 22·6. $C_{11}H_{14}N_4O_3$ requires C, 52·8; H, 5·6; N, 22·4%.

Meconine-3-acetanilide (II). To a solution of aniline (1·8 g) in ether (10 ml) was added meconine-3-acetyl chloride (2·58 g) and left at room temperature for 24 hr. The precipitate was filtered off, washed with water and crystallised from ethanol m.p. 199°–200°. Found: C, 66·1; H, 5·1; H, 4·2. $C_{18}H_{17}NO_5$ requires C, 66·05; H, 5·2; N, 4·3%.

Meconine-3-acetmorpholide (III). To a solution of morpholine (1·74 g) in ether (10 ml) was added meconine-3-acetyl chloride (2·58 g) slowly at 5°. It was kept at room temperature for 24 hr. The precipitate was filtered off and washed with water and crystallised from ethanol m.p. 175–177°. Found: C, 59·55; H, 5·75; N, 4·3. $C_{16}H_{19}NO_6$ requires C, 59·8; H, 5·9; N, 4·4%.

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